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Identificação de RNAs longos não-codificadores em pacientes com Leishmaniose Tegumentar Americana

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Orientadora: Profa. Dra. Flavia Lombardi Lopes

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Título: Identificação de RNAs longos não-codificadores em pacientes com Leishmaniose Tegumentar Americana

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"Por vezes sentimos que aquilo que fazemos não é senão uma gota de água no mar. Mas o mar seria menor se lhe faltasse uma gota".

(Madre Teresa de Calcutá)

ALMEIDA, M. C. **Identificação de RNAs longos não-codificadores em pacientes com Leishmaniose Tegumentar Americana.** 2023. 128 f. Dissertação (Mestrado) - Faculdade de Medicina Veterinária de Araçatuba, Universidade Estadual Paulista, Araçatuba, 2023.

RESUMO

Nas Américas, a leishmaniose cutânea é comumente conhecida como leishmaniose tegumentar Americana, tendo como principal agente causador a espécie *Leishmania (Viannia) braziliensis*, responsável pelas três formas da doença: leishmaniose cutânea localizada (LCL), leishmaniose mucocutânea ou mucosa (LM) e leishmaniose disseminada (LD). A LCL é a forma mais comum, caracterizada por uma ou até dez lesões no local da picada do flebotomíneo. Após a cura da lesão cutânea inicial com o uso ou não de medicamentos, pode ocorrer o desenvolvimento da LM em até 20% dos pacientes, caracterizada pela destruição das mucosas oral e nasal. Essa progressão envolve diversos fatores relacionados ao parasito e ao hospedeiro que ainda não estão totalmente esclarecidos. As interações patógeno-hospedeiro envolvem diversas mudanças dinâmicas na expressão gênica no curso da infecção que podem ser reguladas por RNAs longos não-codificadores (lncRNAs). Os lncRNAs são capazes de regular a expressão gênica a nível transcricional e pós-transcricional, atuando em condições fisiológicas e patológicas. Nesse contexto, o presente estudo visa analisar se a coexpressão de lncRNAs e seu possíveis mRNAs alvos estão envolvidos no eventual desenvolvimento de LM. Os dados públicos de RNA-Seq (NCBI - GEO DataSets GSE33601) foram obtidos a partir da biópsia de lesões cutâneas primárias de 6 indivíduos. Após a cura completa da lesão, 3 indivíduos não apresentaram recidiva da doença (grupo LCL), enquanto os outros 3 desenvolveram lesões na mucosa oral e nasal (grupo LM). Após o alinhamento e contagem das *reads* e análise de expressão diferencial, identificamos 579 mRNAs e 46 lncRNAs diferencialmente expressos (p-valor<0.05 e log2(FC)≥1) no contraste entre grupos LM e LCL. A partir do cálculo do coeficiente da correlação de Pearson, nós identificamos 1324 pares lncRNAs-mRNAs coexpressos (|r|≥0.9 e p-valor<0.05). O lncRNA SNHG29 é um potencial regulador do mRNA S100A8, ambos mais expressos no grupo LM. Em conjunto com seu parceiro heterodimérico S100A9, formam um complexo que atua como mediador pró-inflamatório sendo reconhecidos por

receptores de células da imunidade inata e queratinócitos. Sendo assim, nossos resultados sugerem que a regulação do mRNA alvo pelo lncRNA pode resultar em um ambiente pró-inflamatório contribuindo para o eventual desenvolvimento da lesão mucosa característica da LM.

Palavras-chave: Bioinformática. Epigenética. Leishmaniose.

ALMEIDA, M. C. **Identification of long non-coding RNAs in patients with American Tegumentary Leishmaniasis.** 2023. 128 f. Dissertação (Mestrado) - Faculdade de Medicina Veterinária de Araçatuba, Universidade Estadual Paulista, Araçatuba, 2023.

ABSTRACT

In the Americas, cutaneous leishmaniasis is commonly known as American tegumentary leishmaniasis, having as the main causative agent the species *Leishmania (Viannia) braziliensis*, responsible for the three forms of the disease: localized cutaneous leishmaniasis (LCL), mucocutaneous or mucosal leishmaniasis (ML) and disseminated leishmaniasis (DL). LCL is the most common form, characterized by one or ten lesions at the sandfly bite site. After healing of the initial skin lesion with or without the use of medication, ML may develop in up to 20% of patients, characterized by destruction of the oral and nasal mucosa. This progression involves several factors related to the parasite and the host that are not yet fully understood. Pathogen-host physiological changes involve several dynamic changes in gene expression over the course of infection that can be regulated by long non-coding RNAs (lncRNAs). LncRNAs are capable of regulating gene expression at the transcriptional and post-transcriptional level in regulatory and pathological conditions. In this context, the present study aims to analyse whether the co-expression of lncRNAs and their possible target mRNAs are involved in the eventual development of ML. Public RNA-Seq data (NCBI - GEO DataSets GSE33601) were obtained from biopsy of primary skin lesions from 6 individuals. After complete healing of the lesion, 3 individuals had no recurrence of the disease (LCL group), while the other 3 developed lesions in the oral and nasal mucosa (ML group). After read alignment and counting, differential expression analysis identified 579 mRNAs and 46 lncRNAs differentially expressed (p-value<0.05 and log2(FC)≥1) in the contrast between ML and LCL groups. From Pearson's correlation coefficient, we identified 1324 co-expressed lncRNAs-mRNA pairs (|r|≥0.9 and p-value<0.05). LncRNA SNHG29 is a potential regulator of mRNA S100A8, both upregulated in the LM group. Together with its heterodimeric partner S100A9, these proteins form a complex that acts as a pro-inflammatory mediator and is recognized by innate immune cell receptors and keratinocytes. Our results suggest that target mRNA regulation by lncRNA may result

in a pro-inflammatory environment for the eventual development of the mucosal lesion characteristic of ML.

Keywords: Bioinformatics. Epigenetics. Leishmaniasis.

LISTA DE ABREVIATURAS

IFN-γ	Interferon gama
IL	Interleucina
LC	Leishmaniose cutânea
LCL	Leishmaniose cutânea localizada
LD	Leishmaniose disseminada
LM	Leishmaniose mucosa
LMC	Leishmaniose mucocutânea
lncRNAs	RNAs longos não-codificadores
LTA	Leishmaniose tegumentar Americana
LV	Leishmaniose visceral
miRNAs	microRNAs
mRNAs	RNAs mensageiros
NO	Óxido nítrico
OMS	Organização Mundial da Saúde
PBMCs	Células mononucleares de sangue periférico
piRNAs	RNAs de interação com PIWI
ROS	Espécies reativas de oxigênio
rRNAs	RNAs ribossomais
siRNAs	RNAs curtos de interferência
snoRNAs	Pequenos RNAs nucleolares
snRNAs	Pequenos RNAs nucleares
TGF-β	Fator de crescimento transformador beta
TNF-α	Fator de necrose tecidual alfa
tRNAs	RNAs transportadores

SUMÁRIO

1 INTRODUÇÃO GERAL

A leishmaniose integra a lista das 20 Doenças Tropicais Negligenciadas segundo a Organização Mundial da Saúde (OMS), afetando principalmente populações vulneráveis de países tropicais que vivem nas proximidades dos vetores e reservatórios da doença, onde o saneamento básico e o acesso aos serviços de saúde são precários (NIH, 2016; WHO, 2022a). Essa doença é causada por mais de 20 espécies de protozoários parasitos do gênero *Leishmania* (família *Trypanosomatidae*) e é transmitida entre hospedeiros mamíferos através da picada de mais de 90 espécies de flebotomíneos fêmeas infectadas. Devido à variedade de espécies, a leishmaniose é dividida geograficamente em Velho Mundo, que se refere ao Hemisfério Oriental (Ásia, Oriente Médio, África e Sul da Europa), e em Novo mundo, referindo-se ao Hemisfério Ocidental (México, América Central, América do Sul e EUA) (MANN et al., 2021). Estima-se que ocorram mais de 1 milhão de novos casos de leishmaniose anualmente, que permanece sendo o maior problema de saúde pública em 4 regiões epidemiológicas do mundo: Américas; leste e norte da África; e oeste e sudeste da Ásia (WHO, 2022b, 2022c).

A *Leishmania* possui 2 estágios diferentes durante o seu ciclo de vida: promastigota e amastigota. Durante o repasto sanguíneo, a fêmea do flebotomíneo (*Phlebotomus* no Velho Mundo e *Lutzomyia* no Novo Mundo) transmite para humanos e outro reservatórios animais a forma promastigota flagelada, que é fagocitada por macrófagos e outras células do hospedeiro. No interior dessas células, as promastigotas se transformam na forma amastigota que se multiplica e passa a infectar outras células, sendo responsável pelas formas sintomática e assintomática da doença. Os flebotomíneos se infectam quando, no repasto sanguíneo, ingerem células infectadas com amastigotas, que irão se desenvolver em promastigotas no intestino desses insetos. Quando o desenvolvimento ocorre no intestino posterior, são formados parasitos do subgênero *Viannia* e no intestino médio são formados parasitos do subgênero *Leishmania* (CDC, 2020a; MANN et al., 2021). As manifestações clínicas da doença variam de acordo com a espécie de *Leishmania* e vão desde lesões cutâneas auto curativas a infecções viscerais fatais. O desfecho da infecção é influenciado pelas características do parasito, biologia do vetor e principalmente a resposta imune do hospedeiro (BURZA; CROFT; BOELAERT, 2018).

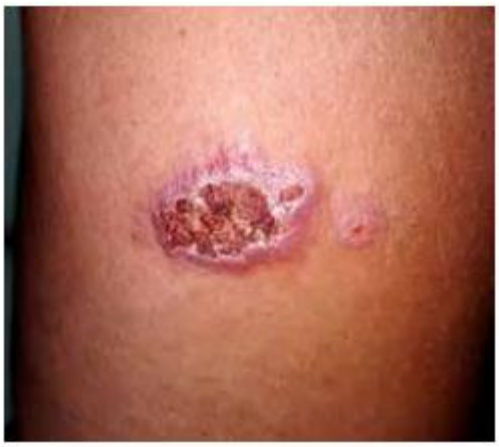
De acordo com os sintomas clínicos, existem 3 formas principais da leishmaniose: leishmaniose visceral, leishmaniose cutânea e leishmaniose mucocutânea (WHO, 2022b). A leishmaniose visceral (LV), também conhecida como calazar, é a forma mais grave e se não tratada é fatal em 95% dos casos. Essa doença atinge principalmente órgãos como o baço, fígado e medula óssea, podendo se desenvolver após meses ou anos da picada do flebotomíneo. Estima-se que 50.000 a 90.000 novos casos de LV ocorram anualmente em todo o mundo, concentrando-se no Brasil, África Oriental e na Índia. É causada pelas espécies *Leishmania (Leishmania) donovani* na África e Ásia e pela espécie *Leishmania (Leishmania) infantum* (*L. chagasi*) na Bacia do Mediterrâneo, Oriente Médio, Ásia Central, América do Sul e América Central (BURZA; CROFT; BOELAERT, 2018; WHO, 2022b). A leishmaniose cutânea (LC) é a forma mais comum da doença e é caracterizada por lesões de pele geralmente em partes expostas do corpo como braços, pernas e face. Essas feridas se desenvolvem dentro de semanas ou meses após a picada do flebotomíneo. São registrados anualmente entre 600 mil e 1 milhão de novos casos de LC, principalmente nas Américas, bacia do Mediterrâneo, Oriente Médio e Ásia Central (CDC, 2020b; WHO, 2022b). No Velho Mundo, as principais espécies causadoras da doença são *Leishmania (Leishmania) major*, *Leishmania (Leishmania) tropica* e *Leishmania (Leishmania) aethiopica*, enquanto no Novo Mundo, as espécies causadoras são *Leishmania (Leishmania) amazonensis*, *Leishmania (Leishmania) mexicana*, *Leishmania (Viannia) braziliensis* e *Leishmania (Viannia) guyanensis*. Embora as manifestações de LC sejam consideradas mais leves, com lesões que podem se curar sem tratamento, os pacientes infectados por espécies do subgênero *Viannia* podem desenvolver a forma mucocutânea (BURZA; CROFT; BOELAERT, 2018). A leishmaniose mucocutânea (LMC), também conhecida como leishmaniose mucosa (LM), são lesões menos típicas, caracterizadas por deformidades na mucosa e cartilagem oronasofaríngea. Os casos de LMC são mais frequentes na América do Sul e mais de 90% dos casos ocorrem na Bolívia, Brasil, Etiópia e Peru (BURZA; CROFT; BOELAERT, 2018; SCORZA; CARVALHO; WILSON, 2017; WHO, 2022b).

No Novo Mundo, a LC é comumente conhecida como leishmaniose tegumentar Americana (LTA), tendo como principal agente causador no Brasil e na América do Sul a espécie *Leishmania (Viannia) braziliensis*, responsável pelas três formas da doença: leishmaniose cutânea localizada (LCL), leishmaniose mucocutânea ou mucosa (LM) e leishmaniose disseminada (LD) (COUTINHO DE

OLIVEIRA; DUTHIE; ALVES PEREIRA, 2020; LAGO et al., 2018). Os principais reservatórios incluem cães, humanos, roedores e cavalos (BURZA; CROFT; BOELAERT, 2018).

De acordo com a Organização Pan-Americana da Saúde (OPAS/OMS), de 2001 a 2021, uma média de 52.645 casos por ano de LCL e LM foram registrados nas Américas (PAHO, 2022). A LCL é a forma mais comum da doença caracterizada por uma ou até dez lesões cutâneas em áreas expostas do corpo. A lesão, no local ou próximo ao local da picada do flebotomíneo, é uma úlcera redonda, indolor, com bordas delimitadas e uma crosta central (Figura 1) (GOTO; LINDOSO, 2014). O desenvolvimento da lesão e o início dos sintomas clínicos no hospedeiro varia de alguns dias até 3 anos, comumente ocorrendo de 2 a 8 semanas. Cerca de 70% dos pacientes se curam sem o uso de tratamento medicamentoso (VOLPEDO et al., 2021). O antimônio pentavalente é o tratamento de primeira linha para LCL na maioria dos pacientes, tendo como dose recomendada 20 mg/kg/dia por via intravenosa ou intramuscular por 20 dias, porém apresenta toxicidades e reações adversas (DAVID; CRAFT, 2009). O diagnóstico de LCL pode ser realizado através de métodos parasitológicos ou imunológicos. O diagnóstico parasitológico é considerado o padrão ouro devido sua alta especificidade. O material para esse tipo de diagnóstico pode ser obtido através de raspagem, aspiração por agulha fina ou biópsia de lesões, que permite que sejam realizados exame microscópico, cultura e técnicas de diagnóstico molecular. O diagnóstico sorológico tem uso limitado, pois apresenta baixa sensibilidade e especificidade variável (WHO, 2010).

Figura 1 - Lesão característica de LCL antes do tratamento

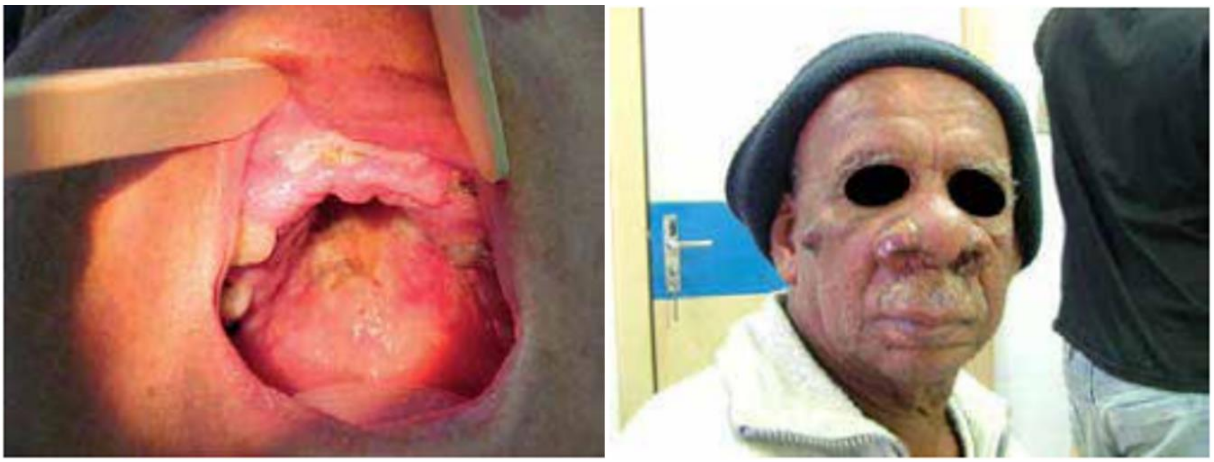


Fonte: BRASIL, 2017

Após a cura da lesão com o uso ou não de medicamentos, alguns parasitos e DNA parasitário podem permanecer nas cicatrizes por muito anos, o que pode implicar na resistência contra uma reinfecção ou no desenvolvimento de lesões mais severas como nas mucosas, já que o parasito é capaz de migrar da pele para a mucosa nasofaríngea através do sistema hematogênico e linfático (MANN et al., 2021; VOLPEDO et al., 2021). Esse agravamento pode ocorrer em até 20% dos pacientes com LCL e envolve diversos fatores relacionados ao parasito e ao hospedeiro que ainda não estão totalmente esclarecidos. Entre esses fatores estão tamanho e número de lesões cutâneas, espécie e fatores de virulência do parasito, fatores genéticos e resposta imune do hospedeiro, além de fatores nutricionais do paciente, idade e sexo (DAVID; CRAFT, 2009; MARETTI-MIRA et al., 2012; VOLPEDO et al., 2021).

A LM também é conhecida como “espundia” sendo caracterizada pela destruição progressiva dos tecidos e cartilagens da cavidade oral, nasal e faríngea que evoluem para lesões desfigurantes (Figura 2). Os sintomas iniciais são brandos, com inflamação e congestão nasal. O aparecimento da lesão mucosa pode ocorrer em paralelo com as lesões de LCL ou se desenvolver em até 5 anos após a cicatrização da lesão inicial (DAVID; CRAFT, 2009; GOTO; LINDOSO, 2014). As lesões de LM não se curam espontaneamente e comumente são acompanhadas de infecções bacterianas secundárias que podem levar o paciente a óbito (WHO, 2010). O antimônio pentavalente também é a primeira droga de escolha para o tratamento da LM, seguido da anfotericina B. Se a doença estiver em estágios avançados, os pacientes devem ser monitorados quanto as complicações do tratamento e, geralmente, os pacientes com LM são resistentes ao tratamento com antimônios e podem necessitar de mais de um ciclo de tratamento, quando não ocorrem falhas ou recidiva (DAVID; CRAFT, 2009). O diagnóstico de LM deve se iniciar com a suspeita de pacientes com lesões mucosas características, história prévia de LCL com cicatrizes ou com LCL ativa. Um resultado de sorologia e teste cutâneo de Montenegro positivos aumenta a suspeita, enquanto a busca por parasitos nas lesões mucosas por exame microscópico ou por cultura tem baixa sensibilidade, já que essas lesões apresentam poucos parasitos devido à forte resposta imune no local. As técnicas de diagnóstico molecular que buscam o DNA parasitário são as mais sensíveis para confirmar a LM (WHO, 2010).

Figura 2 - Leishmaniose mucosa representada por lesões ulceradas nas mucosas oral e nasal desenvolvidas após a cicatrização da forma cutânea



Fonte: BRASIL, 2017

Ainda não há como prever o desenvolvimento de lesões desfigurantes nas mucosas a partir de lesões cutâneas primárias de leishmaniose e, atualmente, as estratégias para a redução dos casos estão limitadas ao controle do vetor e ao tratamento com antimônios pentavalentes, que por sua vez apresentam toxicidade gerando abandono do tratamento pelo paciente. Além disso, não há vacinas profiláticas contra a leishmaniose cutânea, apenas vacinas que podem ser utilizadas para imunoterapia combinadas com tratamento convencionais (COUTINHO DE OLIVEIRA; DUTHIE; ALVES PEREIRA, 2020).

A interação entre o parasito e a resposta imune do hospedeiro é complexa e variável, levando a diferentes desfechos da doença. As diversas espécies do parasito são responsáveis pela determinação das manifestações clínicas da leishmaniose, enquanto a imunidade e genética do hospedeiro são fatores determinantes para gravidade da doença (PANAHI et al., 2022). Nas lesões de LCL, a resposta imune inicial é o principal fator contribuinte para a auto cura ou para a formação de lesões crônicas. Em um panorama geral, os fagócitos são as primeiras células recrutadas para o local de infecção, produzindo espécies reativas de oxigênio (ROS) e óxido nítrico (NO) para a morte intracelular do parasito (VOLPEDO et al., 2021). Os macrófagos são fortemente estimulados por interferon gama (IFN-γ) e fator de necrose tecidual alfa (TNF-α) para gerar o *burst* oxidativo (SCORZA; CARVALHO; WILSON, 2017). Uma resposta mista de T *helper* (CD4) Th1 e Th2 foi observada em lesões ativas. A citocina pró-inflamatória IL-17, que atua no recrutamento de neutrófilos, está aumentada em células mononucleares de sangue periférico (PBMCs) de pacientes com LCL e foi associada a promoção de dano tecidual, no entanto a

produção de IL-17 e TNF-α é reduzida por meio de IL-10 e fator de crescimento transformador beta (TGF-β) que contribuem para o equilíbrio da inflamação (VOLPEDO et al., 2021).

A LM é caracterizada por uma inflamação crônica, alta hipersensibilidade e baixo número de parasitos. Diferente da LCL, o predomínio do perfil TCD4+ Th1 e TCD8+ é prejudicial devido a destruição tecidual ocasionada. Pacientes com LM apresentam PBMCs produzindo níveis elevados de IFN-γ e TNF-α e baixos níveis de IL-10. As células TCD8+ possuem atividade citotóxica dada principalmente pela produção de granzima A, que nas lesões causadas por *L. braziliensis*, a citotoxicidade é característica principal da lesão devido a destruição tecidual. Além disso, essas lesões tendem a apresentar maior expressão de IL-17 quando comparadas as lesões de LCL, uma citocina que pode estar envolvida na patogênese da doença. Diante do cenário imunológico apresentado pelas diferentes formas da leishmaniose cutânea, acredita-se que uma resposta imunológica exacerbada e baixa atividade regulatória pode gerar a destruição dos tecidos que é observada na LM (SCORZA; CARVALHO; WILSON, 2017; VOLPEDO et al., 2021).

As interações patógeno-hospedeiro envolvem diversas mudanças dinâmicas na expressão gênica no curso da infecção, de forma que todos os recursos mobilizados de ambos os lados dessa interação refletem no perfil de transcriptoma, e a identificação dos genes expressos nessas condições pode revelar mecanismos envolvidos na resposta do hospedeiro à infecção (SHADAB et al., 2019; TANG et al., 2020). A *Leishmania*, sendo um parasito intracelular obrigatório, é capaz de modular a expressão gênica do hospedeiro, o que reflete em sua resposta imune contra o patógeno (AFRIN; KHAN; HEMEG, 2019). A expressão gênica depende de diversas etapas regulatórias, tendo a epigenética como a principal responsável por esse controle (GIBNEY; NOLAN, 2010). A epigenética abrange uma variedade de processos que modulam a expressão gênica, e as características fenotípicas associadas, sem que haja alteração na sequência de nucleotídeos do DNA, e essas alterações podem ser transmitidas hereditariamente, além de serem afetadas por exposições ambientais que levam a fenótipos de doença (LI et al., 2021; WEINHOLD, 2006). Os mecanismos epigenéticos incluem a metilação do DNA, modificações e remodelamento de histonas e os RNAs não-codificadores (WEI et al., 2017). Esses processos são dinâmicos e podem agir simultaneamente ou separadamente, permitindo a rápida repressão ou ativação de um gene específico, de um conjunto de

genes ou mesmo de proteínas, atuando em processos fisiológicos e patológicos (GIBNEY; NOLAN, 2010; BUSSLINGER, 2014).

Parte do genoma dá origem a transcritos de RNA que, em sua maioria, não codificam proteínas. Em geral, esse RNAs não-codificadores são classificados de acordo com o número de nucleotídeos em sua composição, localização subcelular, orientação em relação ao gene codificador de proteína mais próximo e/ou função quando conhecida (GIBNEY; NOLAN, 2010). Além disso, podem ser divididos em RNAs não-codificadores de manutenção ou regulatórios. Aqueles de manutenção incluem os RNAs transportadores (tRNAs), RNAs ribossomais (rRNAs), pequenos RNAs nucleares (snRNAs) e pequenos RNAs nucleolares (snoRNAs). Enquanto os regulatórios incluem microRNAs (miRNAs), RNAs curtos de interferência (siRNAs), RNAs de interação com PIWI (piRNAs) e RNAs longos não-codificadores (lncRNAs) (GIBNEY; NOLAN, 2010; ZHANG et al., 2019a).

Os lncRNAs são transcritos com mais de 200 nucleotídeos que não possuem potencial de codificação. Assim como os mRNAs, os lncRNAs são transcritos pela RNA polimerase II e são processados após a transcrição, através do *splicing* alternativo, *capping* 5’ e poliadenilação. De acordo com a posição genômica de sua biogênese, esses transcritos não-codificadores podem ser classificados em: A) sense, quando se sobrepõem a um ou mais éxons de outro transcrito na mesma fita; B) antisense, quando se sobrepõem a um ou mais éxons de outro transcrito na fita oposta; C) bidirecional, quando a expressão do lncRNA e de um gene codificador de proteína vizinho na fita oposta é iniciada em regiões próximas; D) intrônico, quando está posicionado dentro de uma região intrônica de um outro transcrito; e E) intergênico, quando está posicionado entre dois genes (FERNANDES et al., 2019; GIBNEY; NOLAN, 2010). LncRNAs são transcritos que possuem alta especificidade celular e temporal, e são encontrados no núcleo, nucléolo, citoplasma e em mitocôndrias. Através de sua interação com o DNA, RNA e proteínas, os lncRNAs são capazes de regular a expressão gênica a nível transcricional e pós-transcricional, assim podem recrutar complexos modificadores da cromatina, controlando sua estrutura e função, modular a transcrição gênica guiando fatores de transcrição para seus promotores ou sequestrando esses fatores de transcrição para evitar o processo de transcrição, funcionam como esponjas de miRNA prejudicando o funcionamento da interação do miRNA e seu gene alvo, ligam-se diretamente ao seu mRNA alvo modulando seu processamento, como inibição da tradução, regulação do *splicing* e

degradação, e ligam-se a combinações específicas de proteínas reguladoras, atuando como elementos de *scaffolding* (FERNANDES et al., 2019; ZHANG et al., 2019b).

Os lncRNAs também podem atuar tanto em *cis* quanto em *trans*. A ação de um lncRNA em *cis* é caracterizada pela regulação da expressão de genes alvos que estão localizados no mesmo *locus* cromossômico, ou seja, são restritos ao cromossomo do qual são transcritos, enquanto a ação *trans* ocorre quando o lncRNA regula a expressão de genes em outros cromossomos, distante do local onde foi transcrito (KORNIENKO et al., 2013). Na regulação em *cis*, os lncRNAs podem atuar através de três possíveis mecanismos, sendo eles: 1) o transcrito do lncRNA regula a expressão de genes vizinhos através do recrutamento de fatores reguladores para o *locus*; 2) a transcrição e/ou *splicing* do lncRNA no *locus* confere um efeito na regulação gênica; e 3) elementos do DNA dentro do *locus* do lncRNA confere a regulação de forma independente da produção ou sequência do RNA transcrito. E na regulação em *trans*, os lncRNAs também podem atuar através de três potenciais mecanismos: 1) lncRNAs interagem com promotores e *enhancers* que influenciam no estado da cromatina; 2) lncRNAs influenciam a estrutura e organização nuclear; e 3) lncRNAs modulam a atividade de RNAs os quais se ligam diretamente por complementariedade de sequência. Essas interações podem ocorrer no núcleo ou citoplasma das células (KOPP; MENDELL, 2018).

Os diversos papéis que os lncRNAs podem exercer sobre o genoma e na expressão de genes torna evidente a importância desses transcritos não-codificadores em condições fisiológicas e patológicas. O exemplo mais conhecido de um lncRNA que atua em um processo fisiológico de uma célula é o *Xist.* Esse lncRNA de ação *cis* é responsável pelo silenciamento de um dos cromossomos X durante o desenvolvimento embrionário inicial em mamíferos fêmeas para que haja compensação de dose desse cromossomo. Ele é transcrito a partir de um cromossomo X, o qual será silenciado, e é responsável por diversos processos que geram a relocalização do cromossomo para a periferia nuclear, deposição de marcas repressivas da cromatina e o silenciamento da transcrição de quase todo o cromossomo (KOPP; MENDELL, 2018). Em condições patológicas, os lncRNAs já foram descritos em doenças crônicas como o câncer e também em doenças cardiovasculares e neurológicas. Além disso, esses transcritos não-codificadores têm sido relacionados a regulação de processos inflamatórios em doenças infecciosas

(FERNANDES et al., 2019). No entanto, há uma escassez de estudos com lncRNAs na infecção por *Leishmania*.

Dada a carência de banco de dados abrangentes para a busca da função de lncRNAs verificados experimentalmente, a análise de coexpressão entre lncRNAs e RNAs mensageiros (mRNAs) é frequentemente empregada e torna-se eficaz para compreender o papel dos lncRNAs em contextos biológicos e patológicos, e para identificar o perfil transcriptômico em uma determinada condição, a técnica de sequenciamento de RNA é amplamente empregada (CONESA et al., 2016; GIBNEY; NOLAN, 2010; SUN et al., 2021).

Sabendo que a progressão de LCL para LM envolve fatores que não estão completamente elucidados, considerando que na interação patógeno-hospedeiro ocorrem mudanças na expressão gênica induzidas pela *Leishmania*, e que os lncRNAs são reguladores da expressão gênica atuando em processo patológicos, supõe-se que lncRNAs e seus possíveis mRNA alvos podem estar associados ao eventual desenvolvimento de lesões nas mucosas como observado na LM.

1.1 Objetivo

Analisar se a coexpressão de lncRNAs e seus possíveis mRNAs alvos está associada ao eventual desenvolvimento da leishmaniose mucosa.

2 CAPÍTULO 1 - CO-EXPRESSION ANALYSIS OF LNCRNA AND MRNA SUGGESTS A ROLE FOR NCRNA-MEDIATED REGULATION OF HOST-PARASITE INTERACTIONS IN PRIMARY SKIN LESIONS OF PATIENTS WITH AMERICAN TEGUMENTARY LEISHMANIASIS

CO-EXPRESSION OF LNCRNA-MRNA IN LESIONS OF AMERICAN TEGUMENTARY LEISHMANIASIS

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2.1 Resumo

A infecção por *Leishmania (Viannia) braziliensis* é responsável pela leishmaniose mucosa (LM), forma mais grave da leishmaniose tegumentar Americana (LTA), que se desenvolve após a cicatrização de até 20% de lesões cutâneas localizadas, levando a lesões desfigurantes nas mucosas oral e nasal. Até o momento, os fatores envolvidos nessa progressão não são totalmente conhecidos, no entanto, evidências indicam que há uma mudança nos padrões globais de expressão gênica do hospedeiro em resposta à infecção por *Leishmania*, e que o parasito é capaz de modular a resposta imune do hospedeiro, o que pode contribuir para a progressão da doença. Por sua vez, o controle da expressão gênica é mediado por mecanismos epigenéticos, com destaque para os RNAs longos não-codificadores (lncRNAs). Assim, avaliamos se a coexpressão de lncRNAs e seus potenciais mRNAs alvos em lesões cutâneas primárias de pacientes com LTA poderia estar associada ao desenvolvimento de LM. Para isso, usamos um conjunto de dados de RNA-Seq público previamente disponível e identificamos 579 mRNAs e 46 lncRNAs expressos diferencialmente na lesão que posteriormente progrediu para mucocutânea. Também identificamos 1324 pares de lncRNA-mRNA correlacionados. A análise de coexpressão e o enriquecimento de vias revelaram que mRNAs potencialmente regulados por lncRNAs participam de vias do sistema imunológico com papéis na patogênese da doença. O mRNA *S100A8* é potencialmente regulado pelo lncRNA *SNHG29* e, junto com seu parceiro heterodimérico, forma um complexo que atua como mediador pró-inflamatório em células do sistema imune inato como neutrófilos, monócitos/macrófagos e queratinócitos. O ambiente pró-inflamatório gerado pode contribuir para o eventual desenvolvimento de lesões mucocutâneas mais graves. Esses achados ampliam o conhecimento da interação *Leishmania*-hospedeiro e os

possíveis papéis que os lncRNAs podem desempenhar na progressão da doença e como biomarcadores e alvos terapêuticos.

2.2 Abstract

Leishmania (Viannia) braziliensis infection is responsible for mucosal leishmaniasis (ML), the most severe form of American tegumentary leishmaniasis (ATL), which develops after healing of up to 20% of localized skin lesions, leading to disfiguring lesions in the oral and nasal mucosa. So far, the factors involved in this progression are not fully known, however, evidence indicates that there is a change in the global patterns of host gene expression in response to *Leishmania* infection, and that the parasite is able to modulate the immune response of the host, which may contribute to disease progression. In turn, the control of gene expression is mediated by epigenetic mechanisms, with emphasis on long non-coding RNAs (lncRNAs). Thus, we evaluated whether the co-expression of lncRNAs and their potential target mRNAs in primary cutaneous lesions of patients with ATL could be associated with the development of ML. For this, we used a previously available public RNA-Seq dataset and identified 579 mRNAs and 46 lncRNAs differentially expressed in the lesion that subsequently progressed to mucocutaneous. We also identified 1324 correlated lncRNA-mRNA pairs. Co-expression analysis and pathway enrichment revealed that mRNAs potentially regulated by lncRNAs participate in immune system pathways with roles in disease pathogenesis. The *S100A8* mRNA is potentially regulated by the lncRNA *SNHG29* and, together with its heterodimeric partner, forms a complex that acts as a pro-inflammatory mediator in cells of the innate immune system such as neutrophils, monocytes/macrophages and keratinocytes. The resulting pro-inflammatory environment generated may contribute to the eventual development of more severe mucocutaneous lesions. These findings expand the knowledge of the *Leishmania*-host interaction and the possible roles that lncRNAs may play in disease progression, and as biomarkers and therapeutic targets.

2.3 Author Summary

Leishmaniasis is a neglected tropical disease transmitted by the sand fly. At the site of the bite, individuals can develop a single lesion that, after healing, can progress to a serious lesion that affects the mucosa of the nose and mouth. Currently, the factors that contribute to this evolution are not fully known and there is still no way to predict the development of mucosal lesions. RNA molecules are synthesized from DNA and their expression can be altered by infection. We focus on the interaction between two classes of RNA, the first being the mRNAs that give rise to proteins and the second being the lncRNAs, long RNAs that are not translated into proteins, but have multiple regulatory function over gene expression. Our results suggest that altered expression of coding and non-coding RNAs in the primary lesion of future mucosal form of the disease may plays several roles in the host immune response that may contribute to the pathogenesis of the disease and to the development of mucocutaneous lesions.

2.4 Introduction

American tegumentary leishmaniasis (ATL) is a disease that causes clinical manifestations ranging from self-healing skin lesions to disfiguring mucosal lesions [1]. The main causative agent of the disease in South America is *Leishmania (Viannia) braziliensis*, responsible for the following forms of ATL: localized cutaneous leishmaniasis (LCL), mucosal leishmaniasis (ML) and disseminated leishmaniasis (DL) [2].

LCL is the most prevalent form, characterized by lesion at the sand fly bite site, commonly located in exposed areas of the body, such as face, arms and legs [3,4]. The primary skin lesion can heal spontaneously even without drug therapy, however, parasites or remnants can often be found at the post-healing site, which can contribute to resistance to reinfection or the development of more serious lesions [5,6]. In fact, up to 20% of LCL cases progress to ML [5]. Currently, there is no prophylactic vaccine against human cutaneous leishmaniasis, only vaccines used as immunotherapy in cases where there is no favorable response to conventional antimonial treatment [7].

ML has severe clinical manifestations, characterized by the progressive destruction of tissues of the oral and nasal mucosa, resulting in lesions which, in most cases, become disfiguring [4,5]. Mucosal involvement may occur in parallel with LCL lesions or develop months to years after healing of the primary skin lesion [5]. Most patients affected by mucosal leishmaniasis are resistant to antimony treatment, which causes many adverse reactions, with treatment failure and recurrence of lesions being common [4]. Studies relate the development of mucocutaneous lesions to factors such as size and number of skin lesions, species and virulence factors of the parasite, genetic factors and host immune response, in addition to nutritional factors of the

*Text according to the Guidelines for Authors of the Journal PLOS Neglected Tropical Diseases - Available in ANEXO A.

patient, age and sex [4–6]. However, these factors are not fully elucidated and there is still no way to predict the risk of developing the most severe mucosal lesion [6].

Evidences show that the *Leishmania* parasite may generate distinct immune responses in the host, which contribute to disease outcome, either the complete healing of the lesion or progressive tissue destruction [1,8]. In this pathogen-host interaction, there are changes in host gene expression pattern modulated by the pathogen [9]. In turn, control of gene expression can occur through epigenetic mechanisms mediated by long non-coding RNAs (lncRNAs) [10].

LncRNAs are non-protein-coding RNAs formed by more than 200 nucleotides that are capable of regulating gene expression at the transcriptional and post-transcriptional levels, through their interaction with DNA, RNA and proteins [11,12]. These non-coding transcripts have high cellular and temporal specificity, and can regulate expression of neighboring and/or distant genes, characterizing their actions in *cis* and *trans*, respectively [13,14]. LncRNAs have been associated with several biological and pathological processes, and studies show patterns of differential expression of these transcripts in response to infection by pathogens, acting as potent regulators of host immune response [15]. However, there is a paucity of studies that relate the expression of lncRNAs and *Leishmania* infection. In this context, we hypothesize that lncRNAs and their possible target genes may be associated with the eventual development of severe lesions in the mucosa, acting on key mechanisms of the immune response process.

2.5 Methods

2.5.1 RNA-Seq dataset

Public RNA-Seq data were obtained from the Gene Expression Omnibus (GEO) database (www.ncbi.nlm.nih.gov/geo/) under bioproject PRJNA148519, with accession number GSE33601. This dataset was elegantly generated by Maretti-Mira *et al*. [6] from cutaneous tissue fragments from 10 patients, obtained through biopsies of primary cutaneous lesions characteristic of tegumentary leishmaniasis. After diagnosis confirmation for infection by *Leishmania (Viannia) braziliensis*, all patients were treated with pentavalent antimony (Glucantime) and had complete healing of the primary skin lesions. Out of these 10 patients, 5 of them had no disease recurrence after complete healing (LCL group), while the other 5 developed mucosal lesions, at the nasopharynx, long after initial healing of the primary lesion (ML group). In LCL group, the age of patients ranged between 15-67 years and in ML group between 23-63 years. Average (± std) from the appearance of the primary lesion reported by the patients according to their recollections was 1.4±0.5 months in the LCL group and 2.3±1.3 months in the ML group. 5 patients in the LCL group and 3 in the ML group had only one primary skin lesion, while the other 2 patients in the ML group had more than one primary skin lesion. Authors used the following inclusion criteria: time of evolution of the lesion (1-4 months); good response for the treatment (completely re-epithelialization of the cutaneous lesion and no lesion reactivation) and final outcome of the disease, which should be no disease recurrence (LCL) or development of lesions at the nasopharynx mucosa (ML). Following quality analysis of the RNA-Seq reads (FastQC), 4 samples with Phred Score lower than 25 were excluded. Therefore, from a total of 10 samples, only 6 samples were used for our analysis, consisting of 3 samples from the LCL group and 3 samples from ML group.

2.5.2 Bioinformatic analysis of RNA-Seq

Download of reads, quality analysis, alignment, read count and differential expression were performed on the Galaxy platform (www.usegalaxy.org/). Single-end RNA-Seq read files from the ML and LCL groups were downloaded from the Sequence Read Archive (SRA) database at NCBI and converted to FASTQ format using Download and Extract Reads in the FASTA/Q. Quality of reads was evaluated with FastQC (Galaxy Version 2.10.8+galaxy0). Next, reads were aligned with the human genome assembly GRCh38.p13 provided by GENCODE, using HISAT2 tool (Galaxy Version 2.1.0+galaxy5), which results in a single BAM file based on the Burrows-Wheeler Transformation (BWT) and the Ferragina-Manzini (FM) index [16]. Counting aligned reads was performed using the HTSeq-count tool (Galaxy Version 0.9.1) [17] and annotation GENCODE v34 (Human) as reference. Quality control of all steps was performed using MultiQC (Galaxy Version 1.8+galaxy1).

2.5.3 Differential gene expression analysis

DESeq2 (Galaxy Version 2.11.40.6+galaxy1) was used to perform differential expression of transcripts between samples from the ML group and LCL group. Differential expression tests used were based on a negative binomial generalized linear model to estimate the average variance in the count data, followed by Wald test [18]. Differentially expressed (DE) transcripts was set to p-value<0.05 and log2(FC)≥1. Using the BioMart tool, available on the Ensembl platform (www.ensembl.org/biomart/martview/), we obtained the classification of DE transcripts according to their biotype. Transcripts of the “lncRNA” biotype were considered as lncRNAs, while those of the “protein_coding” biotype were considered as mRNAs. DE lncRNAs were clusterized using the heatmap3 package in R using method “complete linkage” and Euclidian distance as

parameters (https://www.rdocumentation.org/packages/heatmap3/versions/1.1.7/topics/heatmap3).

2.5.4 LncRNA-mRNA correlation analysis

To reveal co-expression between DE lncRNAs-mRNAs, Pearson's correlation coefficient was calculated based on the normalized expression value of all DE lncRNA and mRNA pairs. A lncRNA-mRNA significant interaction was set to Pearson's correlation coefficient of $|r| \geq 0.9$ and p-value<0.05. Interactions considered significant between lncRNAs and putative target mRNAs were then analyzed in the LncTar tool (http://www.cuilab.cn/lnctar) and were classified using the classifier module of the FEELnc tool (Flexible Extraction of Long non-coding RNAs). LncTar tool predicts the interaction between two RNA molecules by calculating the approximate normalized free energy (ndG) of binding. The lncRNA-mRNA pairs with a ndG≤ -0.10 were predicted to have binding potential. In the FEELnc tool, based on the genomic locus, lncRNA-mRNA interactions that had target mRNA within a 100kbps window upstream or downstream the lncRNA location were classified as *cis*-acting and those interactions that showed binding potential (ndG≤ -0.10) and are outside the established 100kbps window were classified as *trans*-acting.

2.5.5 Functional enrichment analysis

All *cis* and *trans* mRNAs targeted by lncRNAs that met the criteria for co-expression ($|r| \geq 0.9$; p-value<0.05) and binding potential (ndG≤ -0.10) were used for pathway analysis with the Kyoto Encyclopedia of Genes and Genomes (KEGG Pathways) using the g:GOSt (Function Profiling) tool within g:Profiler (https://biit.cs.ut.ee/gprofiler/gost). P-values were adjusted using the Benjamini-Hochberg (FDR) multiple testing correction method (FDR<0.05).

2.5.6 Network of lncRNA-mRNA co-expression

LncRNAs and their corresponding *cis* and *trans* target mRNAs were used to construct genes co-expression networks using Cytoscape software (Version 3.9.0). Also in Cytoscape, the Analyze Network tool was used to rank the top 10 lncRNAs according to the number of interactions with target mRNAs. Then, a co-expression network was constructed from the top 10 lncRNAs and their corresponding targets and the pathways in which they participate.

A schematic overview of the pipeline employed in the analysis is depicted in Fig 1.

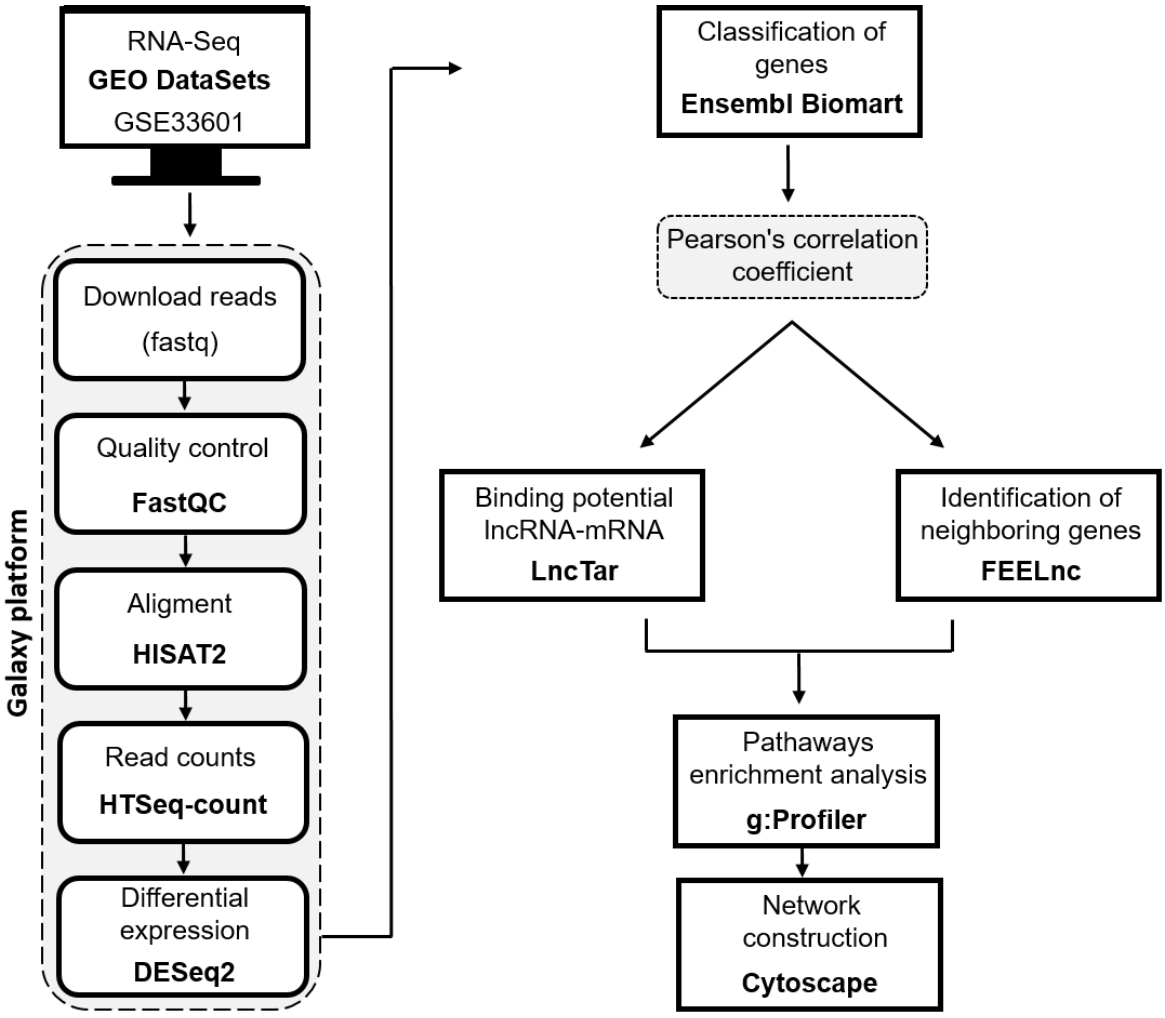

Fig 1. **Pipeline employed in the analysis of lncRNA-mRNA co-expression.**

This workflow describes all the steps used for bioinformatic analysis comprised of alignment, read count, differential expression, RNA classification, correlation, lncRNA binding prediction and pathway enrichment analysis of data.

2.6 Results

The RNA-Seq analysis revealed 702 differentially expressed transcripts with threshold of p-value<0.05 and log2(FC)≥1 in the contrast of ML and LCL groups. Of this total, we identified 579 transcripts (82.48%) annotated as protein coding and 46 (6.55%) as lncRNAs, according to gene biotype annotations available in Ensembl BioMart tool (S1A and S1B Table). Of these 46 DE lncRNAs, 25 showed increased expression in the ML group when compared to LCL group, and 21 lncRNAs were down regulated in the ML group. Pattern of expression of all DE lncRNAs can be observed in the heatmap shown in Fig 2.

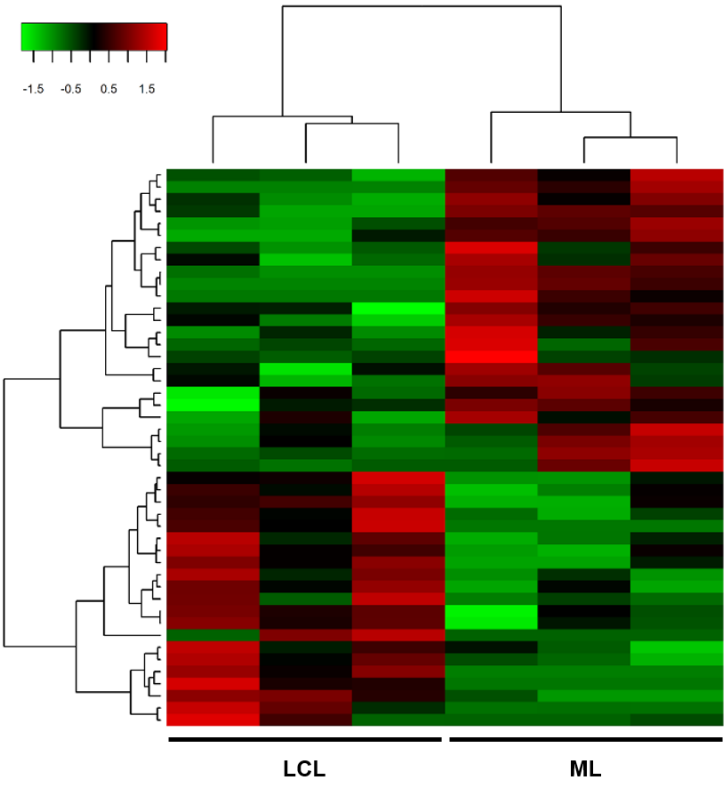

Fig 2. Heatmap of 46 differentially expressed lncRNAs in the contrast between ML and LCL groups.

The color scale shown at the top corresponds to the z-score and represents the expression of the lncRNAs hierarchically grouped. The red and green colors represent up- and down-regulated lncRNAs, respectively.

To investigate the potential regulation of mRNA expression by lncRNAs, a correlation matrix (Pearson's correlation $|r| \geq 0.9$ and p-value<0.05) identified 1324 interactions between DE lncRNA-mRNA. Of this total, 604 interactions showed binding potential according to normalized free energy deltaG analysis in the LncTar tool ($ndG \leq -0.10$) and the pairs were not within the 100kbps window set in FEELnc, suggesting a potential *trans* action (S2 Table). Only 1 lncRNA-mRNA interaction was found considering a 100 kbps window between transcripts, suggesting *cis* action potential (S3 Table).

Functional enrichment analysis was conducted to identify the potential biological functions of *cis* and *trans* target mRNAs that showed significant correlation with lncRNAs. Analysis showed enrichment of 71 KEGG pathways involving 111 mRNAs identified as targets, potentially regulated by 36 lncRNAs.

Next, we identified the top 10 lncRNAs, based on the highest number of interactions with target mRNAs that were enriched in KEGG pathways (Table 1). Co-expression networks were constructed to visualize the interactions between the top 10 lncRNAs and their target mRNAs, as well as to illustrate the KEGG pathways in which they participate (Fig 3; S4 Table).

Table 1. Top 10 lncRNAs according to the number of interactions with their target mRNAs that were enriched in KEGG pathways.

LncRNA name	Interactions
SNHG29	35

AC009961.3	23
AL355987.4	20
TSPOAP1-AS1	15
PDE2A-AS2	14
MEG3	12
AC007686.3	7
ZNF236-DT	7
GPRC5D-AS1	7
LINC01750	7

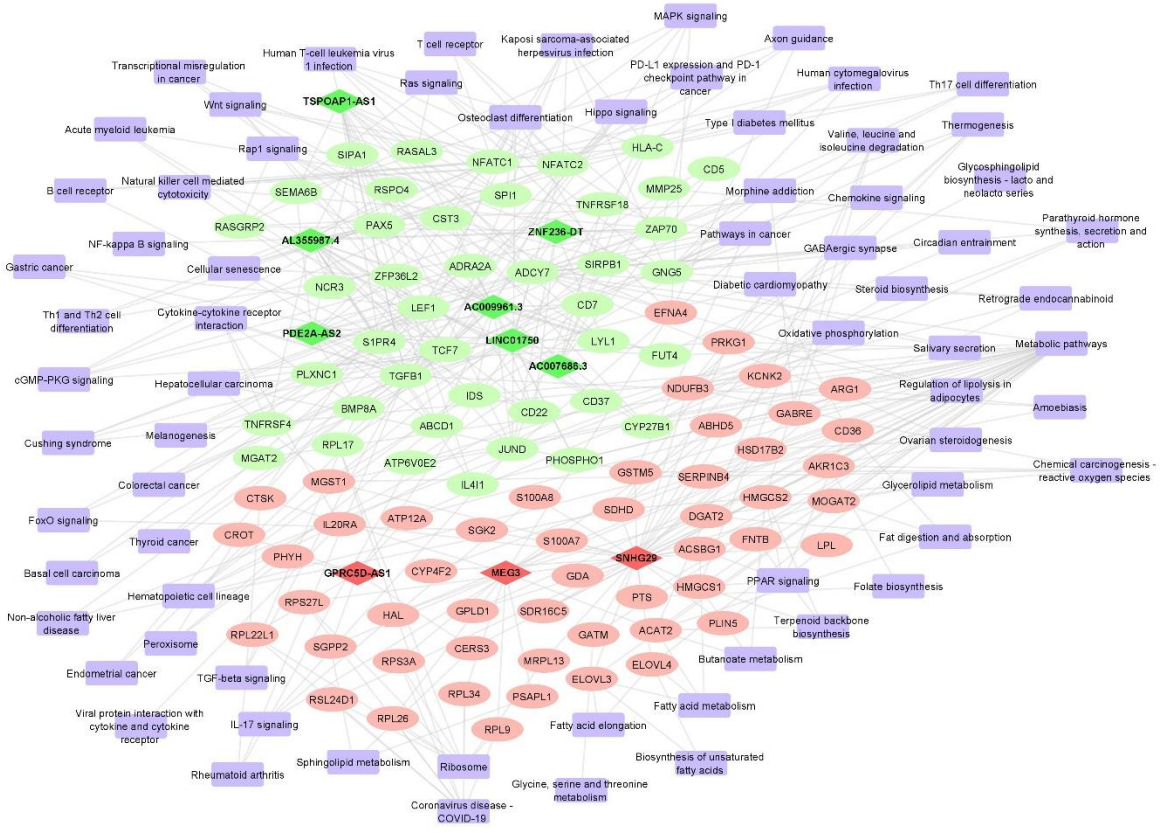

Fig 3. Network analysis of the top 10 lncRNAs.

Elliptical shaped objects represent mRNAs, diamonds represent lncRNAs (also highlighted in bold), and light blue rectangles represent enriched KEGG pathways. Red and green colors indicate the expression of lncRNAs and mRNAs corresponding to high and low expression, respectively.

2.7 Discussion

Development of severe and disfiguring mucosal lesions as a result of *Leishmania braziliensis* infection is associated with several factors related to the parasite-host interactions, which are not fully elucidated. Focusing on possible effects of the *Leishmania* parasite on the epigenetic control of host response, we used RNA-Seq data previously generated by Maretti-Mira *et al.* [6]. In their study, the authors elegantly planned a model in which LCL patients were followed after collection of lesion biopsies, enabling the comparison of primary lesions that were resolved with treatment (LCL only group) to those of patients that evolved to ML, despite the use of antimonial treatment. We employed this dataset to analyse the lncRNA-mRNA co-expression profiles in these primary skin lesions that characterize the beginning of the clinical forms ML and LCL, in addition to associating them with the eventual development of mucocutaneous lesions, as previous evidence demonstrates the crucial roles of these non-coding transcripts in the control of gene expression, including pathogen-host interaction. Despite the sample size being a limiting factor, we were able to demonstrate the differential lncRNA-mRNA co-expression profile, suggesting a role for ncRNAs in the control of host innate immune response that may contribute to disease progression to severe mucosal lesions.

Among the 1324 lncRNA-mRNA correlated pairs, we identified 604 with binding potential that points to target regulation. Of these, expression of the lncRNA *SNHG29* (Small Nucleolar RNA Host Gene 29) correlated in a *trans* action with the expression of the highest number of genes, 35 in total. Among these interactions, lncRNA SNHG29 is positively correlated with coding transcript *S100A8* (S100 Calcium Binding Protein A8), both being up-regulated in the ML group. In fact, a *trans* action between these transcripts is characterized by the chromosomal distance between the lncRNA

SNHG29, located on chromosome 17, and the mRNA *S100A8*, located on chromosome 1. Through their ability to link by sequence complementarity, lncRNAs regulate their target mRNA at the post-transcriptional level through mechanisms such as nascent mRNA transcript capping, splicing, editing, transport, translation, modification and stability [12]. *S100A8* encodes a protein member of the S100 family of calcium-binding proteins, S100A8 also known as MRP8 [19]. Although this protein exists as a homodimer, S100A8 and S100A9 (also known as MRP14) form a calcium-dependent heterodimeric complex known as calprotectin, which corresponds to the most functionally relevant form of these proteins [19,20]. Interestingly, the heterodimeric partner *S100A9* is also up-regulated in the ML group, albeit no correlation with DE lncRNAs was predicted. The S100A8/S100A9 complex is constitutively expressed in cells of the early myeloid lineage such as monocytes, neutrophils and dendritic cells and is also expressed in other cell types such as mature macrophages, vascular endothelial cells and keratinocytes after activation of these cell types. Their expression is induced following tissue injury, cellular stress, infection and inflammatory processes and they act as pro-inflammatory mediators [21–23].

This complex exerts intra and extracellular functions. Considering that infection-induced inflammation is one of the events responsible for the secretion and release of S100A8/S100A9, the extracellular roles of these proteins are essential for immune response. S100A8 and S100A9 act as alarmins or damage-associated molecular pattern molecules (DAMPs) which stimulate cellular responses by binding to cell surface receptors to activate several signaling pathways, including mitogen-activated protein kinase (MAPK) and factor nuclear kappa B (NF-κB), leading to the production of pro-inflammatory cytokines capable of recruiting neutrophils, monocytes and macrophages to the site of infection, activating the innate immune system. Among the

receptors that S100A8/S100A9 bind are toll-like receptor 4 (TLR4), receptor for advanced glycation end products (RAGE) and extracellular matrix metalloprotease inducer (EMMPRIN). Of note, TLR4 is the main receptor of the aforementioned innate immune cells [21,22,24–26]. S100A8/A9 complex induces the expression of cytokines and chemokines capable of stimulating keratinocytes and cells of the innate immune system, such as neutrophils and macrophages, to synthesize and secrete S100A8 and S100A9, suggesting a positive feedback mechanism between these proteins and pro-inflammatory agents [24].

Given the evident role of this complex in the induction of the inflammatory process, their use as diagnostic biomarkers and/or therapeutic targets in inflammatory diseases such as Alzheimer's disease, cancer and rheumatoid arthritis has been previously suggested [25]. Furthermore, *S100A8* and *S100A9* are overexpressed in psoriatic skin lesions, affecting inflammatory response [27]. We are going to focus below on the effects of this complex on the many cell types present on the skin lesions of leishmaniasis, as it is a likely target of the DE lncRNA with the highest number of targets.

Mucosal leishmaniasis lesions present a chronic and hyperactive immunological scenario, despite containing a low number of parasites. As discussed in the review by Volpedo *et al*. [5], peripheral blood mononuclear cells (PBMCs) from patients with ML show intense activity of Th1-type CD4+ T cells that produce interferon-gama (IFN-γ) and tumor necrosis factor alpha (TNF-α), pro-inflammatory cytokines, and cytotoxic CD8+ T cells that together can contribute to tissue destruction. Lower levels of monocytes that produce the anti-inflammatory cytokine interleukin 10 (IL-10) are observed when compared to patients who do not have mucosal lesions. In addition,

ML lesions show increased numbers of CD68+ macrophages and high levels of Th17 cells, neutrophils and consequent increase in the expression of the cytokine IL-17.

Goto *et al*. [28] showed that the S100A8/S100A9 complex is present in dermal and subcutaneous tissue of skin lesions of BALB/c mice infected with *Leishmania major* due to the accumulation of macrophages, while in healthy skin these proteins are not present. In addition, expression of F4/80+ cells, a marker of mature macrophages, was lower in the skin lesions of these mice, which suggests accumulation of macrophages of the inflammatory subtype, differing in phenotype from mature macrophages. In fact, macrophages expressing S100A9 have a lower ability to fight the *Leishmania* parasite than those that express F4/80 [28,29]. Furthermore, Steinbrink *et al*. [30] showed that MPR14+ mononuclear cells phagocytosed *Leishmania major* parasites after 4 hours of co-incubation. These cells were stimulated for 24h and 48h with IFN-γ, a pro-inflammatory cytokine capable of increasing the microbicide capacity of macrophages, and no decrease in parasite load was observed, while F4/80+ macrophages also infected with parasites responded to IFN-γ cytokine and had a reduced parasite load [30].

S100A8/A9 complex may be a marker for monocytes and monocyte-derived cells. In these cells, this protein complex corresponds to 1-5% of the cytosolic proteins [31]. Individuals infected by *Leishmania braziliensis* have a higher frequency of monocytes (intermediate and non-classical) in peripheral blood, and intermediate monocytes are the main source of the cytokine TNF, increased during cutaneous leishmaniasis, and also associated with tissue damage and development of lesions [32]. A study hypothesized that monocytes from patients with cutaneous leishmaniasis caused by *Leishmania braziliensis* could have an impaired ability to generate an oxidative burst to kill the parasite. Authors showed *in vitro* that monocytes from these

patients have a higher oxidative burst when compared to monocytes from healthy patients due to the increase in reactive oxygen species (ROS) and not nitric oxide (NO), but it is still insufficient to prevent the parasite from multiplying. Production of NO has a positive correlation with lesion size and not with parasite elimination [33]. In addition, proteins S100A8 and S100A9 are capable of inducing the expression of inducible NO synthase (*iNOS*) (increased in ML by ~1.7 fold-change, albeit not statistically significant) and the consequent increase in NO production in macrophages *in vitro* [34].

The increased expression of *S100A8* and *S100A9* that we have observed in the initial lesions of patients who progressed to ML, suggests an accumulation of monocytes/macrophages expressing high levels of these proteins, that may not respond adequately to cytokines such as IFN-γ. We suggest that this leads to a reduced ability to fight the *Leishmania* parasite, accompanied by NO expression, which has been associated with the size of skin lesions and tissue damage. In turn, the immunological response mounted may contributes to the development of more serious lesions in the mucosa of patients infected with *Leishmania braziliensis*.

Besides the aforementioned effects on monocytes/macrophages, S100A8/A9 complex is also expressed on keratinocytes. These cells, present in greater numbers in the epidermis, play crucial roles in *Leishmania* infection. They participate in the communication of other cells present in the skin, participating in the immune response, and are recruited to the lesion site mainly through the exchange of cytokines. This entire network of cells can influence the outcome of infection [35]. A combination of the pro-inflammatory cytokines TNF-α and IL-17A induces expression of high levels of *S100A8* in human keratinocytes [36]. In addition, S100A8 and S100A9 are up-regulated in skin inflammation and IL-17 is able to up-regulate the expression of these

proteins during the inflammatory response of keratinocytes in mice [19]. S100A8 and S100A9 induce expression of IL-6 and IL-8 cytokines and monocyte chemoattractant protein-1 (MCP-1) chemokine in human keratinocytes *in vitro*. These proteins were also able to activate the NF-κB pathway through the TLR4, protein kinase C-delta (PKCδ), extracellular signal-regulated kinase (ERK) and p38 MAPK signaling pathways [37]. From 3-6 hours after *Leishmania* infection, IL-6 secreted by keratinocytes acts on defense immunity related to Th1 lymphocytes and can lead to the differentiation of Th17 cells, which secrete IL-17. IL-8, also induced by the complex, acts as a strong chemoattractant for neutrophils [35]. Lastly, MCP-1 chemokine is responsible for recruiting monocytes to the site of active inflammation [38]. It is possible to observe a positive feedback mechanism, in which the expression of the S100A8/A9 complex in human keratinocytes induces the expression of cytokines that contribute to neutrophil recruitment and IL-17 production. Meanwhile, this cytokine induces the expression of S100A8 and S100A9 in keratinocytes, recruiting more neutrophils to the injury site. Some studies suggest that the S100A8/A9 complex, when released from leukocytes at the time of transmigration, that is, on the way from peripheral blood to tissue, may contribute to the recruitment of more leukocytes, as it facilitates leukocyte-endothelial cell interaction [23]. In agreement, the *S100A8* mRNA was enriched for the IL-17 signaling pathway in our study, which corroborates the role of this cytokine in the expression of the *S100A8* mRNA and in the regulation of a positive feedback mechanism, as suggested above.

After inoculation of the promastigote form of *Leishmania* by the sand fly into the skin of the host, neutrophils are the first cells to arrive at the site of tissue damage. In addition, a study indicated the presence of neutrophils in human mucosal lesions, concentrated in the epithelium and in the ulcerous edges of the lesions [39]. These

cells act on the front line of the innate immune response and play roles in the protection or progression of leishmaniasis [40]. A study showed that IL-17 was higher in cells, including mononuclear cells, from mucosal lesions of patients infected with *Leishmania braziliensis* when compared to normal mucosa. In addition, tissue-infiltrating IL-17+ cells co-expressed CCR6, a chemokine receptor that can be found on neutrophils and Th17 cells and is involved in their migration process. In agreement, they observed neutrophils in all mucosal lesions, indicating that IL-17 favors inflammatory responses in patients with ML by recruiting neutrophils [39]. Furthermore, the recruitment of neutrophils through IL-17 is related to the progression of cutaneous leishmaniasis [41]. Proteins S100A8 and S100A9 correspond to about 45% of the proteins in the neutrophil cytoplasm [20]. S100A8/A9 have recently been described in neutrophil extracellular traps (NETs) *in vitro* [42]. NETs are composed of histone-covered chromatin that, together with antimicrobial peptides, form web-like structures that are capable of trapping and killing pathogens. The process by which NETs are formed is called NETosis, a type of programmed cell death in which neutrophils eject their genetic material into the extracellular environment [43]. Simultaneously with NETosis, the release of the S100A8/A9 complex occurs after 1.5-2h of neutrophil activation, and neutrophils themselves are capable of being activated by S100A8/A9 in the presence of human serum [42].

Although we are unable to separate cell types within the lesion, overexpression of *S100A8* and *S100A9* mRNAS in the ML group suggests that the keratinocytes present in the epidermis are highly stimulated by the S100A8/A9 complex to secrete cytokines such as IL-17 that recruit large numbers of neutrophils to the lesion site. This whole process can generate a pro-inflammatory environment, with the accumulation of cells of the innate immune system that can contribute to the eventual development of

the mucocutaneous lesion. We observed that expression of *S100A8* is potentially upregulated by the lncRNA *SNHG29* (also known as *LRRC75A-AS1*) through *trans* regulatory mechanisms. Interaction between lncRNA *SNHG29* and its target mRNA *S100A8* occurs by sequence complementarity and this regulation can occur through interference with mechanisms such as: capping, splicing, editing, transport, translation, modification and stability of nascent mRNA transcription. To elucidate how this regulation actually occurs, additional studies are needed (Fig. 4). Knockout of this lncRNA and analysis based in its neighboring gene *LRRC75A* (p-value and fold change not significant in our study) in bovine mammary epithelial cells, was associated with reduced expression of inflammatory genes such as IL-1α, IL-1β, IL-6 and IL-8, which reinforces a potential regulatory role of this lncRNA on genes that mediate innate immune responses [44].

We conclude that primary cutaneous lesions caused by *Leishmania braziliensis* infection that later progress to mucosal lesions show higher expression of lncRNA *SNHG29*, which is predicted to be a regulator of *S100A8* mRNA that acts together with its heterodimeric partner *S100A9*. Proteins of the same name encoded by this genes, S100A8 and S100A9, respectively, act as pro-inflammatory mediators that initiates and amplifies inflammatory responses, and their communication with innate immune cells and cytokines can generate an environment conducive to tissue damage and possible development of severe mucosal lesions. Additional studies with a greater number of samples and validation of these results are interesting to confirm the biological function of coding and non-coding transcripts in the context of cutaneous leishmaniasis and a possible way to predict and prevent the clinical development of mucosal lesions.

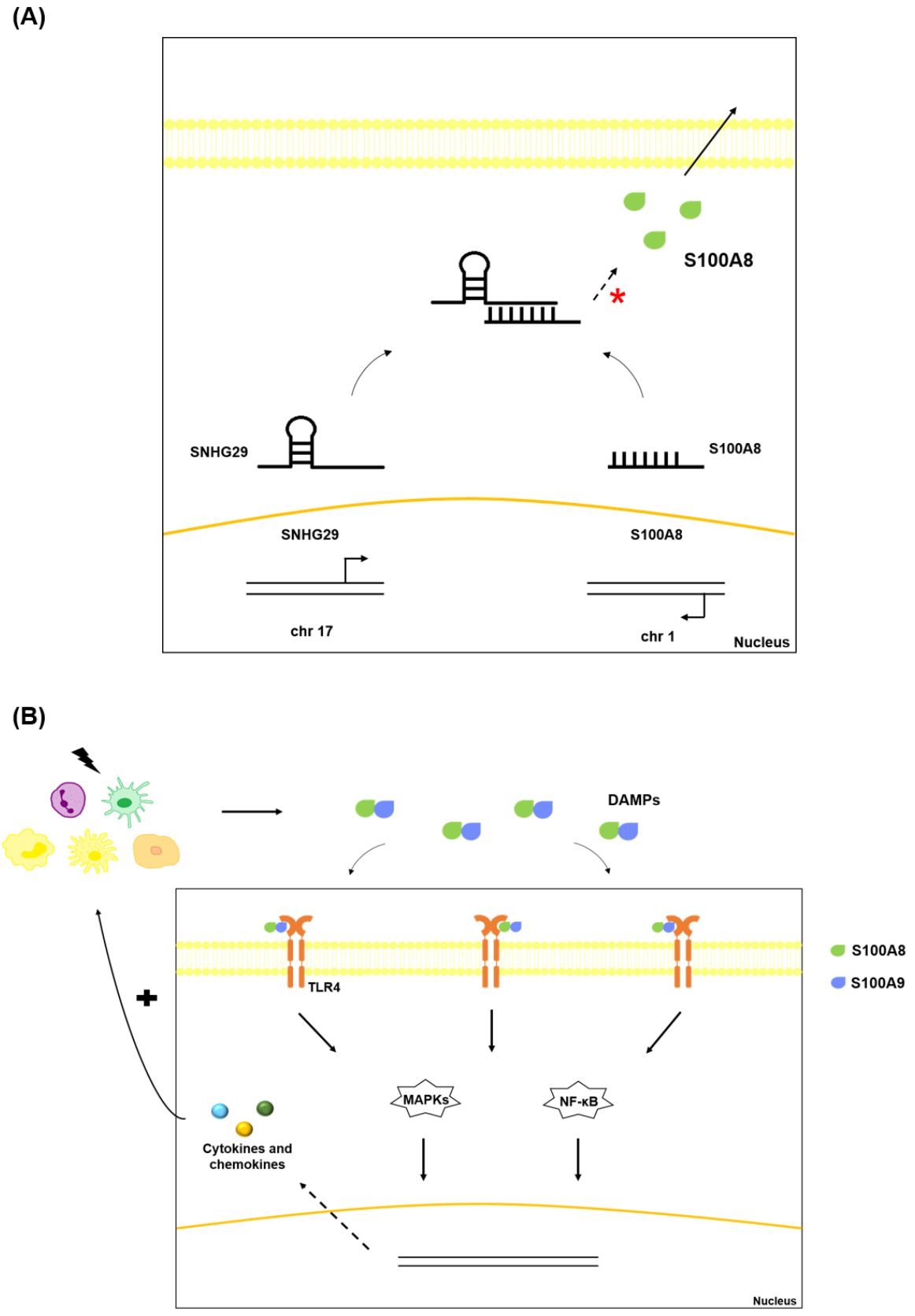

Fig 4. Interaction between lncRNA *SNHG29* and its putative target *S100A8*, and role of the S100A8/A9 complex.

(A) LncRNA *SNHG29* is predicted to be a regulator of mRNA *S100A8*. LncRNA *SNHG29*, transcribed on chromosome 17, has potential to bind by sequence complementarity with mRNA *S100A8*, transcribed on chromosome 1. S100A8 protein is commonly exported in order to exert extracellular functions. * represents regulatory mechanisms of lncRNA *SNHG29* on its target mRNA *S100A8.* (B) Cells of the innate immune system, such as neutrophils, dendritic cells, monocytes and macrophages, and keratinocyte epithelial cells, release S100A8 and its heterodimeric partner S100A9 when they undergo cellular stress and/or tissue damage. The S100A8/S100A9 complex acts like DAMPs and binds to cell surface receptors, such as TLR4, signaling through MAPKs and NF-KB, to promote expression of pro-inflammatory cytokines and chemokines. These cytokines and chemokines are capable of stimulating the same cells to release the S100A8/S100A9 complex, in a positive feedback mechanism.

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2.9 Supporting Information

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

S1B Table. Differentially expressed lncRNAs in the contrast ML and LCL.

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

S3 Table. LncRNA-mRNA *cis* interactions according to FEELnc.

S4 Table. KEGG pathways for the top 10 differentially expressed lncRNAs based

on interaction numbers.

APÊNDICE A - Referências da Introdução Geral

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APÊNDICE B - Material Suplementar Referente ao Capítulo 1

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

(Continua)

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000005175.10	RPAP3	-1.386278511	DOWN	0.013731018
ENSG00000005469.12	CROT	1.519181504	UP	0.002892451
ENSG00000007129.18	CEACAM21	-1.04119027	DOWN	0.037393175
ENSG00000008394.13	MGST1	2.334584717	UP	3.02358E-06
ENSG00000008516.17	MMP25	-1.574149626	DOWN	0.000533863
ENSG00000010404.18	IDS	-1.295905967	DOWN	0.010636179
ENSG00000011198.10	ABHD5	1.060937189	UP	0.019560619
ENSG00000011201.12	ANOS1	-1.125130886	DOWN	0.03516971
ENSG00000011347.10	SYT7	1.100854386	UP	0.029115534
ENSG00000011638.10	TMEM159	1.039620597	UP	0.011365496
ENSG00000012124.17	CD22	-1.246733221	DOWN	0.005433029
ENSG00000012171.20	SEMA3B	1.355059009	UP	0.008901437
ENSG00000012779.11	ALOX5	-1.178781005	DOWN	0.008094884
ENSG00000016402.13	IL20RA	1.843096229	UP	0.000691049
ENSG00000018236.15	CNTN1	2.034866316	UP	0.000134893
ENSG00000020633.18	RUNX3	-1.028691883	DOWN	0.020711897
ENSG00000021300.14	PLEKHB1	-1.301465918	DOWN	0.007742981
ENSG00000035115.22	SH3YL1	1.459903555	UP	0.005194624
ENSG00000043039.7	BARX2	1.325752462	UP	0.007948058
ENSG00000043143.20	JADE2	-1.018711508	DOWN	0.010833558
ENSG00000052344.16	PRSS8	1.004735891	UP	0.032974327
ENSG00000052802.13	MSMO1	1.941882755	UP	5.21173E-05
ENSG00000055957.11	ITIH1	-1.295132907	DOWN	0.014888837
ENSG00000057149.16	SERPINB3	1.111408528	UP	0.010206515
ENSG00000062282.15	DGAT2	1.236946464	UP	0.003732275
ENSG00000064270.12	ATP2C2	1.122849434	UP	0.022301841
ENSG00000064655.19	EYA2	1.469797061	UP	0.004574631
ENSG00000064886.14	CHI3L2	1.223711991	UP	0.016514305
ENSG00000066279.18	ASPM	-1.155666483	DOWN	0.039306961
ENSG00000066336.12	SPI1	-1.062273932	DOWN	0.010441036
ENSG00000068831.19	RASGRP2	-1.293102939	DOWN	0.003773287
ENSG00000069812.11	HES2	1.386250015	UP	0.006594095
ENSG00000070087.14	PFN2	1.466089433	UP	0.00311608
ENSG00000070729.14	CNGB1	1.146501354	UP	0.037241028
ENSG00000071246.11	VASH1	-1.022372262	DOWN	0.010062855
ENSG00000072422.17	RHOBTB1	1.062707606	UP	0.049828135
ENSG00000072832.15	CRMP1	1.147831675	UP	0.023333697
ENSG00000073737.16	DHRS9	1.468797337	UP	0.002596112
ENSG00000073803.14	MAP3K13	1.026860754	UP	0.032597129
ENSG00000074660.16	SCARF1	-1.048906696	DOWN	0.019058431

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

(Continuação)

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000075340.23	ADD2	-1.186717139	DOWN	0.035585637
ENSG00000075673.11	ATP12A	2.972405728	UP	2.04355E-09
ENSG00000078114.18	NEBL	1.212944748	UP	0.012681368
ENSG00000080603.17	SRCAP	-1.0055329	DOWN	0.032127426
ENSG00000081059.20	TCF7	-1.861829509	DOWN	6.24243E-06
ENSG00000082482.13	KCNK2	1.302163974	UP	0.021457258
ENSG00000082684.16	SEMA5B	1.314096055	UP	0.01397623
ENSG00000084110.11	HAL	1.158817992	UP	0.013596621
ENSG00000085563.15	ABCB1	-1.190177641	DOWN	0.02907762
ENSG00000085741.13	WNT11	1.209715208	UP	0.028870723
ENSG00000086696.11	HSD17B2	2.143000181	UP	0.000165778
ENSG00000087448.11	KLHL42	-1.005711154	DOWN	0.047737678
ENSG00000088386.17	SLC15A1	1.657939487	UP	0.001154242
ENSG00000089351.14	GRAMD1A	-1.116336302	DOWN	0.004368605
ENSG00000089639.11	GMIP	-1.138742656	DOWN	0.004254445
ENSG00000089692.9	LAG3	-1.218784825	DOWN	0.007519008
ENSG00000089820.16	ARHGAP4	-1.030914093	DOWN	0.010556905
ENSG00000089847.12	ANKRD24	-1.11194655	DOWN	0.0435304
ENSG00000092445.12	TYRO3	1.012039598	UP	0.036018937
ENSG00000092607.15	TBX15	1.012717508	UP	0.038538922
ENSG00000092621.12	PHGDH	1.116901047	UP	0.009558691
ENSG00000093134.15	VNN3	1.114358794	UP	0.036284155
ENSG00000094963.14	FMO2	1.225470801	UP	0.029293254
ENSG00000095713.14	CRTAC1	-1.186081213	DOWN	0.035359169
ENSG00000095970.17	TREM2	1.502752998	UP	0.00236415
ENSG00000096092.6	TMEM14A	1.341876566	UP	0.01772715
ENSG00000099260.11	PALMD	1.002373976	UP	0.039044623
ENSG00000099953.10	MMP11	1.472548079	UP	0.008955482
ENSG00000100003.18	SEC14L2	1.348232635	UP	0.00253665
ENSG00000100092.23	SH3BP1	-1.299218467	DOWN	0.001959276
ENSG00000100170.10	SLC5A1	1.201847511	UP	0.010284023
ENSG00000100196.11	KDELR3	1.036456687	UP	0.029827388
ENSG00000100271.17	TTLL1	1.076866503	UP	0.022496427
ENSG00000100314.4	CABP7	1.145326428	UP	0.041952741
ENSG00000100373.10	UPK3A	-1.512746637	DOWN	0.007509582
ENSG00000100385.14	IL2RB	-1.011781526	DOWN	0.015782449
ENSG00000100479.13	POLE2	1.346421565	UP	0.01675282
ENSG00000100599.16	RIN3	-1.007358317	DOWN	0.011882896
ENSG00000101049.17	SGK2	1.252107527	UP	0.021471463
ENSG00000101084.18	RAB5IF	-1.044077836	DOWN	0.029847117

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

(Continuação)

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000101096.20	NFATC2	-1.039007878	DOWN	0.02352302
ENSG00000101198.15	NKAIN4	1.202518763	UP	0.021913409
ENSG00000101282.9	RSPO4	-1.047375708	DOWN	0.037475845
ENSG00000101307.16	SIRPB1	-1.14716928	DOWN	0.014967861
ENSG00000101439.9	CST3	-1.15812479	DOWN	0.004285825
ENSG00000101986.12	ABCD1	-1.098425944	DOWN	0.00624698
ENSG00000102109.9	PCSK1N	-1.633372885	DOWN	0.002536829
ENSG00000102287.19	GABRE	1.139796208	UP	0.041529917
ENSG00000102743.15	SLC25A15	1.222202528	UP	0.010312357
ENSG00000103034.14	NDRG4	1.743335527	UP	0.001091028
ENSG00000103089.9	FA2H	1.507846456	UP	0.006155793
ENSG00000103546.18	SLC6A2	1.241367536	UP	0.02914005
ENSG00000103740.10	ACSBG1	1.892825128	UP	0.000736967
ENSG00000103888.17	CEMIP	-1.253825231	DOWN	0.011405961
ENSG00000103942.13	HOMER2	1.214509886	UP	0.003483552
ENSG00000104894.12	CD37	-1.041572531	DOWN	0.013627239
ENSG00000104903.5	LYL1	-1.128978478	DOWN	0.014199631
ENSG00000104921.15	FCER2	-1.218808803	DOWN	0.031726468
ENSG00000104951.16	IL4I1	-1.248136882	DOWN	0.00390268
ENSG00000104974.12	LILRA1	-1.142823859	DOWN	0.018287962
ENSG00000105088.8	OLFM2	1.309935914	UP	0.004807935
ENSG00000105122.13	RASAL3	-1.09306849	DOWN	0.012761633
ENSG00000105251.11	SHD	-1.143253359	DOWN	0.042557574
ENSG00000105329.10	TGFB1	-1.231621473	DOWN	0.003219222
ENSG00000105352.10	CEACAM4	-1.137237244	DOWN	0.019051688
ENSG00000105464.3	GRIN2D	-1.415244064	DOWN	0.005119525
ENSG00000105516.11	DBP	-1.411383312	DOWN	0.002034866
ENSG00000105852.11	PON3	1.994351806	UP	0.000395251
ENSG00000105880.7	DLX5	1.135590186	UP	0.028812877
ENSG00000105929.16	ATP6V0A4	1.189308114	UP	0.036055843
ENSG00000105963.15	ADAP1	-1.095731638	DOWN	0.019068454
ENSG00000106483.12	SFRP4	-2.444205364	DOWN	1.15947E-05
ENSG00000107165.13	TYRP1	-1.201907572	DOWN	0.016853554
ENSG00000107537.14	PHYH	1.084976435	UP	0.019796019
ENSG00000107742.13	SPOCK2	-1.24266288	DOWN	0.002685573
ENSG00000108244.17	KRT23	1.126741096	UP	0.020601089
ENSG00000108309.14	RUNDC3A	1.047864208	UP	0.025969337
ENSG00000108506.12	INTS2	-1.315193004	DOWN	0.018573062
ENSG00000108666.10	C17orf75	1.556819666	UP	0.004911413
ENSG00000109182.12	CWH43	1.278323812	UP	0.003616507

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

(Continuação)

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000109472.14	CPE	1.185127469	UP	0.013358459
ENSG00000109475.16	RPL34	1.088711263	UP	0.025887874
ENSG00000109610.6	SOD3	-1.323421272	DOWN	0.001025051
ENSG00000110448.11	CD5	-1.055145391	DOWN	0.01312517
ENSG00000110675.13	ELMOD1	1.151584648	UP	0.04099297
ENSG00000111012.10	CYP27B1	-1.159629392	DOWN	0.01711493
ENSG00000111254.8	AKAP3	-1.078044785	DOWN	0.046819536
ENSG00000111261.14	MANSC1	1.241799789	UP	0.010153348
ENSG00000111907.21	TPD52L1	1.606107581	UP	0.000718855
ENSG00000112195.9	TREML2	-1.124183294	DOWN	0.043310594
ENSG00000112293.15	GPLD1	1.258405815	UP	0.023532483
ENSG00000112787.13	FBRSL1	-1.223821601	DOWN	0.0037376
ENSG00000112972.15	HMGCS1	1.66618737	UP	0.000325114
ENSG00000114115.10	RBP1	1.419094016	UP	0.005945647
ENSG00000114771.14	AADAC	1.137537249	UP	0.034880281
ENSG00000114812.13	VIPR1	1.435619145	UP	0.003176788
ENSG00000115085.13	ZAP70	-1.149016695	DOWN	0.007088044
ENSG00000115112.8	TFCP2L1	1.335699443	UP	0.00721024
ENSG00000115129.14	TP53I3	1.026439769	UP	0.016311311
ENSG00000115540.15	MOB4	1.091431483	UP	0.048079621
ENSG00000115687.14	PASK	-1.092245547	DOWN	0.013343157
ENSG00000116133.13	DHCR24	1.037297273	UP	0.005642744
ENSG00000116690.13	PRG4	-1.099611334	DOWN	0.046142886
ENSG00000116717.13	GADD45A	1.042211871	UP	0.012809272
ENSG00000116774.12	OLFML3	1.050984609	UP	0.023351254
ENSG00000116922.14	C1orf109	1.411595203	UP	0.008973782
ENSG00000117281.16	CD160	-2.090889704	DOWN	0.000219526
ENSG00000117475.14	BLZF1	-1.168128131	DOWN	0.035077917
ENSG00000118096.8	IFT46	1.114400655	UP	0.01915563
ENSG00000118402.6	ELOVL4	1.15596456	UP	0.017481089
ENSG00000118520.15	ARG1	1.962975765	UP	0.000299432
ENSG00000118785.14	SPP1	2.844126094	UP	5.83204E-08
ENSG00000119013.9	NDUFB3	1.246711562	UP	0.023684676
ENSG00000119125.17	GDA	1.107312355	UP	0.045210445
ENSG00000119411.11	BSPRY	1.054960255	UP	0.008117123
ENSG00000119915.5	ELOVL3	2.604797757	UP	2.09202E-06
ENSG00000120437.9	ACAT2	1.269387919	UP	0.005488471
ENSG00000121207.12	LRAT	1.340514831	UP	0.013771674
ENSG00000121281.13	ADCY7	-1.047180387	DOWN	0.029971742
ENSG00000121486.12	TRMT1L	-1.034783084	DOWN	0.046628253

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

(Continuação)

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000121552.4	CSTA	1.678790096	UP	0.000113616
ENSG00000121742.19	GJB6	1.077316178	UP	0.023024171
ENSG00000121769.8	FABP3	1.332692068	UP	0.005291094
ENSG00000123352.18	SPATS2	1.03573962	UP	0.014531978
ENSG00000123500.10	COL10A1	1.766662656	UP	0.001647229
ENSG00000123892.12	RAB38	1.075576014	UP	0.016879765
ENSG00000124102.5	PI3	1.202721428	UP	0.034033489
ENSG00000124107.5	SLPI	1.259845426	UP	0.01548262
ENSG00000124134.9	KCNS1	1.822840622	UP	0.001100222
ENSG00000124143.10	ARHGAP40	1.482390069	UP	0.008575565
ENSG00000124191.18	TOX2	-1.152137558	DOWN	0.007530112
ENSG00000124203.6	ZNF831	-1.118236158	DOWN	0.023127699
ENSG00000124374.9	PAIP2B	1.372572448	UP	0.011125068
ENSG00000124496.12	TRERF1	-1.024489957	DOWN	0.023765428
ENSG00000125089.17	SH3TC1	-1.011487552	DOWN	0.020975574
ENSG00000125144.14	MT1G	-1.48471291	DOWN	0.005857253
ENSG00000125375.16	DMAC2L	1.322862914	UP	0.0096721
ENSG00000125398.8	SOX9	1.418878051	UP	0.004481046
ENSG00000125740.14	FOSB	-1.095713372	DOWN	0.017601982
ENSG00000125869.10	LAMP5	1.29031706	UP	0.015752113
ENSG00000125910.6	S1PR4	-1.163812122	DOWN	0.006628598
ENSG00000126264.10	HCST	-1.064871649	DOWN	0.01928309
ENSG00000126353.3	CCR7	-1.484771416	DOWN	0.00030142
ENSG00000126368.6	NR1D1	-1.663396927	DOWN	0.000342535
ENSG00000126878.13	AIF1L	1.269624251	UP	0.004113548
ENSG00000127124.16	HIVEP3	-1.023233813	DOWN	0.013171242
ENSG00000127249.15	ATP13A4	1.320138662	UP	0.020221323
ENSG00000127528.6	KLF2	-1.589420571	DOWN	0.00070169
ENSG00000127561.15	SYNGR3	-1.141477161	DOWN	0.028629891
ENSG00000127954.12	STEAP4	1.058615308	UP	0.033642897
ENSG00000128011.4	LRFN1	-1.295658347	DOWN	0.010572154
ENSG00000128482.16	RNF112	1.310642255	UP	0.02070858
ENSG00000128512.23	DOCK4	-1.114092965	DOWN	0.014313737
ENSG00000129151.9	BBOX1	1.309326091	UP	0.010452739
ENSG00000130203.10	APOE	-1.06304709	DOWN	0.032610849
ENSG00000130479.11	MAP1S	-1.264099293	DOWN	0.003574715
ENSG00000130511.16	SSBP4	-1.055117503	DOWN	0.009499353
ENSG00000130522.6	JUND	-1.163538018	DOWN	0.007255915
ENSG00000130748.7	TMEM160	-1.125241199	DOWN	0.010759017
ENSG00000131097.7	HIGD1B	1.558592935	UP	0.005016677

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

(Continuação)

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000131174.7	COX7B	1.177010037	UP	0.020716001
ENSG00000131188.12	PRR7	-1.444970127	DOWN	0.002806447
ENSG00000131196.17	NFATC1	-1.017580988	DOWN	0.021103451
ENSG00000131503.21	ANKHD1	-1.223676982	DOWN	0.030427644
ENSG00000131686.15	CA6	2.156354427	UP	0.000141138
ENSG00000131737.5	KRT34	2.913324188	UP	9.35853E-08
ENSG00000131969.15	ABHD12B	1.449704107	UP	0.008239287
ENSG00000133246.12	PRAM1	-1.219707509	DOWN	0.014996454
ENSG00000133710.16	SPINK5	1.273220145	UP	0.003867741
ENSG00000134184.13	GSTM1	1.972689664	UP	0.00052251
ENSG00000134201.12	GSTM5	1.526333691	UP	0.003847631
ENSG00000134202.11	GSTM3	1.395195803	UP	0.007189529
ENSG00000134240.12	HMGCS2	1.136495037	UP	0.03461277
ENSG00000134438.10	RAX	-1.772656976	DOWN	0.00045225
ENSG00000134490.14	TMEM241	1.122601816	UP	0.020903524
ENSG00000135063.19	FAM189A2	1.409424708	UP	0.012548026
ENSG00000135069.14	PSAT1	1.137658173	UP	0.011273543
ENSG00000135119.14	RNFT2	-1.145209289	DOWN	0.04187969
ENSG00000135218.19	CD36	1.818639496	UP	0.000657676
ENSG00000135245.10	HILPDA	1.51182626	UP	0.001402596
ENSG00000136002.19	ARHGEF4	1.069575316	UP	0.018766628
ENSG00000136040.9	PLXNC1	-1.088911787	DOWN	0.021482592
ENSG00000136044.12	APPL2	1.197742059	UP	0.006505413
ENSG00000136155.17	SCEL	1.114772116	UP	0.040258053
ENSG00000136286.16	MYO1G	-1.108444728	DOWN	0.006578654
ENSG00000136573.14	BLK	-1.278640567	DOWN	0.010118734
ENSG00000136695.15	IL36RN	1.313240813	UP	0.004487683
ENSG00000136783.10	NIPSNAP3A	1.227889879	UP	0.025193236
ENSG00000136828.19	RALGPS1	1.076570743	UP	0.039239669
ENSG00000136943.11	CTSV	1.223217447	UP	0.022034881
ENSG00000137571.11	SLCO5A1	-1.14039607	DOWN	0.044796916
ENSG00000137573.14	SULF1	-1.09642772	DOWN	0.015686739
ENSG00000137747.16	TMPRSS13	1.288630164	UP	0.002773382
ENSG00000137876.10	RSL24D1	1.061658498	UP	0.045809978
ENSG00000137878.17	GCOM1	1.113725022	UP	0.034489247
ENSG00000137880.6	GCHFR	-1.529415777	DOWN	0.004676095
ENSG00000137976.7	DNASE2B	1.917112747	UP	0.000656955
ENSG00000138111.14	MFSD13A	-1.146270387	DOWN	0.010334249
ENSG00000138135.7	CH25H	1.055131377	UP	0.027954855
ENSG00000138795.10	LEF1	-1.070459023	DOWN	0.022183578

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

(Continuação)

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000138821.13	SLC39A8	-1.200956398	DOWN	0.01038087
ENSG00000139433.10	GLTP	1.376023616	UP	0.000204197
ENSG00000139725.8	RHOF	-1.24910448	DOWN	0.007856317
ENSG00000140090.17	SLC24A4	-1.346756513	DOWN	0.016602588
ENSG00000140511.12	HAPLN3	-1.059411888	DOWN	0.006377677
ENSG00000141404.16	GNAL	1.112224816	UP	0.034617877
ENSG00000141441.16	GAREM1	1.021703361	UP	0.044778151
ENSG00000141664.10	ZCCHC2	-1.101958483	DOWN	0.016505669
ENSG00000141933.9	TPGS1	-1.050729488	DOWN	0.027466724
ENSG00000142185.16	TRPM2	-1.111683771	DOWN	0.011129177
ENSG00000143185.4	XCL2	-1.076657531	DOWN	0.047485247
ENSG00000143320.9	CRABP2	1.706842142	UP	0.000105184
ENSG00000143387.13	CTSK	1.498734137	UP	0.001575662
ENSG00000143502.15	SUSD4	1.271345392	UP	0.023140451
ENSG00000143520.6	FLG2	1.320452012	UP	0.006249654
ENSG00000143546.10	S100A8	1.47042375	UP	0.001206863
ENSG00000143556.9	S100A7	1.697877989	UP	5.79299E-05
ENSG00000143590.14	EFNA3	1.076616199	UP	0.013574533
ENSG00000143742.13	SRP9	1.098450135	UP	0.035843349
ENSG00000143771.12	CNIH4	1.054406709	UP	0.024289336
ENSG00000144452.15	ABCA12	1.165556058	UP	0.008925724
ENSG00000144730.18	IL17RD	1.265413695	UP	0.025786197
ENSG00000145107.16	TM4SF19	1.393182321	UP	0.014347566
ENSG00000145425.10	RPS3A	1.154791686	UP	0.016638821
ENSG00000145781.9	COMMD10	1.177392952	UP	0.033362632
ENSG00000145879.11	SPINK7	2.029178541	UP	0.0003157
ENSG00000146013.11	GFRA3	1.579569033	UP	0.00508484
ENSG00000147604.14	RPL7	1.095190018	UP	0.035560667
ENSG00000147883.12	CDKN2B	1.399025898	UP	0.002776642
ENSG00000148204.12	CRB2	-1.270599832	DOWN	0.021404973
ENSG00000148219.16	ASTN2	1.134718465	UP	0.036417384
ENSG00000148346.12	LCN2	1.23665822	UP	0.028254792
ENSG00000148734.8	NPFFR1	-1.658797155	DOWN	0.001231117
ENSG00000149451.18	ADAM33	1.125076801	UP	0.024209131
ENSG00000149573.9	MPZL2	1.035237531	UP	0.011747286
ENSG00000150594.7	ADRA2A	-1.470331541	DOWN	0.001582678
ENSG00000150787.8	PTS	1.174523301	UP	0.022498778
ENSG00000151651.16	ADAM8	-1.206026954	DOWN	0.009968522
ENSG00000151715.8	TMEM45B	1.021961197	UP	0.034922208
ENSG00000151729.11	SLC25A4	1.188062969	UP	0.006984356

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

(Continuação)

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000151835.16	SACS	-1.102674728	DOWN	0.041112151
ENSG00000151892.14	GFRA1	1.291196667	UP	0.009325255
ENSG00000152128.13	TMEM163	-1.463168676	DOWN	0.009694249
ENSG00000152518.8	ZFP36L2	-1.169084765	DOWN	0.012868082
ENSG00000152661.9	GJA1	1.162952442	UP	0.004348653
ENSG00000152784.16	PRDM8	-1.473843304	DOWN	0.00368185
ENSG00000153294.12	ADGRF4	1.006317105	UP	0.047909698
ENSG00000153898.13	MCOLN2	-1.201555104	DOWN	0.03125217
ENSG00000154227.13	CERS3	1.210862493	UP	0.005130204
ENSG00000154639.19	CXADR	1.29351373	UP	0.020426771
ENSG00000154856.13	APCDD1	1.142649959	UP	0.008611916
ENSG00000154917.11	RAB6B	1.145266652	UP	0.033999179
ENSG00000155906.19	RMND1	1.104119594	UP	0.041023654
ENSG00000156467.10	UQCRB	1.004233037	UP	0.046422559
ENSG00000158023.10	WDR66	1.193672729	UP	0.027577723
ENSG00000158106.14	RHPN1	-1.150961407	DOWN	0.020208879
ENSG00000158220.14	ESYT3	1.27039674	UP	0.011100226
ENSG00000158315.11	RHBDL2	1.064312674	UP	0.049383186
ENSG00000158717.11	RNF166	-1.184761074	DOWN	0.008180451
ENSG00000158806.14	NPM2	-1.373718257	DOWN	0.010644067
ENSG00000158825.6	CDA	1.264543133	UP	0.012974767
ENSG00000159212.12	CLIC6	-1.057166587	DOWN	0.015583311
ENSG00000159337.7	PLA2G4D	1.016080052	UP	0.049753641
ENSG00000159516.9	SPRR2G	1.364678474	UP	0.005162351
ENSG00000159753.14	CARMIL2	-1.172333131	DOWN	0.006276092
ENSG00000159784.17	FAM131B	-1.145502165	DOWN	0.031522641
ENSG00000160062.15	ZBTB8A	1.172015654	UP	0.039068415
ENSG00000160326.14	SLC2A6	-1.165047892	DOWN	0.006718344
ENSG00000160588.10	MPZL3	1.054329599	UP	0.041716136
ENSG00000160862.13	AZGP1	1.78725829	UP	4.86521E-05
ENSG00000161265.15	U2AF1L4	-1.022686143	DOWN	0.029561919
ENSG00000161798.7	AQP5	1.14492903	UP	0.042221279
ENSG00000161847.14	RAVER1	-1.23498119	DOWN	0.008779708
ENSG00000161970.15	RPL26	1.423482159	UP	0.002773095
ENSG00000162040.7	HS3ST6	1.059458551	UP	0.029485653
ENSG00000162444.12	RBP7	1.354577685	UP	0.01535076
ENSG00000162631.18	NTNG1	1.131770097	UP	0.036585631
ENSG00000162894.12	FCMR	-1.234588084	DOWN	0.002641062
ENSG00000163082.10	SGPP2	1.046126711	UP	0.007379814
ENSG00000163202.5	LCE3D	1.645091883	UP	0.001234638

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

(Continuação)

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000163216.7	SPRR2D	1.332497482	UP	0.009914863
ENSG00000163220.11	S100A9	1.056933551	UP	0.007503227
ENSG00000163251.4	FZD5	-1.138828345	DOWN	0.01525052
ENSG00000163331.12	DAPL1	1.759195596	UP	0.00199186
ENSG00000163584.18	RPL22L1	1.159805958	UP	0.020085056
ENSG00000163682.16	RPL9	1.075992809	UP	0.014282302
ENSG00000163684.11	RPP14	1.173107546	UP	0.026878452
ENSG00000163879.11	DNALI1	1.225613586	UP	0.031250386
ENSG00000163898.10	LIPH	1.175644808	UP	0.038683575
ENSG00000163993.7	S100P	2.202117671	UP	1.18251E-05
ENSG00000164124.11	TMEM144	-1.244244684	DOWN	0.028085619
ENSG00000164220.7	F2RL2	1.021719973	UP	0.046030812
ENSG00000164687.11	FABP5	1.112624876	UP	0.004975931
ENSG00000164919.11	COX6C	1.131268165	UP	0.017928313
ENSG00000164929.17	BAALC	1.485878532	UP	0.006165542
ENSG00000165474.8	GJB2	1.091039974	UP	0.019467309
ENSG00000165633.13	VSTM4	1.122452447	UP	0.013376805
ENSG00000165794.10	SLC39A2	1.638264617	UP	0.00028234
ENSG00000165795.23	NDRG2	1.217229421	UP	0.002565504
ENSG00000165799.5	RNASE7	1.432023437	UP	0.006912039
ENSG00000165953.9	SERPINA12	1.088988083	UP	0.037921795
ENSG00000166033.13	HTRA1	1.220947296	UP	0.009983909
ENSG00000166106.3	ADAMTS15	1.10647578	UP	0.027579207
ENSG00000166347.19	CYB5A	1.049878348	UP	0.014677811
ENSG00000166391.15	MOGAT2	1.133366336	UP	0.043258978
ENSG00000166394.15	CYB5R2	1.17674678	UP	0.015308476
ENSG00000166396.13	SERPINB7	2.405077027	UP	7.329E-07
ENSG00000166482.12	MFAP4	1.283791648	UP	0.008995552
ENSG00000166535.20	A2ML1	1.51073607	UP	0.002705518
ENSG00000166634.6	SERPINB12	1.923935145	UP	0.000475016
ENSG00000166676.16	TVP23A	-1.114561058	DOWN	0.036290509
ENSG00000167103.12	PIP5KL1	1.067207848	UP	0.041387899
ENSG00000167664.8	TMIGD2	-1.0984778	DOWN	0.020995766
ENSG00000167680.16	SEMA6B	-1.052750684	DOWN	0.022721503
ENSG00000167703.15	SLC43A2	-1.248745742	DOWN	0.000894238
ENSG00000167720.13	SRR	-1.120605343	DOWN	0.048899832
ENSG00000167723.15	TRPV3	1.474604785	UP	0.00519759
ENSG00000167759.13	KLK13	1.111314378	UP	0.02174004
ENSG00000167984.18	NLRC3	-1.116573561	DOWN	0.024508035
ENSG00000167992.13	VWCE	1.189794511	UP	0.035670272

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

(Continuação)

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000167996.16	FTH1	-1.40773131	DOWN	0.003183313
ENSG00000168071.22	CCDC88B	-1.12431766	DOWN	0.012453483
ENSG00000168079.17	SCARA5	-1.473970421	DOWN	0.006525998
ENSG00000168229.4	PTGDR	-1.287039897	DOWN	0.021035724
ENSG00000168282.6	MGAT2	-1.063632779	DOWN	0.049095335
ENSG00000168447.11	SCNN1B	1.13286363	UP	0.014434661
ENSG00000168453.15	HR	1.099240451	UP	0.013696666
ENSG00000168477.19	TNXB	-1.027165059	DOWN	0.047819952
ENSG00000168685.15	IL7R	-1.565248886	DOWN	0.000688232
ENSG00000168703.5	WFDC12	1.400934566	UP	0.005635813
ENSG00000169213.7	RAB3B	1.242884998	UP	0.027924662
ENSG00000169758.13	TMEM266	-1.135946556	DOWN	0.045459117
ENSG00000169908.12	TM4SF1	1.008026495	UP	0.040190416
ENSG00000170054.15	SERPINA9	1.823916342	UP	0.001330115
ENSG00000170209.5	ANKK1	1.375161372	UP	0.01534583
ENSG00000170271.11	FAXDC2	1.715444062	UP	0.000249761
ENSG00000170426.2	SDR9C7	1.362903826	UP	0.002944405
ENSG00000170439.7	METTL7B	1.095549489	UP	0.045020504
ENSG00000170454.6	KRT75	1.092065916	UP	0.039756914
ENSG00000170786.12	SDR16C5	1.111885961	UP	0.021274837
ENSG00000170899.11	GSTA4	1.195540109	UP	0.017068809
ENSG00000171056.8	SOX7	1.181650726	UP	0.013546472
ENSG00000171130.18	ATP6V0E2	-1.308625865	DOWN	0.000873708
ENSG00000171243.8	SOSTDC1	1.688673255	UP	0.002998495
ENSG00000171303.7	KCNK3	-1.248434563	DOWN	0.027897771
ENSG00000171346.16	KRT15	1.129610144	UP	0.023844304
ENSG00000171476.22	HOPX	1.393053197	UP	0.002740251
ENSG00000171700.14	RGS19	-1.038173238	DOWN	0.016129188
ENSG00000171766.16	GATM	1.157089171	UP	0.031096281
ENSG00000171791.13	BCL2	-1.015119772	DOWN	0.044945294
ENSG00000171956.7	FOXB1	-1.384748305	DOWN	0.014923865
ENSG00000172137.19	CALB2	1.65829955	UP	0.002245855
ENSG00000172172.8	MRPL13	1.178740045	UP	0.032927079
ENSG00000172296.13	SPTLC3	1.40804506	UP	0.004533616
ENSG00000172350.10	ABCG4	1.223868018	UP	0.026358039
ENSG00000172379.21	ARNT2	-1.070072727	DOWN	0.024796958
ENSG00000172508.10	CARNS1	-1.253126459	DOWN	0.022494897
ENSG00000172554.12	SNTG2	-1.032734587	DOWN	0.041525627
ENSG00000172780.17	RAB43	-1.726727088	DOWN	0.000793732
ENSG00000172782.12	FADS6	1.276645608	UP	0.013610314

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

(Continuação)

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000172867.4	KRT2	-1.101887298	DOWN	0.025458945
ENSG00000172901.20	LVRN	1.188249277	UP	0.030584747
ENSG00000173418.12	NAA20	1.028100408	UP	0.021793064
ENSG00000173762.8	CD7	-1.931405718	DOWN	6.64491E-06
ENSG00000173868.11	PHOSPHO1	-1.054253668	DOWN	0.044788137
ENSG00000174021.11	GNG5	-1.090837224	DOWN	0.020312593
ENSG00000174502.19	SLC26A9	1.264371403	UP	0.014219768
ENSG00000174564.13	IL20RB	1.052859057	UP	0.024003907
ENSG00000174586.11	ZNF497	-1.089749842	DOWN	0.044199248
ENSG00000175121.11	WFDC5	1.276676026	UP	0.002496779
ENSG00000175183.10	CSRP2	1.504631789	UP	0.004253945
ENSG00000175315.3	CST6	2.112080617	UP	6.64913E-06
ENSG00000175356.13	SCUBE2	1.583297657	UP	0.002093302
ENSG00000175445.17	LPL	1.36005513	UP	0.015147694
ENSG00000175471.19	MCTP1	-1.12333079	DOWN	0.044058489
ENSG00000175602.4	CCDC85B	-1.101625634	DOWN	0.010069162
ENSG00000175920.18	DOK7	-1.287118254	DOWN	0.017988672
ENSG00000175984.15	DENND2C	1.205849007	UP	0.022647779
ENSG00000176083.17	ZNF683	-1.928014263	DOWN	1.45419E-05
ENSG00000176153.12	GPX2	1.617920426	UP	0.001586349
ENSG00000176194.18	CIDEA	2.418578699	UP	2.31571E-07
ENSG00000176920.13	FUT2	2.173564506	UP	4.8066E-06
ENSG00000177098.8	SCN4B	2.170317857	UP	1.83002E-05
ENSG00000177425.11	PAWR	1.244694394	UP	0.014747582
ENSG00000177706.9	FAM20C	-1.09992961	DOWN	0.007087542
ENSG00000177989.13	ODF3B	-1.268607236	DOWN	0.002037275
ENSG00000178026.13	LRRC75B	1.080974099	UP	0.040606785
ENSG00000178150.10	ZNF114	-1.010109371	DOWN	0.044961502
ENSG00000178175.12	ZNF366	-1.129069697	DOWN	0.021247799
ENSG00000178597.7	PSAPL1	1.189330139	UP	0.011700739
ENSG00000178719.17	GRINA	-1.122521434	DOWN	0.003999798
ENSG00000178773.15	CPNE7	-1.035418201	DOWN	0.022965727
ENSG00000178776.5	C5orf46	1.461943967	UP	0.009781105
ENSG00000178860.8	MSC	-1.037854015	DOWN	0.010713626
ENSG00000179593.16	ALOX15B	1.285401565	UP	0.008482155
ENSG00000179772.8	FOXS1	-1.109856059	DOWN	0.048597721
ENSG00000179846.9	NKPD1	1.144376847	UP	0.009263646
ENSG00000179921.15	GPBAR1	-1.395034179	DOWN	0.00207212
ENSG00000180096.12	SEPTIN1	-1.103275176	DOWN	0.009079843
ENSG00000180155.20	LYNX1	1.02407707	UP	0.028424592

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

(Continuação)

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000180340.7	FZD2	-1.087921646	DOWN	0.021296715
ENSG00000180354.16	MTURN	1.183293539	UP	0.013982756
ENSG00000180448.10	ARHGAP45	-1.080788973	DOWN	0.01504924
ENSG00000180638.17	SLC47A2	1.33548805	UP	0.017557416
ENSG00000180758.12	GPR157	1.000856585	UP	0.009731371
ENSG00000181004.10	BBS12	-1.585666688	DOWN	0.004559643
ENSG00000181019.13	NQO1	1.2697257	UP	0.014600652
ENSG00000181029.9	TRAPPC5	-1.290093242	DOWN	0.011666141
ENSG00000181061.13	HIGD1A	1.305397657	UP	0.006647071
ENSG00000181291.8	TMEM132E	-1.267738546	DOWN	0.022199727
ENSG00000181392.17	SYNE4	1.072184746	UP	0.041407916
ENSG00000181458.10	TMEM45A	1.410618042	UP	0.001245079
ENSG00000182183.15	SHISAL2A	-1.276601281	DOWN	0.016346633
ENSG00000182263.14	FIGN	1.064818527	UP	0.037316001
ENSG00000182853.12	VMO1	-1.022070757	DOWN	0.023065719
ENSG00000183111.12	ARHGEF37	1.059715918	UP	0.022361343
ENSG00000183682.8	BMP8A	-1.124764024	DOWN	0.02355437
ENSG00000183734.4	ASCL2	-1.086980863	DOWN	0.024576666
ENSG00000183760.11	ACP7	1.42142903	UP	0.00511493
ENSG00000184148.4	SPRR4	3.139789994	UP	3.72591E-10
ENSG00000184307.16	ZDHHC23	1.297096225	UP	0.01990919
ENSG00000184330.12	S100A7A	1.77780707	UP	0.000196719
ENSG00000184828.10	ZBTB7C	1.367064562	UP	0.003826635
ENSG00000184831.14	APOO	1.021654528	UP	0.039930923
ENSG00000184838.15	PRR16	-1.112285737	DOWN	0.041680606
ENSG00000184860.10	SDR42E1	1.029998039	UP	0.035371349
ENSG00000184922.14	FMNL1	-1.11252814	DOWN	0.004150174
ENSG00000185088.14	RPS27L	1.443179562	UP	0.003751849
ENSG00000185269.12	NOTUM	1.278566164	UP	0.017344221
ENSG00000185338.6	SOCS1	-1.472069775	DOWN	0.001052209
ENSG00000185532.20	PRKG1	1.262588715	UP	0.02628617
ENSG00000185565.12	LSAMP	1.264523182	UP	0.016746256
ENSG00000185640.6	KRT79	1.294180681	UP	0.017861073
ENSG00000185669.6	SNAI3	-1.089620326	DOWN	0.032493829
ENSG00000185966.4	LCE3E	1.591835384	UP	0.002023102
ENSG00000186115.13	CYP4F2	1.16684753	UP	0.037542892
ENSG00000186787.8	SPIN2B	1.280169904	UP	0.024421309
ENSG00000186827.11	TNFRSF4	-1.37531699	DOWN	0.001394936
ENSG00000186844.6	LCE1A	1.943801766	UP	1.05818E-06
ENSG00000186891.14	TNFRSF18	-1.349649632	DOWN	0.000432709

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

(Continuação)

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000187134.14	AKR1C1	1.150599884	UP	0.02697785
ENSG00000187180.3	LCE2C	1.480537538	UP	0.000361526
ENSG00000187223.4	LCE2D	1.444781351	UP	0.00130724
ENSG00000187775.17	DNAH17	1.286052201	UP	0.012562812
ENSG00000187957.8	DNER	1.181731924	UP	0.03317498
ENSG00000188001.10	TPRG1	1.172552548	UP	0.025758284
ENSG00000188322.7	SBK1	-1.778244683	DOWN	6.34921E-05
ENSG00000188373.5	C10orf99	1.097820776	UP	0.018267152
ENSG00000188508.11	KRTDAP	1.314048192	UP	0.000495815
ENSG00000188536.13	HBA2	-1.108131723	DOWN	0.035833712
ENSG00000188624.3	IGFL3	1.449529606	UP	0.01066382
ENSG00000188820.13	CALHM6	-1.668738523	DOWN	0.000757975
ENSG00000188868.14	ZNF563	1.358159259	UP	0.013425309
ENSG00000188883.5	KLRG2	1.336616812	UP	0.018775474
ENSG00000189043.10	NDUFA4	1.100354643	UP	0.015354628
ENSG00000189308.11	LIN54	-1.092791163	DOWN	0.048354754
ENSG00000189430.13	NCR1	-1.155457176	DOWN	0.042053379
ENSG00000189433.7	GJB4	1.148848583	UP	0.025487599
ENSG00000196092.14	PAX5	-1.300737299	DOWN	0.00977684
ENSG00000196139.14	AKR1C3	1.806499197	UP	0.000617427
ENSG00000196371.3	FUT4	-1.094932225	DOWN	0.021314533
ENSG00000196421.8	C20orf204	-1.343789025	DOWN	0.012808716
ENSG00000196456.13	ZNF775	-1.004373625	DOWN	0.037530123
ENSG00000196542.8	SPTSSB	1.184703893	UP	0.034809238
ENSG00000196611.5	MMP1	-1.997844634	DOWN	4.59365E-05
ENSG00000196734.9	LCE1B	1.509663083	UP	0.000382343
ENSG00000197057.9	DTHD1	-1.203158004	DOWN	0.021727593
ENSG00000197084.5	LCE1C	1.405499927	UP	0.000404856
ENSG00000197208.6	SLC22A4	-1.105347055	DOWN	0.043479358
ENSG00000197272.2	IL27	-1.125784427	DOWN	0.044293975
ENSG00000197540.8	GZMM	-1.268729463	DOWN	0.004899766
ENSG00000197557.7	TTC30A	1.196658019	UP	0.034848393
ENSG00000197641.12	SERPINB13	1.366631546	UP	0.006017336
ENSG00000197953.6	AADACL2	1.158353303	UP	0.0415411
ENSG00000198113.3	TOR4A	-1.206935774	DOWN	0.011917903
ENSG00000198417.7	MT1F	-1.255653877	DOWN	0.008951118
ENSG00000198478.8	SH3BGRL2	1.496661497	UP	0.007892167
ENSG00000198502.6	HLA-DRB5	-1.684879964	DOWN	7.2375E-05
ENSG00000198515.14	CNGA1	1.251953242	UP	0.017839045
ENSG00000198643.7	FAM3D	1.364292678	UP	0.015298977

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

(Continuação)

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000198691.13	ABCA4	1.3822258	UP	0.014395977
ENSG00000198729.5	PPP1R14C	1.141957528	UP	0.009471931
ENSG00000198948.12	MFAP3L	1.171589784	UP	0.038198187
ENSG00000198959.12	TGM2	-1.414594604	DOWN	0.000859368
ENSG00000203785.9	SPRR2E	1.684760239	UP	7.18305E-05
ENSG00000203786.6	KPRP	1.26180731	UP	0.006720312
ENSG00000203837.5	PNLIPRP3	1.904835254	UP	0.000813642
ENSG00000204291.11	COL15A1	-1.010187795	DOWN	0.007626835
ENSG00000204370.12	SDHD	1.168353	UP	0.025430665
ENSG00000204475.10	NCR3	-1.172608427	DOWN	0.023447878
ENSG00000204525.16	HLA-C	-1.055936333	DOWN	0.003650771
ENSG00000204540.11	PSORS1C1	1.213971359	UP	0.028725458
ENSG00000204866.8	IGFL2	2.080266703	UP	1.46376E-05
ENSG00000204869.8	IGFL4	1.144610929	UP	0.034055708
ENSG00000205221.12	VIT	1.261282148	UP	0.026450435
ENSG00000205358.4	MT1H	-3.182353294	DOWN	7.39836E-09
ENSG00000205426.10	KRT81	-1.279869102	DOWN	0.015854062
ENSG00000206073.11	SERPINB4	1.096585656	UP	0.027053631
ENSG00000206384.10	COL6A6	1.029062315	UP	0.041696192
ENSG00000213445.10	SIPA1	-1.159920192	DOWN	0.006563458
ENSG00000213638.6	ADAT3	-1.248055346	DOWN	0.00759581
ENSG00000214456.8	PLIN5	1.336243467	UP	0.016577101
ENSG00000215790.7	SLC35E2A	1.154440477	UP	0.035014212
ENSG00000220008.3	LINGO3	-1.332242142	DOWN	0.014865031
ENSG00000221866.9	PLXNA4	-1.779884242	DOWN	0.000435443
ENSG00000221955.10	SLC12A8	1.206910768	UP	0.025377852
ENSG00000223573.7	TINCR	1.0579419	UP	0.016644978
ENSG00000226979.8	LTA	-1.191253266	DOWN	0.012450305
ENSG00000227507.3	LTB	-1.243909039	DOWN	0.004012091
ENSG00000232434.2	AJM1	-1.049594315	DOWN	0.037672191
ENSG00000235109.7	ZSCAN31	1.581044697	UP	0.005441506
ENSG00000235942.3	LCE6A	1.501550395	UP	0.000565172
ENSG00000240386.3	LCE1F	1.389442638	UP	0.001074187
ENSG00000241644.2	INMT	1.081993003	UP	0.043608298
ENSG00000243364.8	EFNA4	1.126413937	UP	0.011117095
ENSG00000243772.8	KIR2DL3	-1.055360508	DOWN	0.049405777
ENSG00000244094.2	SPRR2F	2.212761278	UP	2.25796E-05
ENSG00000244274.7	DBNDD2	-1.33396826	DOWN	0.014094809
ENSG00000244482.10	LILRA6	-1.159513747	DOWN	0.031194883
ENSG00000244617.2	ASPRV1	1.122364211	UP	0.00741543

S1A Table. Differentially expressed coding transcripts in the contrast ML and LCL.

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000250644.3	AC068580.4	-1.119867565	DOWN	0.041295544
ENSG00000253958.2	CLDN23	-1.05058566	DOWN	0.041799787
ENSG00000254126.8	CD8B2	-1.736950986	DOWN	0.002167999
ENSG00000254521.7	SIGLEC12	-2.549374071	DOWN	7.03723E-06
ENSG00000255346.10	NOX5	1.285890565	UP	0.023709443
ENSG00000255501.3	CARD18	2.787364624	UP	8.64494E-07
ENSG00000255529.9	POLR2M	1.117676844	UP	0.047961309
ENSG00000256812.2	CAPNS2	1.338605029	UP	0.003559076
ENSG00000257365.8	FNTB	1.242235996	UP	0.008592278
ENSG00000261594.4	TPBGL	-1.286056409	DOWN	0.02267453
ENSG00000262874.2	C19orf84	-1.676975882	DOWN	0.002474535
ENSG00000265681.7	RPL17	-1.124669045	DOWN	0.028536976
ENSG00000266524.3	GDF10	-1.21363363	DOWN	0.029664254
ENSG00000267673.6	FDX2	1.185447994	UP	0.029887872
ENSG00000267710.9	EDDM13	1.197235395	UP	0.026899116
ENSG00000272325.2	NUDT3	-1.019712978	DOWN	0.032250117
ENSG00000272398.6	CD24	1.185839864	UP	0.010949949
ENSG00000275111.5	ZNF2	1.285828672	UP	0.015197162
ENSG00000275385.2	CCL18	-1.14581821	DOWN	0.008962174

S1B Table. Differentially expressed lncRNAs in the contrast ML and LCL.

(Continua)

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000175061.18	SNHG29	1.21314139	UP	0.005273983
ENSG00000198468.9	FLVCR1-DT	1.40113781	UP	0.013150365
ENSG00000203739.4	AL645568.1	-1.13016935	DOWN	0.040088093
ENSG00000203875.13	SNHG5	1.05816407	UP	0.030343818
ENSG00000204682.8	MIR1915HG	1.17412018	UP	0.034480608
ENSG00000214548.18	MEG3	1.27221619	UP	0.019599108
ENSG00000231437.3	LINC01750	-1.03626473	DOWN	0.040381672
ENSG00000232677.8	LINC00665	1.03899966	UP	0.035796088
ENSG00000233321.2	LINC02669	1.26049606	UP	0.026567442
ENSG00000235903.9	CPB2-AS1	1.15264374	UP	0.030205519
ENSG00000236882.8	LINC01554	1.66367076	UP	0.003017701
ENSG00000237101.1	AC092809.5	1.29627646	UP	0.019159265
ENSG00000237753.2	AC079922.2	-1.11360053	DOWN	0.046066609
ENSG00000239636.1	AC004865.2	-1.5341215	DOWN	0.006945701
ENSG00000242861.1	AL591895.1	-1.29764041	DOWN	0.021550045
ENSG00000245164.8	LINC00861	-1.32065574	DOWN	0.018815294
ENSG00000245954.8	LINC02273	-1.32107831	DOWN	0.020043729
ENSG00000247498.10	GPRC5D-AS1	1.26774473	UP	0.022257393
ENSG00000249641.2	HOXC13-AS	1.40151283	UP	0.012423327
ENSG00000251616.1	AC113410.3	1.0188826	UP	0.046447088
ENSG00000253417.5	LINC02159	1.1096372	UP	0.048569384
ENSG00000255517.6	AP002748.4	-1.14960843	DOWN	0.030948103
ENSG00000256633.1	PDE2A-AS2	-1.17256582	DOWN	0.038199994
ENSG00000257261.6	AC008014.1	1.11136882	UP	0.039165917
ENSG00000261644.2	AC007728.2	-1.2058034	DOWN	0.021475428
ENSG00000262580.5	AC087741.1	1.17372326	UP	0.037304562
ENSG00000264278.1	ZNF236-DT	-1.33024456	DOWN	0.014981433
ENSG00000265148.6	TSPOAP1-AS1	-1.30245981	DOWN	0.010950799
ENSG00000265743.1	AC138207.5	1.9339764	UP	0.000654675
ENSG00000268362.6	AC092279.1	1.24015411	UP	0.028801214
ENSG00000271133.5	AC004130.2	1.30848095	UP	0.014122577
ENSG00000271781.1	AC026740.1	-1.08641375	DOWN	0.033966459
ENSG00000272021.1	AC008592.4	1.0081371	UP	0.045752938
ENSG00000272502.1	AC104958.2	-1.10675663	DOWN	0.045828959
ENSG00000273066.5	AL355987.4	-1.30608178	DOWN	0.018828229
ENSG00000273174.1	AC108673.2	-1.05418353	DOWN	0.044676181
ENSG00000273669.1	AC015819.1	-1.35455532	DOWN	0.017242077
ENSG00000273729.1	AC007686.3	-1.13766975	DOWN	0.043033557
ENSG00000275620.1	AL121827.2	1.34964579	UP	0.012470722

S1B Table. Differentially expressed lncRNAs in the contrast ML and LCL.

Ensembl ID	Gene Name	Log2(FC)	Expression	P-value
ENSG00000275880.1	AL139385.1	1.05209893	UP	0.047674556
ENSG00000280693.2	SH3PXD2A-AS1	1.27392605	UP	0.009012812
ENSG00000286342.1	AC073210.3	1.17906671	UP	0.018566046
ENSG00000287091.1	AC009961.3	-1.06529229	DOWN	0.036729585
ENSG00000287126.1	AC108488.3	-1.20381432	DOWN	0.027998654
ENSG00000287853.1	AL031668.2	1.82217747	UP	0.001357577
ENSG00000288156.1	AC104530.1	-1.09254318	DOWN	0.032731539

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continua)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000175061.18	SNHG29	ENSG00000255529.9	POLR2M	-0.2452	0.910555735	0.015244888
ENSG00000175061.18	SNHG29	ENSG00000198948.12	MFAP3L	-0.2419	0.952479399	0.015767283
ENSG00000175061.18	SNHG29	ENSG00000011198.10	ABHD5	-0.2347	0.983226301	0.035516507
ENSG00000175061.18	SNHG29	ENSG00000016402.13	IL20RA	-0.2284	0.986841698	0.020326322
ENSG00000175061.18	SNHG29	ENSG00000115540.15	MOB4	-0.2248	0.957204013	0.016803852
ENSG00000175061.18	SNHG29	ENSG00000155906.19	RMND1	-0.2195	0.901287508	0.017663732
ENSG00000175061.18	SNHG29	ENSG00000214456.8	PLIN5	-0.2169	0.986199662	0.015326648
ENSG00000175061.18	SNHG29	ENSG00000127954.12	STEAP4	-0.2135	0.977192824	0.035409531
ENSG00000175061.18	SNHG29	ENSG00000128482.16	RNF112	-0.206	0.988356936	0.014349155
ENSG00000175061.18	SNHG29	ENSG00000171766.16	GATM	-0.2019	0.954410829	0.02223958
ENSG00000175061.18	SNHG29	ENSG00000103089.9	FA2H	-0.2008	0.995920568	0.017686926
ENSG00000175061.18	SNHG29	ENSG00000143742.13	SRP9	-0.2006	0.937169537	0.025140519
ENSG00000175061.18	SNHG29	ENSG00000119915.5	ELOVL3	-0.2005	0.986409709	0.029242032
ENSG00000175061.18	SNHG29	ENSG00000188868.14	ZNF563	-0.1997	0.942714046	0.014949743
ENSG00000175061.18	SNHG29	ENSG00000177425.11	PAWR	-0.1965	0.917874901	0.019552177
ENSG00000175061.18	SNHG29	ENSG00000150787.8	PTS	-0.1952	0.966852273	0.017982337
ENSG00000175061.18	SNHG29	ENSG00000035115.22	SH3YL1	-0.1894	0.941213542	0.025190491
ENSG00000175061.18	SNHG29	ENSG00000119125.17	GDA	-0.1886	0.949538642	0.014703389
ENSG00000175061.18	SNHG29	ENSG00000131969.15	ABHD12B	-0.1884	0.918850112	0.01996993
ENSG00000175061.18	SNHG29	ENSG00000154639.19	CXADR	-0.1877	0.971721802	0.023541174
ENSG00000175061.18	SNHG29	ENSG00000110675.13	ELMOD1	-0.1849	0.96657923	0.015946135
ENSG00000175061.18	SNHG29	ENSG00000185088.14	RPS27L	-0.1849	0.977268772	0.043190789
ENSG00000175061.18	SNHG29	ENSG00000143771.12	CNIH4	-0.1739	0.961862929	0.042664608
ENSG00000175061.18	SNHG29	ENSG00000072832.15	CRMP1	-0.1732	0.933063994	0.021858511

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000175061.18	SNHG29	ENSG00000180638.17	SLC47A2	-0.1725	0.983748086	0.018076834
ENSG00000175061.18	SNHG29	ENSG00000145781.9	COMMD10	-0.1656	0.948646437	0.017118748
ENSG00000175061.18	SNHG29	ENSG00000198729.5	PPP1R14C	-0.1635	0.90044492	0.047097148
ENSG00000175061.18	SNHG29	ENSG00000143546.10	S100A8	-0.1616	0.93187108	0.016711387
ENSG00000175061.18	SNHG29	ENSG00000125375.16	DMAC2L	-0.1612	0.937641483	0.019997846
ENSG00000175061.18	SNHG29	ENSG00000163684.11	RPP14	-0.1612	0.919334993	0.019043883
ENSG00000175061.18	SNHG29	ENSG00000196542.8	SPTSSB	-0.16	0.930480993	0.016524523
ENSG00000175061.18	SNHG29	ENSG00000204370.12	SDHD	-0.1582	0.940192805	0.021114746
ENSG00000175061.18	SNHG29	ENSG00000118402.6	ELOVL4	-0.1566	0.937617956	0.032423072
ENSG00000175061.18	SNHG29	ENSG00000172901.20	LVRN	-0.1563	0.933553444	0.014941669
ENSG00000175061.18	SNHG29	ENSG00000198478.8	SH3BGRL2	-0.1562	0.977737021	0.016705719
ENSG00000175061.18	SNHG29	ENSG00000166106.3	ADAMTS15	-0.1547	0.943176915	0.03127037
ENSG00000175061.18	SNHG29	ENSG00000143502.15	SUSD4	-0.1544	0.970621169	0.019022902
ENSG00000175061.18	SNHG29	ENSG00000160062.15	ZBTB8A	-0.1542	0.989900613	0.01536284
ENSG00000175061.18	SNHG29	ENSG00000185532.20	PRKG1	-0.1534	0.935955243	0.015015039
ENSG00000175061.18	SNHG29	ENSG00000124143.10	ARHGAP40	-0.1533	0.902576614	0.016341203
ENSG00000175061.18	SNHG29	ENSG00000186115.13	CYP4F2	-0.1517	0.95121456	0.01442564
ENSG00000175061.18	SNHG29	ENSG00000154917.11	RAB6B	-0.1515	0.99432428	0.016659932
ENSG00000175061.18	SNHG29	ENSG00000134201.12	GSTM5	-0.1508	0.942707655	0.017616596
ENSG00000175061.18	SNHG29	ENSG00000151892.14	GFRA1	-0.1505	0.95785078	0.020067619
ENSG00000175061.18	SNHG29	ENSG00000105852.11	PON3	-0.1496	0.948299751	0.015473767
ENSG00000175061.18	SNHG29	ENSG00000138135.7	CH25H	-0.149	0.944492378	0.031217643
ENSG00000175061.18	SNHG29	ENSG00000175445.17	LPL	-0.1471	0.951365917	0.027989708
ENSG00000175061.18	SNHG29	ENSG00000267710.9	EDDM13	-0.146	0.970159306	0.014016283

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000175061.18	SNHG29	ENSG00000166391.15	MOGAT2	-0.1458	0.942543492	0.014266269
ENSG00000175061.18	SNHG29	ENSG00000008394.13	MGST1	-0.1436	0.964320731	0.02846949
ENSG00000175061.18	SNHG29	ENSG00000135218.19	CD36	-0.1436	0.991965767	0.02279289
ENSG00000175061.18	SNHG29	ENSG00000112972.15	HMGCS1	-0.142	0.946065707	0.035813182
ENSG00000175061.18	SNHG29	ENSG00000235109.7	ZSCAN31	-0.1405	0.984106587	0.015132423
ENSG00000175061.18	SNHG29	ENSG00000170786.12	SDR16C5	-0.1404	0.978359816	0.025708773
ENSG00000175061.18	SNHG29	ENSG00000197557.7	TTC30A	-0.1383	0.989122075	0.014839214
ENSG00000175061.18	SNHG29	ENSG00000137876.10	RSL24D1	-0.1359	0.96024528	0.023722266
ENSG00000175061.18	SNHG29	ENSG00000086696.11	HSD17B2	-0.1336	0.993578581	0.01678494
ENSG00000175061.18	SNHG29	ENSG00000189433.7	GJB4	-0.1317	0.94105514	0.023685358
ENSG00000175061.18	SNHG29	ENSG00000145107.16	TM4SF19	-0.1313	0.993203381	0.015827909
ENSG00000175061.18	SNHG29	ENSG00000255501.3	CARD18	-0.1307	0.956794539	0.017915644
ENSG00000175061.18	SNHG29	ENSG00000101049.17	SGK2	-0.1297	0.988310595	0.014581185
ENSG00000175061.18	SNHG29	ENSG00000112293.15	GPLD1	-0.1291	0.938227128	0.015550661
ENSG00000175061.18	SNHG29	ENSG00000103740.10	ACSBG1	-0.1264	0.979747611	0.017909892
ENSG00000175061.18	SNHG29	ENSG00000136783.10	NIPSNAP3A	-0.1264	0.930920263	0.017072688
ENSG00000175061.18	SNHG29	ENSG00000102287.19	GABRE	-0.1261	0.968195116	0.016092702
ENSG00000175061.18	SNHG29	ENSG00000184860.10	SDR42E1	-0.1257	0.957124596	0.021418662
ENSG00000175061.18	SNHG29	ENSG00000127249.15	ATP13A4	-0.1255	0.949325235	0.01492897
ENSG00000175061.18	SNHG29	ENSG00000163331.12	DAPL1	-0.1248	0.915866707	0.017902573
ENSG00000175061.18	SNHG29	ENSG00000119013.9	NDUFB3	-0.1214	0.95443888	0.020311263
ENSG00000175061.18	SNHG29	ENSG00000082482.13	KCNK2	-0.1209	0.989164695	0.01583302
ENSG00000175061.18	SNHG29	ENSG00000206073.11	SERPINB4	-0.1196	0.938493675	0.026089233
ENSG00000175061.18	SNHG29	ENSG00000196139.14	AKR1C3	-0.1195	0.991942236	0.019287561

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000175061.18	SNHG29	ENSG00000134240.12	HMGCS2	-0.118	0.986845161	0.014263906
ENSG00000175061.18	SNHG29	ENSG00000257365.8	FNTB	-0.1178	0.926629491	0.026220138
ENSG00000175061.18	SNHG29	ENSG00000160588.10	MPZL3	-0.1176	0.962719334	0.028793769
ENSG00000175061.18	SNHG29	ENSG00000172172.8	MRPL13	-0.1175	0.952592794	0.017600388
ENSG00000175061.18	SNHG29	ENSG00000188001.10	TPRG1	-0.1163	0.970845768	0.023855861
ENSG00000175061.18	SNHG29	ENSG00000170439.7	METTL7B	-0.1141	0.909141994	0.02330741
ENSG00000175061.18	SNHG29	ENSG00000175984.15	DENND2C	-0.1114	0.921723119	0.018023565
ENSG00000175061.18	SNHG29	ENSG00000118520.15	ARG1	-0.1108	0.987268932	0.029804997
ENSG00000175061.18	SNHG29	ENSG00000114771.14	AADAC	-0.1072	0.978815644	0.014381602
ENSG00000175061.18	SNHG29	ENSG00000143556.9	S100A7	-0.1059	0.911727526	0.025045975
ENSG00000175061.18	SNHG29	ENSG00000188508.11	KRTDAP	-0.1011	0.931892219	0.006075127
ENSG00000175061.18	SNHG29	ENSG00000170054.15	SERPINA9	-0.1007	0.954852908	0.016380839
ENSG00000198468.9	FLVCR1-DT	ENSG00000123352.18	SPATS2	-0.1892	0.912004102	0.001502156
ENSG00000198468.9	FLVCR1-DT	ENSG00000165633.13	VSTM4	-0.1714	0.905205157	0.004701575
ENSG00000198468.9	FLVCR1-DT	ENSG00000184828.10	ZBTB7C	-0.1507	0.908149921	0.03204944
ENSG00000198468.9	FLVCR1-DT	ENSG00000154856.13	APCDD1	-0.1332	0.914275458	0.013634555
ENSG00000198468.9	FLVCR1-DT	ENSG00000092621.12	PHGDH	-0.1108	0.90646038	0.005544703
ENSG00000198468.9	FLVCR1-DT	ENSG00000109472.14	CPE	-0.1036	0.938372514	0.008558785
ENSG00000203739.4	AL645568.1	ENSG00000130511.16	SSBP4	-0.2309	0.912044365	0.003563119
ENSG00000203739.4	AL645568.1	ENSG00000068831.19	RASGRP2	-0.1699	0.935119534	0.008156661
ENSG00000203739.4	AL645568.1	ENSG00000021300.14	PLEKHB1	-0.167	0.98998911	0.014743378
ENSG00000203739.4	AL645568.1	ENSG00000171130.18	ATP6V0E2	-0.1593	0.974371411	0.002619018
ENSG00000203739.4	AL645568.1	ENSG00000183111.12	ARHGEF37	-0.1331	-0.913027903	0.002033843
ENSG00000203739.4	AL645568.1	ENSG00000187223.4	LCE2D	-0.1153	-0.930942728	0.006101901

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000203739.4	AL645568.1	ENSG00000184922.14	FMNL1	-0.1071	0.901335665	0.000887006
ENSG00000203739.4	AL645568.1	ENSG00000178719.17	GRINA	-0.106	0.941341795	0.001394141
ENSG00000203739.4	AL645568.1	ENSG00000227507.3	LTB	-0.1029	0.937056421	0.007318253
ENSG00000203739.4	AL645568.1	ENSG00000162894.12	FCMR	-0.1019	0.931746319	0.004866377
ENSG00000203739.4	AL645568.1	ENSG00000081059.20	TCF7	-0.1009	0.908897807	0.016024988
ENSG00000203739.4	AL645568.1	ENSG00000101439.9	CST3	-0.1006	0.943674395	0.004745415
ENSG00000203875.13	SNHG5	ENSG00000115540.15	MOB4	-0.4238	0.930913868	0.025771003
ENSG00000203875.13	SNHG5	ENSG00000275111.5	ZNF2	-0.3294	0.92995752	0.024427978
ENSG00000203875.13	SNHG5	ENSG00000255529.9	POLR2M	-0.2611	0.907226925	0.017966934
ENSG00000203875.13	SNHG5	ENSG00000136783.10	NIPSNAP3A	-0.2359	0.903952526	0.027794879
ENSG00000203875.13	SNHG5	ENSG00000255501.3	CARD18	-0.202	0.903672449	0.038200694
ENSG00000203875.13	SNHG5	ENSG00000155906.19	RMND1	-0.2019	0.96928501	0.031171487
ENSG00000203875.13	SNHG5	ENSG00000108666.10	C17orf75	-0.195	0.930562277	0.019977668
ENSG00000203875.13	SNHG5	ENSG00000163684.11	RPP14	-0.1853	0.907418948	0.042302755
ENSG00000203875.13	SNHG5	ENSG00000100479.13	POLE2	-0.1774	0.959614903	0.015221684
ENSG00000203875.13	SNHG5	ENSG00000096092.6	TMEM14A	-0.1339	0.924312213	0.025646113
ENSG00000203875.13	SNHG5	ENSG00000185565.12	LSAMP	-0.1186	0.933905421	0.027050341
ENSG00000203875.13	SNHG5	ENSG00000124143.10	ARHGAP40	-0.1028	0.904425797	0.023413823
ENSG00000203875.13	SNHG5	ENSG00000203837.5	PNLIPRP3	-0.1003	0.902220571	0.017241055
ENSG00000204682.8	MIR1915HG	ENSG00000069812.11	HES2	-0.1356	0.926980149	0.045274032
ENSG00000204682.8	MIR1915HG	ENSG00000143320.9	CRABP2	-0.1331	0.931518687	0.016153945
ENSG00000204682.8	MIR1915HG	ENSG00000180155.20	LYNX1	-0.1145	0.992284247	0.023428265
ENSG00000204682.8	MIR1915HG	ENSG00000105088.8	OLFM2	-0.1113	0.960773938	0.049943381
ENSG00000204682.8	MIR1915HG	ENSG00000092621.12	PHGDH	-0.1073	0.937842934	0.006337655

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000204682.8	MIR1915HG	ENSG00000114115.10	RBP1	-0.104	0.904981084	0.041750503
ENSG00000204682.8	MIR1915HG	ENSG00000100003.18	SEC14L2	-0.1031	0.948197328	0.023328459
ENSG00000204682.8	MIR1915HG	ENSG00000154856.13	APCDD1	-0.1007	0.975226697	0.014735377
ENSG00000214548.18	MEG3	ENSG00000011198.10	ABHD5	-0.2381	0.921058742	0.042724495
ENSG00000214548.18	MEG3	ENSG00000198729.5	PPP1R14C	-0.2182	0.916633298	0.014248034
ENSG00000214548.18	MEG3	ENSG00000197084.5	LCE1C	-0.1885	0.914125381	0.005654611
ENSG00000214548.18	MEG3	ENSG00000145425.10	RPS3A	-0.1491	0.971005554	0.025973296
ENSG00000214548.18	MEG3	ENSG00000166347.19	CYB5A	-0.1451	0.993398493	0.008503966
ENSG00000214548.18	MEG3	ENSG00000109475.16	RPL34	-0.1422	0.914076817	0.038294774
ENSG00000214548.18	MEG3	ENSG00000171346.16	KRT15	-0.1413	0.928788703	0.023957548
ENSG00000214548.18	MEG3	ENSG00000062282.15	DGAT2	-0.1407	0.986300569	0.011418873
ENSG00000214548.18	MEG3	ENSG00000188508.11	KRTDAP	-0.1312	0.952747995	0.002678287
ENSG00000214548.18	MEG3	ENSG00000161970.15	RPL26	-0.128	0.959018702	0.040124526
ENSG00000214548.18	MEG3	ENSG00000178597.7	PSAPL1	-0.1245	0.915268191	0.038446668
ENSG00000214548.18	MEG3	ENSG00000099260.11	PALMD	-0.124	0.960263358	0.039753616
ENSG00000214548.18	MEG3	ENSG00000084110.11	HAL	-0.1212	0.912549211	0.008672614
ENSG00000214548.18	MEG3	ENSG00000243364.8	EFNA4	-0.1188	0.910130594	0.036264467
ENSG00000214548.18	MEG3	ENSG00000163682.16	RPL9	-0.1146	0.917424261	0.005427671
ENSG00000214548.18	MEG3	ENSG00000139433.10	GLTP	-0.1141	0.914106379	0.002324927
ENSG00000214548.18	MEG3	ENSG00000160862.13	AZGP1	-0.1104	0.925427844	0.016049774
ENSG00000214548.18	MEG3	ENSG00000143387.13	CTSK	-0.1068	0.979471609	0.032538615
ENSG00000214548.18	MEG3	ENSG00000120437.9	ACAT2	-0.1031	0.914274497	0.039641918
ENSG00000214548.18	MEG3	ENSG00000143556.9	S100A7	-0.101	0.962011493	0.012910071
ENSG00000231437.3	LINC01750	ENSG00000112787.13	FBRSL1	-0.1763	0.904060673	0.010216726
ENSG00000231437.3	LINC01750	ENSG00000173868.11	PHOSPHO1	-0.1587	0.937006717	0.025931845

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000231437.3	LINC01750	ENSG00000161847.14	RAVER1	-0.1582	0.930071336	0.029957831
ENSG00000231437.3	LINC01750	ENSG00000141664.10	ZCCHC2	-0.1498	0.923474029	0.009296483
ENSG00000231437.3	LINC01750	ENSG00000136040.9	PLXNC1	-0.148	0.950213796	0.023076593
ENSG00000231437.3	LINC01750	ENSG00000265681.7	RPL17	-0.141	0.908191943	0.030284086
ENSG00000231437.3	LINC01750	ENSG00000121281.13	ADCY7	-0.138	0.945353536	0.011141815
ENSG00000231437.3	LINC01750	ENSG00000131188.12	PRR7	-0.1339	0.907173258	0.036484342
ENSG00000231437.3	LINC01750	ENSG00000182853.12	VMO1	-0.1249	0.901189501	0.003931745
ENSG00000231437.3	LINC01750	ENSG00000138795.10	LEF1	-0.1234	0.902534507	0.016798191
ENSG00000231437.3	LINC01750	ENSG00000158106.14	RHPN1	-0.1226	0.936477155	0.012461575
ENSG00000231437.3	LINC01750	ENSG00000101096.20	NFATC2	-0.1216	0.913863012	0.014964073
ENSG00000231437.3	LINC01750	ENSG00000080603.17	SRCAP	-0.1196	0.945750933	0.005232462
ENSG00000231437.3	LINC01750	ENSG00000168282.6	MGAT2	-0.1196	0.906835284	0.038651514
ENSG00000231437.3	LINC01750	ENSG00000121486.12	TRMT1L	-0.1142	0.98398216	0.024353894
ENSG00000231437.3	LINC01750	ENSG00000124496.12	TRERF1	-0.1079	0.940645778	0.007979559
ENSG00000231437.3	LINC01750	ENSG00000176083.17	ZNF683	-0.1012	0.990169406	0.037483313
ENSG00000232677.8	LINC00665	ENSG00000272398.6	CD24	-0.2769	0.973541934	0.034549747
ENSG00000232677.8	LINC00665	ENSG00000116717.13	GADD45A	-0.1375	0.934399454	0.030222232
ENSG00000232677.8	LINC00665	ENSG00000163898.10	LIPH	-0.1341	0.975005759	0.01874404
ENSG00000232677.8	LINC00665	ENSG00000166394.15	CYB5R2	-0.1185	0.918111236	0.039465198
ENSG00000233321.2	LINC02669	ENSG00000109475.16	RPL34	-0.3488	0.963628529	0.033055014
ENSG00000233321.2	LINC02669	ENSG00000164919.11	COX6C	-0.2852	0.984308947	0.030953511
ENSG00000233321.2	LINC02669	ENSG00000166347.19	CYB5A	-0.278	0.937495601	0.005128836
ENSG00000233321.2	LINC02669	ENSG00000161970.15	RPL26	-0.2492	0.9736092	0.034794224

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000233321.2	LINC02669	ENSG00000143771.12	CNIH4	-0.1567	0.990372565	0.021963814
ENSG00000233321.2	LINC02669	ENSG00000145425.10	RPS3A	-0.1411	0.939953142	0.018928742
ENSG00000233321.2	LINC02669	ENSG00000188508.11	KRTDAP	-0.1206	0.929556354	0.002617395
ENSG00000233321.2	LINC02669	ENSG00000118402.6	ELOVL4	-0.1111	0.906586445	0.021689101
ENSG00000235903.9	CPB2-AS1	ENSG00000109475.16	RPL34	-0.8252	0.95173472	0.031959767
ENSG00000235903.9	CPB2-AS1	ENSG00000166347.19	CYB5A	-0.5952	0.944135247	0.004642002
ENSG00000235903.9	CPB2-AS1	ENSG00000164919.11	COX6C	-0.3326	0.967747189	0.028518034
ENSG00000235903.9	CPB2-AS1	ENSG00000161970.15	RPL26	-0.2594	0.970557865	0.033674828
ENSG00000235903.9	CPB2-AS1	ENSG00000011198.10	ABHD5	-0.1551	0.981014817	0.011233524
ENSG00000235903.9	CPB2-AS1	ENSG00000145425.10	RPS3A	-0.1109	0.923292253	0.01767361
ENSG00000235903.9	CPB2-AS1	ENSG00000143771.12	CNIH4	-0.1082	0.972500967	0.018671134
ENSG00000236882.8	LINC01554	ENSG00000162040.7	HS3ST6	-0.1401	0.966490863	0.013819155
ENSG00000236882.8	LINC01554	ENSG00000184828.10	ZBTB7C	-0.1161	0.958078733	0.030908032
ENSG00000236882.8	LINC01554	ENSG00000154856.13	APCDD1	-0.1063	0.91517376	0.013430985
ENSG00000237753.2	AC079922.2	ENSG00000197084.5	LCE1C	-0.1516	-0.916877912	0.004854122
ENSG00000237753.2	AC079922.2	ENSG00000068831.19	RASGRP2	-0.1433	0.957234262	0.012132692
ENSG00000237753.2	AC079922.2	ENSG00000178150.10	ZNF114	-0.1341	0.927715968	0.036190632
ENSG00000237753.2	AC079922.2	ENSG00000109610.6	SOD3	-0.1282	0.906329706	0.006806974
ENSG00000237753.2	AC079922.2	ENSG00000021300.14	PLEKHB1	-0.1269	0.943527636	0.041701245
ENSG00000237753.2	AC079922.2	ENSG00000171130.18	ATP6V0E2	-0.1243	0.942738531	0.00342191
ENSG00000237753.2	AC079922.2	ENSG00000101307.16	SIRPB1	-0.1113	0.983530981	0.010465164
ENSG00000237753.2	AC079922.2	ENSG00000070087.14	PFN2	-0.1109	-0.922626833	0.046133959
ENSG00000237753.2	AC079922.2	ENSG00000178719.17	GRINA	-0.1086	0.922975216	0.001414971

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000237753.2	AC079922.2	ENSG00000184922.14	FMNL1	-0.1023	0.963530984	0.00091847
ENSG00000237753.2	AC079922.2	ENSG00000167703.15	SLC43A2	-0.1018	0.91795443	0.000913058
ENSG00000237753.2	AC079922.2	ENSG00000186891.14	TNFRSF18	-0.101	0.939219951	0.002472281
ENSG00000239636.1	AC004865.2	ENSG00000115687.14	PASK	-0.2109	0.900654708	0.012179537
ENSG00000239636.1	AC004865.2	ENSG00000109610.6	SOD3	-0.1751	0.938237679	0.006825013
ENSG00000239636.1	AC004865.2	ENSG00000161265.15	U2AF1L4	-0.1525	0.976641949	0.042331214
ENSG00000239636.1	AC004865.2	ENSG00000126353.3	CCR7	-0.1369	0.944281723	0.012814598
ENSG00000239636.1	AC004865.2	ENSG00000198417.7	MT1F	-0.1014	0.956372153	0.040910545
ENSG00000242861.1	AL591895.1	ENSG00000101307.16	SIRPB1	-0.1578	0.921160728	0.006909109
ENSG00000242861.1	AL591895.1	ENSG00000068831.19	RASGRP2	-0.1367	0.928778997	0.008575653
ENSG00000242861.1	AL591895.1	ENSG00000226979.8	LTA	-0.1194	0.992462004	0.016551507
ENSG00000242861.1	AL591895.1	ENSG00000115687.14	PASK	-0.1107	0.95991123	0.003311255
ENSG00000242861.1	AL591895.1	ENSG00000198417.7	MT1F	-0.106	0.964247975	0.030769733
ENSG00000242861.1	AL591895.1	ENSG00000107742.13	SPOCK2	-0.1024	0.909400327	0.002798653
ENSG00000242861.1	AL591895.1	ENSG00000138111.14	MFSD13A	-0.1012	0.949874054	0.004114993
ENSG00000245164.8	LINC00861	ENSG00000021300.14	PLEKHB1	-0.1588	0.942663066	0.036301286
ENSG00000245164.8	LINC00861	ENSG00000115687.14	PASK	-0.1206	0.923951175	0.006542081
ENSG00000245164.8	LINC00861	ENSG00000109610.6	SOD3	-0.1184	0.977143227	0.006765822
ENSG00000245954.8	LINC02273	ENSG00000130511.16	SSBP4	-0.1601	0.959651507	0.003843342
ENSG00000245954.8	LINC02273	ENSG00000105122.13	RASAL3	-0.1262	0.945129783	0.009517442
ENSG00000245954.8	LINC02273	ENSG00000174021.11	GNG5	-0.1228	0.965553023	0.037977057
ENSG00000245954.8	LINC02273	ENSG00000177989.13	ODF3B	-0.1227	0.954088935	0.007256482
ENSG00000245954.8	LINC02273	ENSG00000131196.17	NFATC1	-0.1175	0.987419354	0.010226991

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000245954.8	LINC02273	ENSG00000213445.10	SIPA1	-0.115	0.97644405	0.009121958
ENSG00000245954.8	LINC02273	ENSG00000074660.16	SCARF1	-0.1129	0.903556375	0.00690231
ENSG00000245954.8	LINC02273	ENSG00000158717.11	RNF166	-0.1119	0.97871034	0.021252692
ENSG00000245954.8	LINC02273	ENSG00000130479.11	MAP1S	-0.1117	0.983669508	0.017033688
ENSG00000245954.8	LINC02273	ENSG00000180448.10	ARHGAP45	-0.1109	0.931410513	0.009268712
ENSG00000245954.8	LINC02273	ENSG00000105963.15	ADAP1	-0.1078	0.906436279	0.013237616
ENSG00000245954.8	LINC02273	ENSG00000171700.14	RGS19	-0.1065	0.94518301	0.006727453
ENSG00000245954.8	LINC02273	ENSG00000168071.22	CCDC88B	-0.1059	0.940820253	0.012413652
ENSG00000245954.8	LINC02273	ENSG00000100092.23	SH3BP1	-0.1048	0.953240217	0.009133787
ENSG00000245954.8	LINC02273	ENSG00000167680.16	SEMA6B	-0.1039	0.953347505	0.007319813
ENSG00000245954.8	LINC02273	ENSG00000168477.19	TNXB	-0.1022	0.962365689	0.025293312
ENSG00000247498.10	GPRC5D-AS1	ENSG00000167703.15	SLC43A2	-0.2332	-0.946245256	0.000876967
ENSG00000247498.10	GPRC5D-AS1	ENSG00000005469.12	CROT	-0.2232	0.917237634	0.026058929
ENSG00000247498.10	GPRC5D-AS1	ENSG00000188508.11	KRTDAP	-0.1752	0.944058461	0.002599294
ENSG00000247498.10	GPRC5D-AS1	ENSG00000154227.13	CERS3	-0.1649	0.924072938	0.001408908
ENSG00000247498.10	GPRC5D-AS1	ENSG00000100271.17	TTLL1	-0.1525	0.943129811	0.002611831
ENSG00000247498.10	GPRC5D-AS1	ENSG00000178175.12	ZNF366	-0.1433	-0.912681623	0.008750059
ENSG00000247498.10	GPRC5D-AS1	ENSG00000163082.10	SGPP2	-0.1365	0.925282143	0.000544791
ENSG00000247498.10	GPRC5D-AS1	ENSG00000139433.10	GLTP	-0.1343	0.964580411	0.002042068
ENSG00000247498.10	GPRC5D-AS1	ENSG00000011638.10	TMEM159	-0.1294	0.905996912	0.000600941
ENSG00000247498.10	GPRC5D-AS1	ENSG00000136044.12	APPL2	-0.128	0.901015045	0.003158847
ENSG00000247498.10	GPRC5D-AS1	ENSG00000136828.19	RALGPS1	-0.1168	0.916585689	0.020905877
ENSG00000247498.10	GPRC5D-AS1	ENSG00000075673.11	ATP12A	-0.1164	0.920483164	0.041922352

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000247498.10	GPRC5D-AS1	ENSG00000119411.11	BSPRY	-0.1136	0.948555846	0.00043688
ENSG00000247498.10	GPRC5D-AS1	ENSG00000107537.14	PHYH	-0.1097	0.931762735	0.002443578
ENSG00000247498.10	GPRC5D-AS1	ENSG00000198959.12	TGM2	-0.1072	-0.90897881	0.003876026
ENSG00000247498.10	GPRC5D-AS1	ENSG00000204525.16	HLA-C	-0.1067	-0.951159662	0.000285313
ENSG00000247498.10	GPRC5D-AS1	ENSG00000187180.3	LCE2C	-0.1058	0.938043978	0.003316569
ENSG00000247498.10	GPRC5D-AS1	ENSG00000204291.11	COL15A1	-0.1035	-0.922531348	0.000300718
ENSG00000247498.10	GPRC5D-AS1	ENSG00000186844.6	LCE1A	-0.1019	0.940899631	0.008294765
ENSG00000247498.10	GPRC5D-AS1	ENSG00000163584.18	RPL22L1	-0.1007	0.956240668	0.006379212
ENSG00000251616.1	AC113410.3	ENSG00000161970.15	RPL26	-0.1145	0.946925511	0.033347847
ENSG00000255517.6	AP002748.4	ENSG00000161265.15	U2AF1L4	-0.1341	0.976927669	0.013391729
ENSG00000255517.6	AP002748.4	ENSG00000198417.7	MT1F	-0.1276	0.931377002	0.028425623
ENSG00000255517.6	AP002748.4	ENSG00000126353.3	CCR7	-0.1039	0.964035347	0.010388452
ENSG00000256633.1	PDE2A-AS2	ENSG00000177989.13	ODF3B	-0.1846	0.929759608	0.006967549
ENSG00000256633.1	PDE2A-AS2	ENSG00000130511.16	SSBP4	-0.1525	0.906311944	0.003675383
ENSG00000256633.1	PDE2A-AS2	ENSG00000080603.17	SRCAP	-0.1479	0.964059416	0.008553749
ENSG00000256633.1	PDE2A-AS2	ENSG00000183682.8	BMP8A	-0.1422	0.984879882	0.024612639
ENSG00000256633.1	PDE2A-AS2	ENSG00000112787.13	FBRSL1	-0.1352	0.974206639	0.010576945
ENSG00000256633.1	PDE2A-AS2	ENSG00000139725.8	RHOF	-0.1326	0.93573399	0.037791288
ENSG00000256633.1	PDE2A-AS2	ENSG00000196371.3	FUT4	-0.125	0.906795196	0.017393369
ENSG00000256633.1	PDE2A-AS2	ENSG00000168477.19	TNXB	-0.123	0.94512502	0.02248484
ENSG00000256633.1	PDE2A-AS2	ENSG00000213445.10	SIPA1	-0.1227	0.933164351	0.009004625
ENSG00000256633.1	PDE2A-AS2	ENSG00000150594.7	ADRA2A	-0.1185	0.948239378	0.037957039
ENSG00000256633.1	PDE2A-AS2	ENSG00000012124.17	CD22	-0.1178	0.976036016	0.0096213

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000256633.1	PDE2A-AS2	ENSG00000167680.16	SEMA6B	-0.1166	0.966227931	0.007055233
ENSG00000256633.1	PDE2A-AS2	ENSG00000196456.13	ZNF775	-0.1163	0.935052878	0.015921344
ENSG00000256633.1	PDE2A-AS2	ENSG00000101986.12	ABCD1	-0.116	0.916866675	0.001545607
ENSG00000256633.1	PDE2A-AS2	ENSG00000121281.13	ADCY7	-0.1142	0.91172553	0.012101555
ENSG00000256633.1	PDE2A-AS2	ENSG00000159753.14	CARMIL2	-0.1128	0.926748906	0.006958173
ENSG00000256633.1	PDE2A-AS2	ENSG00000138795.10	LEF1	-0.1127	0.901557155	0.020733058
ENSG00000256633.1	PDE2A-AS2	ENSG00000100092.23	SH3BP1	-0.1124	0.92791546	0.008825002
ENSG00000256633.1	PDE2A-AS2	ENSG00000131196.17	NFATC1	-0.1107	0.954239792	0.009610757
ENSG00000256633.1	PDE2A-AS2	ENSG00000104903.5	LYL1	-0.1104	0.901536762	0.027576005
ENSG00000256633.1	PDE2A-AS2	ENSG00000161847.14	RAVER1	-0.1102	0.945650342	0.031448881
ENSG00000256633.1	PDE2A-AS2	ENSG00000152518.8	ZFP36L2	-0.1101	0.904874676	0.047831467
ENSG00000256633.1	PDE2A-AS2	ENSG00000105329.10	TGFB1	-0.11	0.964473581	0.005124597
ENSG00000256633.1	PDE2A-AS2	ENSG00000173762.8	CD7	-0.1089	0.915590832	0.01425259
ENSG00000256633.1	PDE2A-AS2	ENSG00000105516.11	DBP	-0.1058	0.949633872	0.039904562
ENSG00000256633.1	PDE2A-AS2	ENSG00000158717.11	RNF166	-0.1057	0.901225368	0.019826755
ENSG00000256633.1	PDE2A-AS2	ENSG00000213638.6	ADAT3	-0.1034	0.960999769	0.015779007
ENSG00000256633.1	PDE2A-AS2	ENSG00000100599.16	RIN3	-0.102	0.968060946	0.002007406
ENSG00000256633.1	PDE2A-AS2	ENSG00000043143.20	JADE2	-0.1016	0.948714319	0.00189592
ENSG00000256633.1	PDE2A-AS2	ENSG00000089639.11	GMIP	-0.1008	0.903287751	0.001800354
ENSG00000256633.1	PDE2A-AS2	ENSG00000175602.4	CCDC85B	-0.1008	0.902540439	0.008106521
ENSG00000257261.6	AC008014.1	ENSG00000136002.19	ARHGEF4	-0.1495	0.912817349	0.014210386
ENSG00000257261.6	AC008014.1	ENSG00000069812.11	HES2	-0.1458	0.98458833	0.037615111
ENSG00000257261.6	AC008014.1	ENSG00000176920.13	FUT2	-0.1364	0.977276877	0.048235354

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000257261.6	AC008014.1	ENSG00000180155.20	LYNX1	-0.134	0.923290273	0.017679053
ENSG00000257261.6	AC008014.1	ENSG00000165474.8	GJB2	-0.1294	0.979969145	0.012018158
ENSG00000257261.6	AC008014.1	ENSG00000168453.15	HR	-0.1224	0.904355683	0.00703483
ENSG00000257261.6	AC008014.1	ENSG00000121742.19	GJB6	-0.1198	0.966201934	0.017163438
ENSG00000257261.6	AC008014.1	ENSG00000167103.12	PIP5KL1	-0.1171	0.989103634	0.04982029
ENSG00000257261.6	AC008014.1	ENSG00000147883.12	CDKN2B	-0.1162	0.977217763	0.019226082
ENSG00000257261.6	AC008014.1	ENSG00000115129.14	TP53I3	-0.114	0.946470763	0.00206707
ENSG00000257261.6	AC008014.1	ENSG00000168447.11	SCNN1B	-0.1102	0.952657365	0.00726288
ENSG00000257261.6	AC008014.1	ENSG00000151715.8	TMEM45B	-0.1094	0.909308099	0.008058758
ENSG00000257261.6	AC008014.1	ENSG00000125398.8	SOX9	-0.1093	0.934176221	0.022834727
ENSG00000257261.6	AC008014.1	ENSG00000134490.14	TMEM241	-0.1073	0.912801399	0.010715113
ENSG00000257261.6	AC008014.1	ENSG00000116133.13	DHCR24	-0.1066	0.903065666	0.00055272
ENSG00000257261.6	AC008014.1	ENSG00000114115.10	RBP1	-0.1052	0.971003019	0.036523994
ENSG00000257261.6	AC008014.1	ENSG00000064655.19	EYA2	-0.1051	0.972667941	0.047886405
ENSG00000261644.2	AC007728.2	ENSG00000068831.19	RASGRP2	-0.1272	0.979530695	0.007456094
ENSG00000261644.2	AC007728.2	ENSG00000115687.14	PASK	-0.1161	0.943279789	0.002336501
ENSG00000261644.2	AC007728.2	ENSG00000109610.6	SOD3	-0.1151	0.960508828	0.006569615
ENSG00000261644.2	AC007728.2	ENSG00000134438.10	RAX	-0.1075	0.986480574	0.044576576
ENSG00000261644.2	AC007728.2	ENSG00000101307.16	SIRPB1	-0.1008	0.913190429	0.005830507
ENSG00000262580.5	AC087741.1	ENSG00000173418.12	NAA20	-0.1104	0.927925575	0.006532897
ENSG00000264278.1	ZNF236-DT	ENSG00000177989.13	ODF3B	-0.1898	0.942028499	0.008010086
ENSG00000264278.1	ZNF236-DT	ENSG00000130511.16	SSBP4	-0.1888	0.928683597	0.004280343
ENSG00000264278.1	ZNF236-DT	ENSG00000158717.11	RNF166	-0.1801	0.961454389	0.025086275

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000264278.1	ZNF236-DT	ENSG00000130748.7	TMEM160	-0.1599	0.930141589	0.015406535
ENSG00000264278.1	ZNF236-DT	ENSG00000182853.12	VMO1	-0.1543	0.915808013	0.017873897
ENSG00000264278.1	ZNF236-DT	ENSG00000112787.13	FBRSL1	-0.1535	0.990859506	0.011815282
ENSG00000264278.1	ZNF236-DT	ENSG00000130522.6	JUND	-0.1531	0.93479618	0.012742334
ENSG00000264278.1	ZNF236-DT	ENSG00000180448.10	ARHGAP45	-0.1529	0.90547752	0.009494082
ENSG00000264278.1	ZNF236-DT	ENSG00000174021.11	GNG5	-0.1501	0.970851594	0.04392782
ENSG00000264278.1	ZNF236-DT	ENSG00000104903.5	LYL1	-0.1494	0.973206413	0.035667134
ENSG00000264278.1	ZNF236-DT	ENSG00000213445.10	SIPA1	-0.1464	0.962701442	0.009422944
ENSG00000264278.1	ZNF236-DT	ENSG00000012124.17	CD22	-0.1454	0.951669382	0.025925671
ENSG00000264278.1	ZNF236-DT	ENSG00000089820.16	ARHGAP4	-0.1414	0.915133871	0.002843481
ENSG00000264278.1	ZNF236-DT	ENSG00000081059.20	TCF7	-0.138	0.90161675	0.018665095
ENSG00000264278.1	ZNF236-DT	ENSG00000161847.14	RAVER1	-0.1322	0.982207619	0.036729363
ENSG00000264278.1	ZNF236-DT	ENSG00000121281.13	ADCY7	-0.1321	0.904195662	0.015944876
ENSG00000264278.1	ZNF236-DT	ENSG00000130479.11	MAP1S	-0.1282	0.985801164	0.018073953
ENSG00000264278.1	ZNF236-DT	ENSG00000100092.23	SH3BP1	-0.1148	0.94205237	0.009936942
ENSG00000264278.1	ZNF236-DT	ENSG00000043143.20	JADE2	-0.11	0.943466564	0.002245959
ENSG00000264278.1	ZNF236-DT	ENSG00000074660.16	SCARF1	-0.1079	0.909264646	0.01055204
ENSG00000264278.1	ZNF236-DT	ENSG00000162894.12	FCMR	-0.1066	0.906168992	0.006462324
ENSG00000264278.1	ZNF236-DT	ENSG00000100599.16	RIN3	-0.1009	0.962352456	0.002210911
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000100599.16	RIN3	-0.3044	0.965173852	0.002357175
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000130511.16	SSBP4	-0.2739	0.980079947	0.004728682
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000177989.13	ODF3B	-0.2425	0.990905498	0.008781722
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000081059.20	TCF7	-0.1863	0.957788116	0.020300551

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000130522.6	JUND	-0.1817	0.978347383	0.013007024
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000158717.11	RNF166	-0.1698	0.97431563	0.029206811
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000043143.20	JADE2	-0.1661	0.947242802	0.002505672
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000213445.10	SIPA1	-0.1533	0.968840888	0.009718527
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000111012.10	CYP27B1	-0.1452	0.902744532	0.043197999
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000130748.7	TMEM160	-0.145	0.974440087	0.017695198
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000178773.15	CPNE7	-0.1439	0.949471104	0.036678921
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000089820.16	ARHGAP4	-0.1386	0.960527523	0.003006362
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000105329.10	TGFB1	-0.1376	0.962176882	0.005262952
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000130479.11	MAP1S	-0.1371	0.968541612	0.019114906
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000161847.14	RAVER1	-0.1354	0.929374562	0.040699743
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000071246.11	VASH1	-0.1339	0.904680588	0.001114926
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000197540.8	GZMM	-0.1332	0.954193995	0.019473092
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000180448.10	ARHGAP45	-0.1326	0.935726474	0.009714215
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000104951.16	IL4I1	-0.1308	0.931843008	0.00768212
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000125910.6	S1PR4	-0.1301	0.925351256	0.007698262
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000112787.13	FBRSL1	-0.1279	0.977846586	0.012720659
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000012124.17	CD22	-0.1248	0.97817154	0.044275533
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000141664.10	ZCCHC2	-0.1244	0.931958829	0.041790052
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000104903.5	LYL1	-0.1243	0.95816459	0.042089139
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000162894.12	FCMR	-0.1237	0.966005606	0.00751657
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000175602.4	CCDC85B	-0.1228	0.978657712	0.009127608
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000182853.12	VMO1	-0.1225	0.932546387	0.033286475

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000183734.4	ASCL2	-0.1185	0.921277923	0.021012076
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000141933.9	TPGS1	-0.1184	0.962817019	0.046004114
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000177706.9	FAM20C	-0.1183	0.96856455	0.004437994
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000100092.23	SH3BP1	-0.1179	0.966699902	0.010752481
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000066336.12	SPI1	-0.1175	0.92992935	0.002969145
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000168477.19	TNXB	-0.1148	0.960933853	0.042250838
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000101986.12	ABCD1	-0.1147	0.924153011	0.002208932
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000160326.14	SLC2A6	-0.1147	0.912626065	0.00672381
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000168071.22	CCDC88B	-0.1147	0.931994963	0.01402685
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000131196.17	NFATC1	-0.1126	0.959867293	0.013598854
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000074660.16	SCARF1	-0.1122	0.917223131	0.015148268
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000173762.8	CD7	-0.1113	0.908291003	0.014876068
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000105963.15	ADAP1	-0.1105	0.911094893	0.02297603
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000198113.3	TOR4A	-0.1091	0.905141992	0.029499864
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000159753.14	CARMIL2	-0.1088	0.954425076	0.014109865
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000171700.14	RGS19	-0.1088	0.937894839	0.008270804
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000105122.13	RASAL3	-0.1087	0.947462618	0.01072211
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000167680.16	SEMA6B	-0.1086	0.94448507	0.008709
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000089639.11	GMIP	-0.1061	0.920491542	0.002080431
ENSG00000265148.6	TSPOAP1-AS1	ENSG00000138821.13	SLC39A8	-0.1056	0.936526444	0.01651027
ENSG00000265743.1	AC138207.5	ENSG00000139433.10	GLTP	-0.1813	0.927597427	0.002082947
ENSG00000265743.1	AC138207.5	ENSG00000011198.10	ABHD5	-0.134	0.942748472	0.012206213
ENSG00000265743.1	AC138207.5	ENSG00000166347.19	CYB5A	-0.1213	0.906415198	0.004869599

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000265743.1	AC138207.5	ENSG00000005469.12	CROT	-0.114	0.94057201	0.045230584
ENSG00000265743.1	AC138207.5	ENSG00000167703.15	SLC43A2	-0.1091	-0.917884125	0.000887378
ENSG00000265743.1	AC138207.5	ENSG00000181061.13	HIGD1A	-0.1012	0.973257019	0.031009085
ENSG00000268362.6	AC092279.1	ENSG00000069812.11	HES2	-0.1816	0.993855245	0.042198155
ENSG00000268362.6	AC092279.1	ENSG00000180758.12	GPR157	-0.1686	0.902797448	0.000641095
ENSG00000268362.6	AC092279.1	ENSG00000137747.16	TMPRSS13	-0.1458	0.914066209	0.003659707
ENSG00000268362.6	AC092279.1	ENSG00000115129.14	TP53I3	-0.1256	0.954720223	0.003149907
ENSG00000268362.6	AC092279.1	ENSG00000136002.19	ARHGEF4	-0.104	0.943772647	0.016830765
ENSG00000268362.6	AC092279.1	ENSG00000168453.15	HR	-0.1008	0.94579574	0.007304468
ENSG00000271133.5	AC004130.2	ENSG00000150787.8	PTS	-0.2083	0.977000564	0.034250121
ENSG00000271133.5	AC004130.2	ENSG00000181061.13	HIGD1A	-0.1576	0.974292139	0.020191691
ENSG00000271133.5	AC004130.2	ENSG00000125375.16	DMAC2L	-0.1218	0.975918856	0.035899061
ENSG00000271133.5	AC004130.2	ENSG00000011198.10	ABHD5	-0.1104	0.991740724	0.00922071
ENSG00000271133.5	AC004130.2	ENSG00000164919.11	COX6C	-0.1057	0.971541565	0.026998924
ENSG00000271133.5	AC004130.2	ENSG00000035115.22	SH3YL1	-0.1029	0.926572525	0.031975084
ENSG00000271133.5	AC004130.2	ENSG00000161970.15	RPL26	-0.1024	0.956654875	0.033028828
ENSG00000271133.5	AC004130.2	ENSG00000184860.10	SDR42E1	-0.1021	0.903444864	0.010975729
ENSG00000271781.1	AC026740.1	ENSG00000115687.14	PASK	-0.1556	0.917593387	0.002320854
ENSG00000271781.1	AC026740.1	ENSG00000198417.7	MT1F	-0.1317	0.979746987	0.02787629
ENSG00000271781.1	AC026740.1	ENSG00000109610.6	SOD3	-0.1268	0.938146966	0.006563467
ENSG00000271781.1	AC026740.1	ENSG00000161265.15	U2AF1L4	-0.1036	0.992608741	0.012664969
ENSG00000272021.1	AC008592.4	ENSG00000139433.10	GLTP	-0.2046	0.925909903	0.002003599
ENSG00000272021.1	AC008592.4	ENSG00000125375.16	DMAC2L	-0.1963	0.938918441	0.024552428

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000272021.1	AC008592.4	ENSG00000136828.19	RALGPS1	-0.1833	0.954827473	0.007857406
ENSG00000272021.1	AC008592.4	ENSG00000185269.12	NOTUM	-0.1729	0.925191006	0.024316934
ENSG00000272021.1	AC008592.4	ENSG00000267673.6	FDX2	-0.1695	0.980830564	0.021683599
ENSG00000272021.1	AC008592.4	ENSG00000181061.13	HIGD1A	-0.1577	0.953018554	0.015391397
ENSG00000272021.1	AC008592.4	ENSG00000136044.12	APPL2	-0.1524	0.942468087	0.002632949
ENSG00000272021.1	AC008592.4	ENSG00000116922.14	C1orf109	-0.1463	0.966338683	0.036045864
ENSG00000272021.1	AC008592.4	ENSG00000035115.22	SH3YL1	-0.1389	0.915731406	0.025970906
ENSG00000272021.1	AC008592.4	ENSG00000005469.12	CROT	-0.1314	0.945070196	0.01686271
ENSG00000272021.1	AC008592.4	ENSG00000167703.15	SLC43A2	-0.1296	-0.946458677	0.000867004
ENSG00000272021.1	AC008592.4	ENSG00000143546.10	S100A8	-0.1277	0.938591878	0.012030194
ENSG00000272021.1	AC008592.4	ENSG00000163082.10	SGPP2	-0.1137	0.973305067	0.000492918
ENSG00000272021.1	AC008592.4	ENSG00000107537.14	PHYH	-0.1121	0.928963737	0.001509512
ENSG00000272021.1	AC008592.4	ENSG00000137878.17	GCOM1	-0.1021	0.908465737	0.010465934
ENSG00000272502.1	AC104958.2	ENSG00000184922.14	FMNL1	-0.1499	0.950547535	0.000890419
ENSG00000272502.1	AC104958.2	ENSG00000068831.19	RASGRP2	-0.1411	0.943885193	0.00854437
ENSG00000272502.1	AC104958.2	ENSG00000130748.7	TMEM160	-0.1288	0.944554772	0.012089206
ENSG00000272502.1	AC104958.2	ENSG00000177989.13	ODF3B	-0.1282	0.927598895	0.006836087
ENSG00000272502.1	AC104958.2	ENSG00000130511.16	SSBP4	-0.128	0.971450115	0.003600441
ENSG00000272502.1	AC104958.2	ENSG00000213445.10	SIPA1	-0.1208	0.932959639	0.008947276
ENSG00000272502.1	AC104958.2	ENSG00000178773.15	CPNE7	-0.1203	0.980930389	0.008687956
ENSG00000272502.1	AC104958.2	ENSG00000196456.13	ZNF775	-0.1131	0.917168403	0.013664618
ENSG00000272502.1	AC104958.2	ENSG00000158717.11	RNF166	-0.113	0.92138174	0.019205029
ENSG00000272502.1	AC104958.2	ENSG00000196092.14	PAX5	-0.1106	0.969441591	0.025476177

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000272502.1	AC104958.2	ENSG00000089820.16	ARHGAP4	-0.1076	0.976812203	0.002586012
ENSG00000272502.1	AC104958.2	ENSG00000100599.16	RIN3	-0.1062	0.9151485	0.00198102
ENSG00000272502.1	AC104958.2	ENSG00000130522.6	JUND	-0.1038	0.940453385	0.012312519
ENSG00000272502.1	AC104958.2	ENSG00000066336.12	SPI1	-0.1021	0.977486742	0.002815266
ENSG00000272502.1	AC104958.2	ENSG00000021300.14	PLEKHB1	-0.1018	0.920724637	0.016844343
ENSG00000272502.1	AC104958.2	ENSG00000178719.17	GRINA	-0.101	0.987768303	0.001396406
ENSG00000273066.5	AL355987.4	ENSG00000177989.13	ODF3B	-0.2552	0.970763827	0.006846362
ENSG00000273066.5	AL355987.4	ENSG00000196092.14	PAX5	-0.2278	0.946462192	0.026762309
ENSG00000273066.5	AL355987.4	ENSG00000130511.16	SSBP4	-0.1883	0.99653495	0.00360693
ENSG00000273066.5	AL355987.4	ENSG00000213445.10	SIPA1	-0.1821	0.976637113	0.008950301
ENSG00000273066.5	AL355987.4	ENSG00000139725.8	RHOF	-0.1818	0.956902347	0.034810846
ENSG00000273066.5	AL355987.4	ENSG00000175602.4	CCDC85B	-0.1742	0.995076463	0.008031545
ENSG00000273066.5	AL355987.4	ENSG00000130748.7	TMEM160	-0.1731	0.995871077	0.012121128
ENSG00000273066.5	AL355987.4	ENSG00000130522.6	JUND	-0.1704	0.996481436	0.012315043
ENSG00000273066.5	AL355987.4	ENSG00000178773.15	CPNE7	-0.1681	0.991032846	0.008886738
ENSG00000273066.5	AL355987.4	ENSG00000196456.13	ZNF775	-0.1674	0.975064979	0.014208443
ENSG00000273066.5	AL355987.4	ENSG00000158717.11	RNF166	-0.167	0.987432777	0.019261063
ENSG00000273066.5	AL355987.4	ENSG00000089820.16	ARHGAP4	-0.1651	0.981939231	0.002588068
ENSG00000273066.5	AL355987.4	ENSG00000180448.10	ARHGAP45	-0.1635	0.97295341	0.009139411
ENSG00000273066.5	AL355987.4	ENSG00000160326.14	SLC2A6	-0.1608	0.952165178	0.004801772
ENSG00000273066.5	AL355987.4	ENSG00000100599.16	RIN3	-0.1552	0.947961471	0.001982986
ENSG00000273066.5	AL355987.4	ENSG00000101282.9	RSPO4	-0.1535	0.925395874	0.02251859
ENSG00000273066.5	AL355987.4	ENSG00000104894.12	CD37	-0.1529	0.943759053	0.002927401

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000273066.5	AL355987.4	ENSG00000182853.12	VMO1	-0.151	0.903247962	0.00483043
ENSG00000273066.5	AL355987.4	ENSG00000141933.9	TPGS1	-0.1487	0.992382419	0.024375793
ENSG00000273066.5	AL355987.4	ENSG00000178719.17	GRINA	-0.1474	0.921493219	0.001396631
ENSG00000273066.5	AL355987.4	ENSG00000131188.12	PRR7	-0.1471	0.950074647	0.046636513
ENSG00000273066.5	AL355987.4	ENSG00000089639.11	GMIP	-0.147	0.926042327	0.001780536
ENSG00000273066.5	AL355987.4	ENSG00000066336.12	SPI1	-0.1463	0.95882445	0.002815853
ENSG00000273066.5	AL355987.4	ENSG00000168071.22	CCDC88B	-0.1394	0.953763497	0.011963939
ENSG00000273066.5	AL355987.4	ENSG00000130479.11	MAP1S	-0.1365	0.954194494	0.016451495
ENSG00000273066.5	AL355987.4	ENSG00000111012.10	CYP27B1	-0.1361	0.909784353	0.013087107
ENSG00000273066.5	AL355987.4	ENSG00000186827.11	TNFRSF4	-0.1346	0.986574978	0.012099518
ENSG00000273066.5	AL355987.4	ENSG00000213638.6	ADAT3	-0.1336	0.971413051	0.014185718
ENSG00000273066.5	AL355987.4	ENSG00000043143.20	JADE2	-0.1329	0.930889345	0.00185768
ENSG00000273066.5	AL355987.4	ENSG00000104903.5	LYL1	-0.1326	0.966236948	0.026716372
ENSG00000273066.5	AL355987.4	ENSG00000081059.20	TCF7	-0.1315	0.942124278	0.016186193
ENSG00000273066.5	AL355987.4	ENSG00000105516.11	DBP	-0.1297	0.965491084	0.039048416
ENSG00000273066.5	AL355987.4	ENSG00000197540.8	GZMM	-0.125	0.987048776	0.015662371
ENSG00000273066.5	AL355987.4	ENSG00000105963.15	ADAP1	-0.1238	0.957856014	0.011101332
ENSG00000273066.5	AL355987.4	ENSG00000101439.9	CST3	-0.1237	0.980743553	0.004747196
ENSG00000273066.5	AL355987.4	ENSG00000104951.16	IL4I1	-0.1229	0.965145413	0.007124047
ENSG00000273066.5	AL355987.4	ENSG00000159753.14	CARMIL2	-0.1228	0.948361065	0.006631651
ENSG00000273066.5	AL355987.4	ENSG00000162894.12	FCMR	-0.1215	0.978773968	0.004961031
ENSG00000273066.5	AL355987.4	ENSG00000167984.18	NLRC3	-0.1207	0.92795994	0.038944407
ENSG00000273066.5	AL355987.4	ENSG00000100092.23	SH3BP1	-0.1195	0.969618821	0.008692203

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000273066.5	AL355987.4	ENSG00000177706.9	FAM20C	-0.1194	0.976864289	0.003797924
ENSG00000273066.5	AL355987.4	ENSG00000012124.17	CD22	-0.1189	0.956479587	0.008765923
ENSG00000273066.5	AL355987.4	ENSG00000125910.6	S1PR4	-0.1173	0.964785339	0.005475724
ENSG00000273066.5	AL355987.4	ENSG00000204475.10	NCR3	-0.1171	0.918962243	0.043230081
ENSG00000273066.5	AL355987.4	ENSG00000115085.13	ZAP70	-0.113	0.938417714	0.003836455
ENSG00000273066.5	AL355987.4	ENSG00000105329.10	TGFB1	-0.1116	0.948235276	0.005113638
ENSG00000273066.5	AL355987.4	ENSG00000101986.12	ABCD1	-0.1115	0.924275445	0.00150698
ENSG00000273066.5	AL355987.4	ENSG00000171700.14	RGS19	-0.1106	0.949517945	0.006315914
ENSG00000273066.5	AL355987.4	ENSG00000188322.7	SBK1	-0.1102	0.966601326	0.026479913
ENSG00000273066.5	AL355987.4	ENSG00000007129.18	CEACAM21	-0.1101	0.924159807	0.016226692
ENSG00000273066.5	AL355987.4	ENSG00000168477.19	TNXB	-0.1099	0.906525945	0.02148573
ENSG00000273066.5	AL355987.4	ENSG00000074660.16	SCARF1	-0.1088	0.913386335	0.005326215
ENSG00000273066.5	AL355987.4	ENSG00000183734.4	ASCL2	-0.1085	0.949631154	0.014709642
ENSG00000273066.5	AL355987.4	ENSG00000180096.12	SEPTIN1	-0.1083	0.906877298	0.002717632
ENSG00000273066.5	AL355987.4	ENSG00000010404.18	IDS	-0.1046	0.967277906	0.047073847
ENSG00000273066.5	AL355987.4	ENSG00000089351.14	GRAMD1A	-0.104	0.939096777	0.001603046
ENSG00000273066.5	AL355987.4	ENSG00000112787.13	FBRSL1	-0.1035	0.950612021	0.010427356
ENSG00000273066.5	AL355987.4	ENSG00000101084.18	RAB5IF	-0.1008	0.943763886	0.039136205
ENSG00000273066.5	AL355987.4	ENSG00000196371.3	FUT4	-0.1008	0.95731315	0.014888044
ENSG00000273669.1	AC015819.1	ENSG00000115687.14	PASK	-0.1203	0.906089771	0.007154526
ENSG00000273669.1	AC015819.1	ENSG00000161265.15	U2AF1L4	-0.1081	0.968341175	0.028976466
ENSG00000273669.1	AC015819.1	ENSG00000109610.6	SOD3	-0.107	0.949041517	0.006743131
ENSG00000273729.1	AC007686.3	ENSG00000068831.19	RASGRP2	-0.1771	0.958043077	0.010797195

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000273729.1	AC007686.3	ENSG00000109610.6	SOD3	-0.1525	0.940171553	0.006750149
ENSG00000273729.1	AC007686.3	ENSG00000115687.14	PASK	-0.1414	0.911039812	0.005530124
ENSG00000273729.1	AC007686.3	ENSG00000204525.16	HLA-C	-0.1351	0.908048301	0.000285733
ENSG00000273729.1	AC007686.3	ENSG00000021300.14	PLEKHB1	-0.1311	0.94735097	0.030795279
ENSG00000273729.1	AC007686.3	ENSG00000171130.18	ATP6V0E2	-0.1271	0.931986463	0.00316327
ENSG00000273729.1	AC007686.3	ENSG00000140511.12	HAPLN3	-0.1235	0.911679622	0.000514502
ENSG00000273729.1	AC007686.3	ENSG00000186891.14	TNFRSF18	-0.1227	0.943511568	0.002292546
ENSG00000273729.1	AC007686.3	ENSG00000138111.14	MFSD13A	-0.1129	0.97846484	0.00629403
ENSG00000273729.1	AC007686.3	ENSG00000167703.15	SLC43A2	-0.1089	0.908054075	0.000902758
ENSG00000273729.1	AC007686.3	ENSG00000008516.17	MMP25	-0.1055	0.97747858	0.008364124
ENSG00000273729.1	AC007686.3	ENSG00000184922.14	FMNL1	-0.1028	0.940080786	0.000909233
ENSG00000273729.1	AC007686.3	ENSG00000110448.11	CD5	-0.1009	0.970352791	0.002662401
ENSG00000273729.1	AC007686.3	ENSG00000101307.16	SIRPB1	-0.1002	0.981572493	0.009092608
ENSG00000275620.1	AL121827.2	ENSG00000069812.11	HES2	-0.1397	0.902178062	0.038661456
ENSG00000275620.1	AL121827.2	ENSG00000180155.20	LYNX1	-0.1307	0.990625939	0.018466476
ENSG00000275620.1	AL121827.2	ENSG00000064270.12	ATP2C2	-0.1281	0.957500507	0.035070777
ENSG00000275620.1	AL121827.2	ENSG00000143320.9	CRABP2	-0.12	0.918186038	0.015761257
ENSG00000275620.1	AL121827.2	ENSG00000121742.19	GJB6	-0.1148	0.958723302	0.0173907
ENSG00000275620.1	AL121827.2	ENSG00000154856.13	APCDD1	-0.1134	0.983048112	0.013570957
ENSG00000275620.1	AL121827.2	ENSG00000105088.8	OLFM2	-0.1078	0.972716793	0.045979062
ENSG00000275620.1	AL121827.2	ENSG00000092621.12	PHGDH	-0.1072	0.912021105	0.005509991
ENSG00000275620.1	AL121827.2	ENSG00000168453.15	HR	-0.1052	0.941974539	0.007095713
ENSG00000275620.1	AL121827.2	ENSG00000184330.12	S100A7A	-0.1021	0.97354765	0.045347498

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000275620.1	AL121827.2	ENSG00000100003.18	SEC14L2	-0.1007	0.934793241	0.014182786
ENSG00000275880.1	AL139385.1	ENSG00000180758.12	GPR157	-0.1849	0.950766965	0.000688605
ENSG00000275880.1	AL139385.1	ENSG00000165795.23	NDRG2	-0.1601	0.905675483	0.001263708
ENSG00000275880.1	AL139385.1	ENSG00000186891.14	TNFRSF18	-0.1256	-0.906480061	0.002662854
ENSG00000275880.1	AL139385.1	ENSG00000181392.17	SYNE4	-0.1239	0.981167265	0.010885304
ENSG00000275880.1	AL139385.1	ENSG00000116133.13	DHCR24	-0.1234	0.92740638	0.00057643
ENSG00000275880.1	AL139385.1	ENSG00000011638.10	TMEM159	-0.12	0.906683066	0.001312939
ENSG00000275880.1	AL139385.1	ENSG00000143320.9	CRABP2	-0.1195	0.919090884	0.016099392
ENSG00000275880.1	AL139385.1	ENSG00000109472.14	CPE	-0.1138	0.946059972	0.014985042
ENSG00000275880.1	AL139385.1	ENSG00000140511.12	HAPLN3	-0.1056	-0.900800072	0.000531207
ENSG00000275880.1	AL139385.1	ENSG00000123352.18	SPATS2	-0.1026	0.976307028	0.003904059
ENSG00000280693.2	SH3PXD2A-AS1	ENSG00000223573.7	TINCR	-0.2748	0.911477343	0.008604603
ENSG00000280693.2	SH3PXD2A-AS1	ENSG00000154856.13	APCDD1	-0.1417	0.90149614	0.017262376
ENSG00000286342.1	AC073210.3	ENSG00000089639.11	GMIP	-0.1714	-0.910832239	0.002378719
ENSG00000286342.1	AC073210.3	ENSG00000197084.5	LCE1C	-0.1618	0.933293772	0.009786461
ENSG00000286342.1	AC073210.3	ENSG00000145107.16	TM4SF19	-0.1362	0.904419379	0.047556823
ENSG00000286342.1	AC073210.3	ENSG00000188508.11	KRTDAP	-0.1105	0.976848723	0.002822516
ENSG00000286342.1	AC073210.3	ENSG00000167720.13	SRR	-0.1102	-0.927309725	0.018853189
ENSG00000286342.1	AC073210.3	ENSG00000166347.19	CYB5A	-0.1051	0.931891362	0.026671063
ENSG00000286342.1	AC073210.3	ENSG00000100385.14	IL2RB	-0.1008	-0.934609053	0.001192497
ENSG00000287091.1	AC009961.3	ENSG00000196092.14	PAX5	-0.2613	0.950260922	0.018494256
ENSG00000287091.1	AC009961.3	ENSG00000101084.18	RAB5IF	-0.1904	0.955676475	0.036614536
ENSG00000287091.1	AC009961.3	ENSG00000130511.16	SSBP4	-0.1863	0.983608678	0.003472809

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000287091.1	AC009961.3	ENSG00000089820.16	ARHGAP4	-0.1828	0.977313762	0.002534232
ENSG00000287091.1	AC009961.3	ENSG00000213445.10	SIPA1	-0.174	0.984280831	0.008847072
ENSG00000287091.1	AC009961.3	ENSG00000101439.9	CST3	-0.1575	0.957705122	0.004741254
ENSG00000287091.1	AC009961.3	ENSG00000177989.13	ODF3B	-0.1559	0.987594088	0.006611349
ENSG00000287091.1	AC009961.3	ENSG00000265681.7	RPL17	-0.1504	0.992582678	0.022290539
ENSG00000287091.1	AC009961.3	ENSG00000158717.11	RNF166	-0.1456	0.988275721	0.018161795
ENSG00000287091.1	AC009961.3	ENSG00000178719.17	GRINA	-0.1444	0.90609988	0.001388447
ENSG00000287091.1	AC009961.3	ENSG00000010404.18	IDS	-0.1391	0.980996418	0.035274554
ENSG00000287091.1	AC009961.3	ENSG00000188322.7	SBK1	-0.1378	0.955284944	0.022555928
ENSG00000287091.1	AC009961.3	ENSG00000101096.20	NFATC2	-0.1366	0.933942017	0.0147435
ENSG00000287091.1	AC009961.3	ENSG00000089639.11	GMIP	-0.1355	0.936639834	0.001742102
ENSG00000287091.1	AC009961.3	ENSG00000081059.20	TCF7	-0.1349	0.964134544	0.015678064
ENSG00000287091.1	AC009961.3	ENSG00000141664.10	ZCCHC2	-0.1345	0.953390988	0.008810274
ENSG00000287091.1	AC009961.3	ENSG00000177706.9	FAM20C	-0.1339	0.974549112	0.003715787
ENSG00000287091.1	AC009961.3	ENSG00000138821.13	SLC39A8	-0.1333	0.947804481	0.010411367
ENSG00000287091.1	AC009961.3	ENSG00000105122.13	RASAL3	-0.133	0.969773423	0.008982743
ENSG00000287091.1	AC009961.3	ENSG00000101986.12	ABCD1	-0.1287	0.936983545	0.001428882
ENSG00000287091.1	AC009961.3	ENSG00000178773.15	CPNE7	-0.1278	0.959970285	0.007239633
ENSG00000287091.1	AC009961.3	ENSG00000100599.16	RIN3	-0.1272	0.975684295	0.001935531
ENSG00000287091.1	AC009961.3	ENSG00000198113.3	TOR4A	-0.1261	0.939783234	0.024001084
ENSG00000287091.1	AC009961.3	ENSG00000125089.17	SH3TC1	-0.1233	0.901642628	0.003079086
ENSG00000287091.1	AC009961.3	ENSG00000173762.8	CD7	-0.1224	0.921231545	0.014111385
ENSG00000287091.1	AC009961.3	ENSG00000161847.14	RAVER1	-0.1222	0.94599897	0.029641599

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

(Continuação)

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000287091.1	AC009961.3	ENSG00000162894.12	FCMR	-0.1194	0.970354502	0.004681042
ENSG00000287091.1	AC009961.3	ENSG00000130522.6	JUND	-0.119	0.978703836	0.01222047
ENSG00000287091.1	AC009961.3	ENSG00000139725.8	RHOF	-0.1184	0.986099978	0.028826691
ENSG00000287091.1	AC009961.3	ENSG00000112787.13	FBRSL1	-0.1183	0.984814495	0.010139909
ENSG00000287091.1	AC009961.3	ENSG00000182853.12	VMO1	-0.1181	0.956438133	0.003637443
ENSG00000287091.1	AC009961.3	ENSG00000130479.11	MAP1S	-0.1178	0.983124319	0.016107331
ENSG00000287091.1	AC009961.3	ENSG00000115085.13	ZAP70	-0.1167	0.921885238	0.003710556
ENSG00000287091.1	AC009961.3	ENSG00000196456.13	ZNF775	-0.1158	0.962464517	0.010510174
ENSG00000287091.1	AC009961.3	ENSG00000152518.8	ZFP36L2	-0.1141	0.948237862	0.047252424
ENSG00000287091.1	AC009961.3	ENSG00000150594.7	ADRA2A	-0.1135	0.993648772	0.031795192
ENSG00000287091.1	AC009961.3	ENSG00000111012.10	CYP27B1	-0.1132	0.939804813	0.011016848
ENSG00000287091.1	AC009961.3	ENSG00000167680.16	SEMA6B	-0.1127	0.924242301	0.006725438
ENSG00000287091.1	AC009961.3	ENSG00000151651.16	ADAM8	-0.1122	0.905893825	0.009172522
ENSG00000287091.1	AC009961.3	ENSG00000168477.19	TNXB	-0.1119	0.93755251	0.019514742
ENSG00000287091.1	AC009961.3	ENSG00000136040.9	PLXNC1	-0.1105	0.917799442	0.022542951
ENSG00000287091.1	AC009961.3	ENSG00000160326.14	SLC2A6	-0.1104	0.93305369	0.004580823
ENSG00000287091.1	AC009961.3	ENSG00000074660.16	SCARF1	-0.1095	0.951040641	0.004596988
ENSG00000287091.1	AC009961.3	ENSG00000105329.10	TGFB1	-0.1069	0.970875196	0.005092922
ENSG00000287091.1	AC009961.3	ENSG00000105963.15	ADAP1	-0.1061	0.939930408	0.010018313
ENSG00000287091.1	AC009961.3	ENSG00000213638.6	ADAT3	-0.1061	0.979691398	0.010774634
ENSG00000287091.1	AC009961.3	ENSG00000152784.16	PRDM8	-0.1059	0.982352787	0.0312601
ENSG00000287091.1	AC009961.3	ENSG00000173868.11	PHOSPHO1	-0.1059	0.908346913	0.014268942
ENSG00000287091.1	AC009961.3	ENSG00000104894.12	CD37	-0.1038	0.909153047	0.002891024

S2 Table. LncRNA-mRNA *trans* interactions with potential of ligation according to LncTar.

LncRNA ID	LncRNA Name	mRNA ID	mRNA Name	ndG	Correlation	P-value
ENSG00000287091.1	AC009961.3	ENSG00000104903.5	LYL1	-0.1035	0.977071575	0.02504939
ENSG00000287091.1	AC009961.3	ENSG00000180448.10	ARHGAP45	-0.1035	0.962407754	0.009061172
ENSG00000287091.1	AC009961.3	ENSG00000131188.12	PRR7	-0.1031	0.991378091	0.033216296
ENSG00000287091.1	AC009961.3	ENSG00000159753.14	CARMIL2	-0.1031	0.977718183	0.005964948
ENSG00000287091.1	AC009961.3	ENSG00000176083.17	ZNF683	-0.1029	0.904287072	0.036818677
ENSG00000287091.1	AC009961.3	ENSG00000232434.2	AJM1	-0.1029	0.95394475	0.029017255
ENSG00000287091.1	AC009961.3	ENSG00000080603.17	SRCAP	-0.1014	0.924201818	0.004583223
ENSG00000287091.1	AC009961.3	ENSG00000130748.7	TMEM160	-0.1013	0.978634832	0.011493228
ENSG00000287091.1	AC009961.3	ENSG00000012124.17	CD22	-0.1007	0.976072329	0.006915141
ENSG00000287091.1	AC009961.3	ENSG00000196371.3	FUT4	-0.1007	0.9827898	0.009235826
ENSG00000287091.1	AC009961.3	ENSG00000183734.4	ASCL2	-0.1003	0.954349069	0.013989484
ENSG00000287126.1	AC108488.3	ENSG00000167664.8	TMIGD2	-0.1392	0.992210272	0.004289601
ENSG00000287126.1	AC108488.3	ENSG00000109472.14	CPE	-0.1341	-0.905544976	0.006526908
ENSG00000287126.1	AC108488.3	ENSG00000215790.7	SLC35E2A	-0.1306	-0.966401576	0.028603857
ENSG00000287853.1	AL031668.2	ENSG00000197084.5	LCE1C	-0.1494	0.973466646	0.004655814
ENSG00000287853.1	AL031668.2	ENSG00000139433.10	GLTP	-0.1445	0.953358818	0.002142887
ENSG00000287853.1	AL031668.2	ENSG00000188508.11	KRTDAP	-0.1084	0.946479548	0.002628277
ENSG00000287853.1	AL031668.2	ENSG00000070087.14	PFN2	-0.1072	0.960887657	0.039209425
ENSG00000288156.1	AC104530.1	ENSG00000068831.19	RASGRP2	-0.1662	0.909059138	0.027268441
ENSG00000288156.1	AC104530.1	ENSG00000109610.6	SOD3	-0.1528	0.968301454	0.007192965
ENSG00000288156.1	AC104530.1	ENSG00000158806.14	NPM2	-0.1168	0.920783372	0.020929798
ENSG00000288156.1	AC104530.1	ENSG00000055957.11	ITIH1	-0.1109	0.977700058	0.020726006

S3 Table. LncRNA-mRNA *cis* interactions according to FEELnc.

LncRNA ID	LncRNA Name	mRNA ID	mRNA name	Correlation	P-value	Distance	Location
ENSG00000273066.5	AL355987.4	ENSG00000232434.2	AJM1	0.958754885	0.034318312	34380	upstream

S4 Table. KEGG pathways for the top 10 differentially expressed lncRNAs based on interaction numbers.

(Continua)

KEGG name	mRNAs
Regulation of lipolysis in adipocytes	ABHD5,PRKG1,ADCY7
Cytokine-cytokine receptor interaction	IL20RA,TGFB1,TNFRSF4,BMP8A,TNFRSF18
Viral protein interaction with cytokine and cytokine receptor	IL20RA
PPAR signaling pathway	PLIN5,LPL,CD36,HMGCS1,ACSBG1,HMGCS2
Metabolic pathways	GATM,ELOVL3,PTS,GDA,SDHD,ELOVL4,CYP4F2,GSTM5,MOGAT2,MGST1,HMGCS1, SDR16C5,HSD17B2,GPLD1,ACSBG1,NDUFB3,AKR1C3,HMGCS2,ARG1,IDS,CYP27B1, PHOSPHO1,FUT4,IL4I1,ADCY7,DGAT2,HAL,ACAT2,ATP6V0E2,CERS3,SGPP2,ATP12A ,MGAT2
Glycine, serine and threonine metabolism	GATM
Fatty acid metabolism	ELOVL3,ELOVL4,ACSBG1,ACAT2
Fatty acid elongation	ELOVL3,ELOVL4
Biosynthesis of unsaturated fatty acids	ELOVL3,ELOVL4
Folate biosynthesis	PTS,AKR1C3
Ribosome	RPS27L,RSL24D1,MRPL13,RPL17,RPS3A,RPL34,RPL26,RPL9,RPL22L1
Coronavirus disease - COVID-19	RPS27L,RSL24D1,RPL17,RPS3A,RPL34,RPL26,RPL9,RPL22L1
IL-17 signaling pathway	S100A8,S100A7,JUND
Oxidative phosphorylation	SDHD,NDUFB3,ATP6V0E2,ATP12A
Thermogenesis	SDHD,PRKG1,NDUFB3,BMP8A,ADCY7
Chemical carcinogenesis - reactive oxygen species	SDHD,GSTM5,MGST1,NDUFB3,AKR1C3
Diabetic cardiomyopathy	SDHD,CD36,NDUFB3,TGFB1
Non-alcoholic fatty liver disease	SDHD,NDUFB3,TGFB1
cGMP-PKG signaling pathway	PRKG1,NFATC2,ADRA2A,NFATC1,ADCY7
Salivary secretion	PRKG1,CST3,ADCY7

S4 Table. KEGG pathways for the top 10 differentially expressed lncRNAs based on interaction numbers.

(Continuação)

KEGG name	mRNAs
Circadian entrainment	PRKG1,ADCY7,GNG5
Pathways in cancer	GSTM5,MGST1,TCF7,TGFB1,SPI1,ADCY7,LEF1,RASGRP2,GNG5
Hepatocellular carcinoma	GSTM5,MGST1,TCF7,TGFB1,LEF1
Glycerolipid metabolism	LPL,MOGAT2,DGAT2
Fat digestion and absorption	MOGAT2,CD36,DGAT2,ACAT2
Hematopoietic cell lineage	CD36,CD7,CD37,CD22,CD5
Terpenoid backbone biosynthesis	HMGCS1,HMGCS2,FNTB,ACAT2
Valine, leucine and isoleucine degradation	HMGCS1,HMGCS2,IL4I1,ACAT2
Butanoate metabolism	HMGCS1,HMGCS2,ACAT2
Ovarian steroidogenesis	HSD17B2,AKR1C3,ADCY7
FoxO signaling pathway	SGK2,TGFB1,S1PR4
Retrograde endocannabinoid	GABRE,NDUFB3,ADCY7,GNG5
GABAergic synapse	GABRE,ADCY7,GNG5
Morphine addiction	GABRE,ADCY7,GNG5
Cushing syndrome	KCNK2,TCF7,ADCY7,LEF1
Amoebiasis	SERPINB4,ARG1,TGFB1
Transcriptional misregulation in cancer	PAX5,LYL1,SPI1
Rap1 signaling pathway	SIPA1,ADCY7,EFNA4,RASGRP2
Human T-cell leukemia virus 1 infection	NFATC2,TGFB1,SPI1,NFATC1,ADCY7,HLA-C
Osteoclast differentiation	NFATC2,JUND,TGFB1,SPI1,NFATC1,CTSK,SIRPB1
Cellular senescence	NFATC2,ZFP36L2,TGFB1,NFATC1,HLA-C
Wnt signaling pathway	NFATC2,TCF7,RSPO4,NFATC1,LEF1
Th17 cell differentiation	NFATC2,ZAP70,TGFB1,NFATC1
Natural killer cell mediated cytotoxicity	NFATC2,ZAP70,NCR3,NFATC1,HLA-C
Kaposi sarcoma-associated herpesvirus infection	NFATC2,TCF7,NFATC1,LEF1,HLA-C,GNG5

S4 Table. KEGG pathways for the top 10 differentially expressed lncRNAs based on interaction numbers.

(Continuação)

KEGG name	mRNAs
Th1 and Th2 cell differentiation	NFATC2,ZAP70,NFATC1
Human cytomegalovirus infection	NFATC2,NFATC1,ADCY7,HLA-C,GNG5
B cell receptor signaling pathway	NFATC2,CD22,NFATC1
PD-L1 expression and PD-1 checkpoint pathway in cancer	NFATC2,ZAP70,NFATC1
Axon guidance	NFATC2,SEMA6B,PLXNC1,EFNA4
T cell receptor signaling pathway	NFATC2,ZAP70,NFATC1
Thyroid cancer	TCF7,LEF1
Colorectal cancer	TCF7,TGFB1,LEF1
Gastric cancer	TCF7,TGFB1,LEF1
Endometrial cancer	TCF7,LEF1
Basal cell carcinoma	TCF7,LEF1
Acute myeloid leukemia	TCF7,SPI1,LEF1
Hippo signaling pathway	TCF7,TGFB1,BMP8A,LEF1
Melanogenesis	TCF7,ADCY7,LEF1
Ras signaling pathway	RASAL3,ZAP70,EFNA4,RASGRP2,GNG5
Peroxisome	ABCD1,CROT,PHYH
Parathyroid hormone synthesis, secretion and action	JUND,CYP27B1,ADCY7,MMP25
MAPK signaling pathway	JUND,TGFB1,NFATC1,EFNA4,RASGRP2
NF-kappa B signaling pathway	ZAP70
Steroid biosynthesis	CYP27B1
Rheumatoid arthritis	TGFB1,CTSK,ATP6V0E2
TGF-beta signaling pathway	TGFB1,BMP8A
Glycosphingolipid biosynthesis – lacto and neolacto series	FUT4
Chemokine signaling pathway	ADCY7,RASGRP2,GNG5

S4 Table. KEGG pathways for the top 10 differentially expressed lncRNAs based on interaction numbers.

KEGG name	mRNAs
Sphingolipid metabolism	PSAPL1,CERS3,SGPP2
Type I diabetes mellitus	HLA-C

ANEXO A - Normas da Revista PLOS Neglected Tropical Diseases

Submission Guidelines

About the Journal

PLOS Neglected Tropical Diseases publishes original research articles of importance to the NTDs community and the wider health community. We will consider manuscripts of any length; we encourage the submission of both substantial full-length bodies of work and shorter manuscripts that report novel findings that might be based on a more limited range of experiments.

The writing style should be concise and accessible, avoiding jargon so that the paper is understandable for readers outside a specialty or those whose first language is not English. Editors will make suggestions for how to achieve this, as well as suggestions for cuts or additions that could be made to the article to strengthen the argument. Our aim is to make the editorial process rigorous and consistent, but not intrusive or overbearing. Authors are encouraged to use their own voice and to decide how best to present their ideas, results, and conclusions.

About the Journal

PLOS Neglected Tropical Diseases is committed to the highest ethical standards in medical research. Accordingly, we ask authors to provide specific information regarding ethical treatment of research participants, patient consent, patient privacy, protocols, authorship, and competing interests. We also ask that reports of certain specific types of studies adhere to generally accepted standards. Our requirements are based on the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, issued by the International Committee for Medical Journal Editors.

Related information for authors

- PLOS Writing Center
- Submission system
- Journal scope and publication criteria
- Getting started guide
- Guidelines for other article types
- Guidelines for revisions
- Publication fees

Style and Format

When you first submit to the journal, providing you include all the necessary information needed for editorial assessment and review, we will not ask you to make any formatting changes. During resubmission, we may ask you to meet formatting requirements.

File format	Manuscript files can be in the following formats: DOC, DOCX, RTF or PDF. Microsoft Word documents should not be locked or protected. LaTeX manuscripts must be submitted as PDFs. Read the LaTeX guidelines.
Length	Manuscripts can be any length. There are no restrictions on word count, number of figures, or amount of supporting information. We encourage you to present and discuss your findings concisely.
Font	Use a standard font size and any standard font, except for the font named "Symbol". To add symbols to the manuscript, use the Insert → Symbol function in your word processor or paste in the appropriate Unicode character.
Headings	Limit manuscript sections and sub-sections to 3 heading levels. Make sure heading levels are clearly indicated in the manuscript text.
Layout and spacing	Manuscript text should be double-spaced. Do not format text in multiple columns.
Page and line numbers	Include page numbers and line numbers in the manuscript file. Use continuous line numbers (do not restart the numbering on each page).
Tables	Insert tables immediately after the first paragraph in which they are cited.
Supporting Information	Upload Supporting Information (SI) files separately.
Footnotes	Footnotes are not permitted. If your manuscript contains footnotes, move the information into the main text or the reference list, depending on the content.
Language	Manuscripts must be submitted in English. You may submit translations of the manuscript or abstract as supporting information. Read the supporting information guidelines.
Abbreviations	Define abbreviations upon first appearance in the text. Do not use non-standard abbreviations unless they appear at least three times in the text. Keep abbreviations to a minimum.
Reference style	PLOS uses "Vancouver" style, as outlined in the ICMJE sample references. See reference formatting examples and additional instructions below.

Equations	We recommend using MathType for display and inline equations, as it will provide the most reliable outcome. If this is not possible, Equation Editor or Microsoft's Insert→Equation function is acceptable. Avoid using MathType, Equation Editor, or the Insert→Equation function to insert single variables (e.g., "$a^2 + b^2 = c^2$"), Greek or other symbols (e.g., β, Δ, or ′ [prime]), or mathematical operators (e.g., x, ≥, or ±) in running text. Wherever possible, insert single symbols as normal text with the correct Unicode (hex) values. Do not use MathType, Equation Editor, or the Insert→Equation function for only a portion of an equation. Rather, ensure that the entire equation is included. Equations should not contain a mix of different equation tools. Avoid "hybrid" inline or display equations, in which part is text and part is MathType, or part is MathType and part is Equation Editor.
Nomenclature	Use correct and established nomenclature wherever possible.

Units of measurement	Use SI units. If you do not use these exclusively, provide the SI value in parentheses after each value. Read more about SI units.
Drugs	Provide the Recommended International Non-Proprietary Name (rINN).
Species names	Write in italics (e.g., *Homo sapiens*). Write out in full the genus and species, both in the title of the manuscript and at the first mention of an organism in a paper. After first mention, the first letter of the genus name followed by the full species name may be used (e.g., *H. sapiens*).
Genes, mutations, genotypes, and alleles	Write in italics. Use the recommended name by consulting the appropriate genetic nomenclature database (e.g., HUGO for human genes). It is sometimes advisable to indicate the synonyms for the gene the first time it appears in the text. Gene prefixes such as those used for oncogenes or cellular localization should be shown in roman typeface (e.g., v-fes, c-MYC).
Allergens	The systematic allergen nomenclature of the World Health Organization/International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-committee should be used for manuscripts that include the description or use of allergenic proteins. For manuscripts describing new allergens, the systematic name of the allergen should be approved by the WHO/IUIS Allergen Nomenclature Sub-Committee prior to manuscript publication. Examples of the systematic allergen nomenclature can be found at the WHO/IUIS Allergen Nomenclature site.

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- Abstract
- Author Summary
- Introduction
- Methods
- Results
- Discussion
- Acknowledgments
- References
- Supporting information Captions

Uniformity in format facilitates the experience of readers and users of the journal. To provide flexibility, however, the Results and Discussion can be combined into one Results/Discussion section.

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Include a full title and a short title for the manuscript.

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Short title	70 characters	State the topic of the study	Cigarette smoke exposure and innate immunity SODIS and childhood diarrhoea

Titles should be written in sentence case (only the first word of the text, proper nouns, and genus names are capitalized). Avoid specialist abbreviations if possible. For clinical trials, systematic reviews, or meta-analyses, the subtitle should include the study design.

Author list

Authorship requirements

All authors must meet the criteria for authorship as outlined in the authorship policy. Those who contributed to the work but do not meet the criteria for authorship can be mentioned in the Acknowledgments. Read more about Acknowledgments.

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Enter author names on the title page of the manuscript and in the online submission system.

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Provide at minimum one contribution for each author in the submission system. Use the CRediT taxonomy to describe each contribution. Read the policy and the full list of roles.

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The introduction should put the focus of the manuscript into a broader context. As you compose the Introduction, think of readers who are not experts in this field. Include a brief review of the key literature. If there are relevant controversies or disagreements in the field, they should be mentioned so that a non-expert reader can delve into these issues further. The Introduction should conclude with a brief statement of the overall aim of the experiments and a comment about whether that aim was achieved.

Methods

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This section should also include a section with descriptions of any statistical methods employed. These should conform to the criteria outlined by the Uniform Requirements, as follows:

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For more information on how best to provide data, read our policy on data availability. PLOS does not accept references to "data not shown."

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Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."

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The Discussion should be concise and tightly argued. It should start with a brief summary of the main findings. It should include paragraphs on the generalizability, clinical relevance, strengths, and limitations of your study.

You may wish to discuss the following points also:

- How do the conclusions affect the existing knowledge in the field?
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Acknowledgments

Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution.

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PLOS journals publicly acknowledge the indispensable efforts of our editors and reviewers on an annual basis. To ensure equitable recognition and avoid any appearance of partiality, do not include editors or peer reviewers—named or unnamed—in the Acknowledgments.

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A reference management tool, EndNote, offers a current style file that can assist you with the formatting of your references. If you have problems with any reference management program, please contact the source company's technical support.

Source	Format
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Online articles	Huynen MMTE, Martens P, Hilderlink HBM. The health impacts of globalisation: a conceptual framework. Global Health. 2005;1: 14. Available from: http://www.globalizationandhealth.com/content/1/1/14

Books	Bates B. Bargaining for life: A social history of tuberculosis. 1st ed. Philadelphia: University of Pennsylvania Press; 1992.
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Deposited articles (preprints, e-prints, or arXiv)	Krick T, Shub DA, Verstraete N, Ferreiro DU, Alonso LG, Shub M, et al. Amino acid metabolism conflicts with protein diversity. arXiv:1403.3301v1 [Preprint]. 2014 [cited 2014 March 17]. Available from: https://128.84.21.199/abs/1403.3301v1 Kording KP, Mensh B. Ten simple rules for structuring papers. BioRxiv [Preprint]. 2016 bioRxiv 088278 [posted 2016 Nov 28; revised 2016 Dec 14; revised 2016 Dec 15; cited 2017 Feb 9]: [12 p.]. Available from: https://www.biorxiv.org/content/10.1101/088278v5 doi: 10.1101/088278
Published media (print or online newspapers and magazine articles)	Fountain H. For Already Vulnerable Penguins, Study Finds Climate Change Is Another Danger. The New York Times. 2014 Jan 29 [Cited 2014 March 17]. Available from: http://www.nytimes.com/2014/01/30/science/earth/climate-change-taking-toll-on-penguins-study-finds.html
New media (blogs, web sites, or other written works)	Allen L. Announcing PLOS Blogs. 2010 Sep 1 [cited 17 March 2014]. In: PLOS Blogs [Internet]. San Francisco: PLOS 2006 - . [about 2 screens]. Available from: http://blogs.plos.org/plos/2010/09/announcing-plos-blogs/.
Masters' theses or doctoral dissertations	Wells A. Exploring the development of the independent, electronic, scholarly journal. M.Sc. Thesis, The University of Sheffield. 1999. Available from: http://cumincad.scix.net/cgi-bin/works/Show?2e09
Databases and repositories (Figshare, arXiv)	Roberts SB. QPX Genome Browser Feature Tracks; 2013 [cited 2013 Oct 5]. Database: figshare [Internet]. Available from: http://figshare.com/articles/QPX_Genome_Browser_Feature_Tracks/701214
Multimedia (videos, movies, or TV shows)	Hitchcock A, producer and director. Rear Window [Film]; 1954. Los Angeles: MGM.

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- Chinese

Clinical trials

PLOS follows the World Health Organization’s (WHO) definition of a clinical trial:

A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes [...] Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc.

Registering Clinical Trials

All clinical trials submitted to PLOS journals must be entered in a publicly accessible registry approved by the WHO or ICMJE. See the list of approved registries.

PLOS journals consider prospective trial registration (that is, registration before participant enrollment has begun) to be best publication practice, as recommended by the ICMJE. Clinical trials that began to enroll participants before ICMJE recommendations took effect on July 1, 2005 may be retrospectively registered.

More information about trial registration, including the WHO definition of a clinical trial, is in the ICMJE FAQ.

PLOS Neglected Tropical Diseases is unlikely to publish clinical trials that are not prospectively registered. We recognize, however, that in rare cases late registration may occur for exceptional reasons that merit consideration. Authors seeking evaluation by *PLOS Neglected Tropical Diseases* of a non–prospectively registered clinical trial must provide a compelling reason for lack of prospective registration.

In addition, as for all PLOS journals, authors wishing to submit a clinical trial that was not publicly registered before participant enrollment began must register the trial retrospectively in a publicly accessible registry. They must also:

- Register all related clinical trials and confirm they have done so in the Methods section
- Explain in the Methods the specific reasons for failing to register before participant enrollment
- Confirm that future trials will be registered prospectively

PLOS journal editors may decline to further consider any clinical trial for which, in the editor's judgment, absence of prospective registration raises concerns of selective publication or selective reporting of research outcomes.

PLOS supports the public disclosure of all clinical trial results, as mandated, for example, by the 2007 FDA Amendments Act. Prior disclosure of results on a clinical trial registry site will not affect consideration.

Required Documentation

Clinical trial reports must adhere to the relevant reporting guidelines for their study design, such as CONSORT for randomized controlled trials, TREND for non-randomized trials, and other specialized guidelines as appropriate.

For all clinical trial submissions, authors must include the following:

- Registration details (reported in the Methods section and in the submission form)
- CONSORT checklist or relevant reporting guideline (uploaded as supporting information)
- CONSORT flow diagram (uploaded as Fig 1)
- Trial protocol (uploaded as supporting information)
- Details of prior approval for human subjects research by an institutional review board (IRB) or equivalent ethics committee(s)

The submission will not be considered if documentation is not provided. The checklist, flow diagram, and protocol will be published with the article if the manuscript is accepted.

The manuscript file must include the following information:

- An explanation of any deviation from the trial protocol
- Description of informed consent obtained from participants
- Any information on statistical methods or participants not indicated in the CONSORT documentation

Systematic reviews and meta-analyses

Submissions with systematic reviews and meta-analyses are considered research articles. Submit these manuscripts with the "Research Article" type in the submission system.

Reports of systematic reviews and meta-analyses must adhere to the PRISMA Statement or alternative guidelines appropriate to the study design, and include the completed checklist and flow diagram to accompany the main text. Authors must complete the appropriate reporting checklist not only with page references, but also with sufficient text excerpted from the manuscript to explain how they accomplished all applicable items.

Download blank templates of the checklist and flow diagram from the EQUATOR web site.

Abstracts should follow PRISMA for Abstracts, using the PLOS abstract format. Authors must also state within the Methods section of their paper whether a protocol exists for their systematic review, and if so, provide a copy of the protocol as supporting information.

The journal supports the prospective registration of systematic reviews. Authors whose systematic review was prospectively registered (e.g., in a registry such as PROSPERO) should provide the registry number in their abstract. Registry details and protocols will be made available to editors and reviewers, and included with the paper if the report is ultimately published.

Diagnostic studies

Reports of studies of diagnostic accuracy must adhere to the STARD requirements or alternative guidelines appropriate to the study design (see the EQUATOR web site) and include a completed checklist as supporting information. Authors must complete the appropriate reporting checklist not only with page references, but also with sufficient text excerpted from the manuscript to explain how they addressed all applicable items.

Observational studies

For observational studies, including case control, cohort, and cross-sectional studies, authors must adhere to the STROBE Statement or alternative guidelines appropriate to the study design (see the EQUATOR web site) and include a completed checklist as supporting information. Authors must complete the appropriate reporting checklist not only with page references, but also with sufficient text excerpted from the manuscript to explain how they addressed all applicable items.

For observational studies, authors are required to clearly specify (a) What specific hypotheses the researchers intended to test, and the analytical methods by which they planned to test them; (b) What analyses they actually performed; and (c) When reported analyses differ from those that were planned, authors must provide transparent explanations for differences that affect the reliability of the study's results.

If a prospective analysis plan (from the study's funding proposal, IRB or other ethics committee submission, study protocol, or other planning document written before analyzing the data) was used in designing an observational study, authors must include the relevant prospectively written document with the manuscript submission for access by editors and reviewers and eventual publication alongside the accepted paper. If no prospectively written document exists, authors should explain how and when they determined the analyses being reported.

Microarray experiments

Reports of microarray experiments must conform to the MIAME guidelines, and the data from the experiments must be deposited in a publicly accessible database.

Other Article Types

If you are submitting content other than a research article, read the guidelines for other article types.

You may be eligible for APC support

Many institutional partners globally have publishing agreements with PLOS to allow their corresponding authors to publish with reduced or no APCs. To determine if your corresponding author is eligible, please visit our institutional partners page to determine what kind of agreement your institution has with PLOS.

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