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Juliana Rodrigues Lara

Identificação de eventos moleculares associados à
reestenose coronariana

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista “Júlio de Mesquita Filho”, Campus de Botucatu, para obtenção do título de Doutor em Patologia.

Orientadora: Dra. Daisy Maria Fávero Salvadori
Coorientador: Dr. João Paulo de Castro Marcondes
Coorientadora: Dra. Mariana Gobbo Braz

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RESUMO

Atualmente, o procedimento mais utilizado para o tratamento das lesões coronarianas é a angioplastia com implante de *stent*. Embora existam vantagens com esse procedimento, a reestenose continua sendo um dos principais limitadores do sucesso terapêutico. Sabe-se que inflamação, com acúmulo de células mononucleares ativadas, pode contribuir para o desenvolvimento da reestenose. Assim, estratégias para a identificação de biomarcadores de risco e para a redução das taxas de reestenose representam desafios na área da cardiologia intervencionista. Desta forma, o presente estudo teve como objetivos a identificação de possíveis marcadores genéticos de risco (polimorfismo dos genes *MMP-2*, *MMP-3*, *MMP-9 -1562*, *MMP-9 Arg 279 Gln*, *CYP2C19*2*, *NOS3* e *IL-6*), bem como a avaliação de eventos moleculares e bioquímicos (lesões oxidativas no DNA, perfil de expressão gênica e de citocinas) que possam estar envolvidos no desenvolvimento da reestenose. Foram avaliados 330 indivíduos, 220 pacientes coronarianos com e sem reestenose após implante de *stent* e 110 indivíduos controles (sem implante de *stent* e com obstrução coronariana menor que 20%). Os resultados mostraram aumento significativo de danos no DNA de células do sangue periférico nos pacientes com reestenose *intra-stent*, mas nenhuma alteração nos níveis plasmáticos de citocinas (IL-1 β , IL-6, IL-8, IL-10, IL-12, TNF- α). Com relação aos polimorfismos gênicos, os dados mostraram que o alelo G do gene *MMP-9 (Arg279Gln)* foi mais frequente nos pacientes coronarianos com reestenose *intra-stent*. A análise de perfil de genes de células mononucleares do sangue periférico revelou alvos potenciais para inibição da reestenose *intra-stent*. Com relação aos pacientes com obstrução arterial < 20% (grupo controle) foram 493 (400 hiperexpressos e 93 hipoexpressos) e 21 (6 hiperexpressos e 15 hipoexpressos) transcritos diferencialmente expressos respectivamente em pacientes sem e com reestenose *intra-stent*. Entre os pacientes com e sem reestenose, foram 243 transcritos diferencialmente expressos (91 hiperexpressos e 152 hipoexpressos). A ontologia genética mostrou que nos pacientes com reestenose dentre os processos biológicos com maior número de genes diferencialmente expressos envolvidos estavam os

relacionados ao reparo do DNA, diferenciação de células T α e β , resposta celular à IL-4, produção de citocinas, regulação da transcrição, regulação do metabolismo lipídico, divisão celular, organização da matriz extracelular, migração de leucócitos, cicatrização de feridas, regulação positiva da angiogênese, coagulação sanguínea, regulação da apoptose de células endoteliais e formação de plaquetas. Concluindo, nossos resultados fornecem base para novas hipóteses e testes para o claro entendimento dos mecanismos de reestenose intra-stent e para novas estratégias de tratamento.

ABSTRACT

Currently, angioplasty is the most commonly procedure used for the treatment of flow limitation in coronary arteries. Nevertheless, in-stent restenosis continues to remain the principal reason for treatment failure after contemporary coronary stenting. It is known that inflammation, with the accumulation of activated mononuclear cells, may contribute to the development of restenosis. Therefore, strategies for the identification of risk biomarkers and for the reduction of restenosis rates are challenges in the field of interventional cardiology. The present study aimed to identify genetic markers associated to restenosis. DNA damage, gene expression profile and gene polymorphisms (*MMP-2*, *MMP-3*, *MMP-9 -1562*, *MMP-9 Arg 279 Gln*, *CYP2C19 * 2*, *NOS3* and *IL-6*) were evaluated. A total of 330 subjects, 220 coronary patients with or without restenosis after stent implantation, and 110 control subjects (without stent implantation and coronary obstruction of less than 20%) were invited to participate in this study. Results showed significant increase of DNA damage in peripheral blood cells of patients with intra-stent restenosis, and no alteration in the plasma cytokines concentration (IL-1 β , IL-6, IL-8, IL-10, IL-12, TNF- α). Regarding the gene polymorphisms, data showed that G allele of *MMP-9 (Arg279Gln)* was more frequent in coronary patients with intra-stent restenosis. In the gene profiling analysis of mononuclear cells from peripheral blood 243 probesets with differential expression were identified between patients with and without restenosis, and 21 and 493 between patients without stenting coronary and those with and without in stent restenosis, respectively. The genes identified have varied functions, including some related to cellular growth and metabolism, DNA repair, cytokine production, regulation of transcription, cell division, extracellular matrix organization, leukocyte migration, regulation of endothelial cell apoptosis, and platelet formation, such as the *MMP-9*, *NFAT5*, *REL*, *ATM*, *FOXO3* and *UTS2R* genes. Taken together, our results provide the basis for further specific functional hypothesis generation and testing of the mechanisms of in stent restenosis.

1.INTRODUÇÃO

1.1 Doenças cardiovasculares

As doenças cardiovasculares (DCVs) são responsáveis por altas taxas de morbidade e mortalidade principalmente em países desenvolvidos onde se estima cerca de 17,5 milhões de óbitos, o que representa 31% de todas as mortes (WHO 2016). Segundo dados da Sociedade Brasileira de Cardiologia, as DCVs são responsáveis por cerca de 349.938 óbitos por ano, atingindo cerca de 29% do total de mortes registradas em 2015 (SBC 2016). Em 2016, as DCVs causaram o dobro de mortes daquelas pelos vários tipos de câncer; 2,3 vezes mais do que as causadas por acidentes e violências; 3 vezes as por doenças respiratórias e 6,5 vezes as por infecções, incluindo a síndrome da imunodeficiência adquirida (AIDS) (SBC 2016). Estudos do Instituto Dante Pazzanese de Cardiologia, em São Paulo, mostraram que 60% das vítimas de DCVs são do sexo masculino, com idade de aproximadamente 56 anos, dados que colocam o Brasil entre os 10 países com maior índice de mortes por DCVs (Brasil 2014).

Dentre as DCVs, destacam-se as doenças coronarianas (DCs) resultantes da oclusão ou estreitamento das artérias coronárias devido à formação de placas ateroscleróticas. As DCs, responsáveis por cerca de 7,4 milhões de mortes por ano no Brasil (Brasil 2014; Katz et al. 2015; WHO 2016), estão associadas a um conjunto de fatores de risco, que inclui idade avançada, gênero, tabagismo, obesidade, hipertensão arterial, diabetes, fatores genéticos, hipercolesterolemia e sedentarismo (Thomas 2016; Guasch-Ferré et al. 2016).

A aterosclerose é um processo inflamatório crônico, multifatorial e progressivo, promovido, inicialmente, pela formação de estrias gordurosas na camada íntima das artérias, que são resultantes do acúmulo de lipoproteínas como a lipoproteína de baixa densidade (LDL ou “mau” colesterol) (McLaren et al. 2011). Na parede das artérias, as LDLs são oxidadas e desencadeiam resposta inflamatória que leva à síntese de citocinas pró-inflamatórias e quimiocinas (McLaren et al. 2011; Ramji & Davies 2015). Nesse processo ocorre o recrutamento de monócitos que, ao adentrarem a camada íntima, se diferenciam em macrófagos. Nesses, as citocinas alteram a expressão de genes relacionados à regulação do metabolismo e transporte de colesterol, levando-os a englobar o LDL oxidado e a contribuir para a formação das células espumosas que se acumulam na camada íntima da artéria formando uma lesão inicial que se matura e progride para a placa aterosclerótica (Chistiakov et al. 2015; Buckley & Ramji 2015). Durante a progressão da placa, as células espumosas podem entrar em apoptose ou necrose, liberando conteúdo lipídico e formando um núcleo necrótico. Ao final, macrófagos, células endoteliais e linfócitos T estimulam a migração de células musculares lisas da camada média para a íntima, levando à formação de uma capa fibrótica constituída de matriz extracelular (Figura 1). O balanço entre a formação dessa matriz, que confere estabilidade à placa, e a liberação de enzimas que a degradam devido a apoptose dos macrófagos, irá ser determinante para o processo de ruptura da placa, o qual provoca agregação plaquetária que pode levar à obstrução do fluxo sanguíneo na artéria, trombose, acidente vascular cerebral, infarto agudo do miocárdio (IAM) e, em alguns casos, ao óbito (Figura 2) (McLaren et al. 2011; Chistiakov et al. 2015; Tabas et al. 2015; Buckley & Ramji 2015; Moss & Ramji 2016).

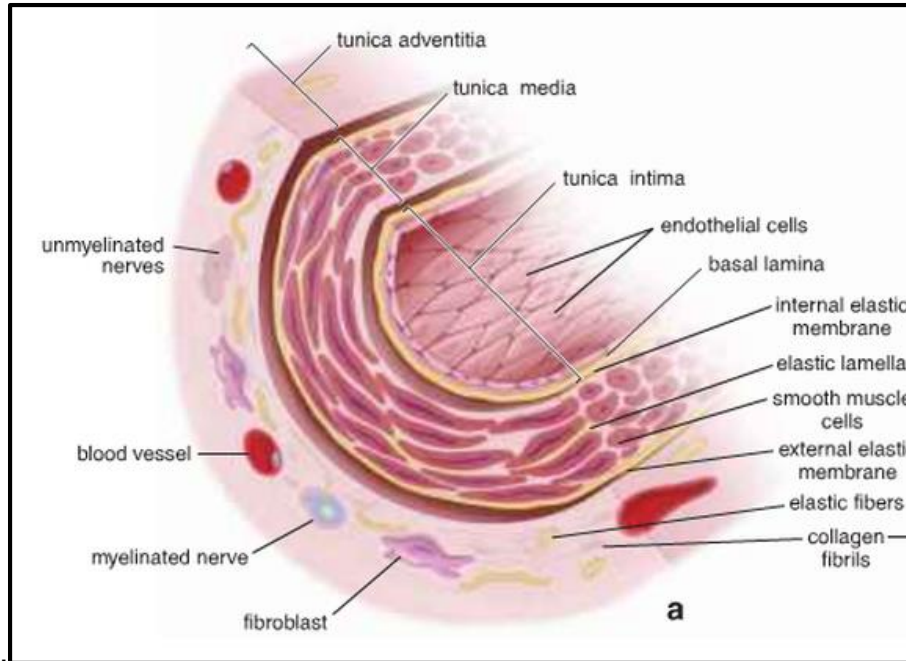


Figura 1: Esquema de corte transversal de uma artéria, evidenciando as camadas íntima, média e adventícia e seus componentes (Ross & Pawlina 2015).

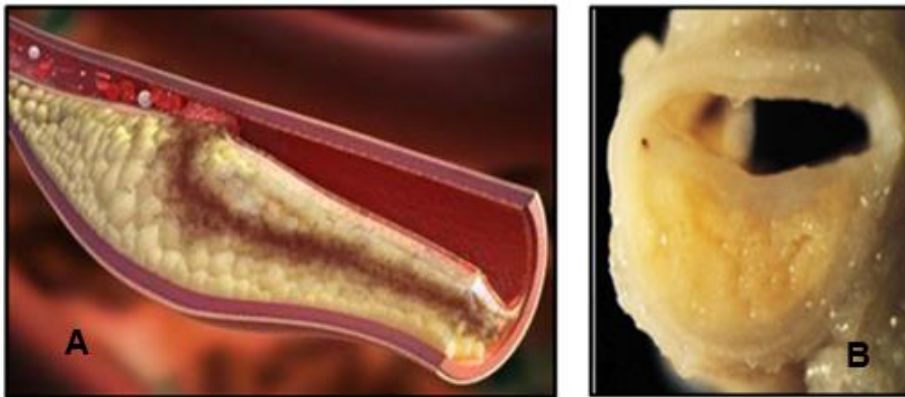


Figura 2. A e B Artérias coronárias com placa aterosclerótica, evidenciando o estreitamento do lúmen arterial. Fonte: *Google imagens* (placa aterosclerótica), 12/01/2016.

Os monócitos são células fagocitárias caracterizadas pela expressão de CD14 e CD16 (Ziegler-Heitbrock et al. 2010; Merino et al. 2011; Wise et al. 2016) e que produzem citocinas pro-inflamatórias (TNF, IL-1 β , IL-6, e IL-12p70) e anti-inflamatória

(IL-10) (Fokkema et al. 2003; Suárez-Santamaría et al. 2010; Yang et al. 2012). A ativação dos monócitos por estímulos inflamatórios provoca sua migração para locais de lesões teciduais e a diferenciação em macrófagos. O acúmulo exacerbado e prolongado de macrófagos nesses locais contribui para o desenvolvimento das doenças inflamatórias, como é o caso da aterosclerose (Yang et al. 2012; Wong et al. 2012; Hilgendorf et al. 2015).

Os monócitos têm papel relevante no processo de reestenose, pois a lesão mecânica local gerada pelo implante de *stent* na parede arterial promove sua ativação e recrutamento, que, juntamente com diversos outros fatores, levam à proliferação de células musculares lisas e consequente hiperplasia da camada neoíntima (Hokimoto et al. 2002; Martin & Boyle 2011).

Diversas citocinas pró-inflamatórias (TNF- α , INF- γ , IL1-B, IL-6, IL-8, IL-12) e anti-inflamatórias (IL-10, TGF- β) são secretadas por células endoteliais, macrófagos ativados e células Th1 (Liao et al. 2013), e desempenham papel crucial na progressão da placa aterogênica por modular a atividade, função e recrutamento dos componentes do sistema imunológico e de células vizinhas, como as musculares lisas (Libby et al. 2013). A interleucina IL-8, por exemplo, pode estar presente em qualquer tecido, sendo liberada durante processos infecciosos, isquemia, traumas e outras perturbações da homeostase. A IL-8 atrai por neutrófilos para a placa aterosclerótica, participando da sua progressão. Dessa forma, a IL-8 vem sendo considerada como possível marcador para a doença aterosclerótica periférica (Araújo et al. 2015).

Duas citocinas anti-inflamatórias, a IL-10 e o TGF- β , podem ter efeitos benéficos, diminuindo a progressão da placa aterosclerótica por meio da modulação da proliferação de células vasculares, da produção de colágeno, além de suprimir a ativação de células imunológicas como macrófagos e linfócitos (Saraiva & O'Garra

2010; Robertson et al. 2012). Adicionalmente, as citocinas IL-4, INF- γ e TNF- α podem inibir a expressão de IL-10 nas células B por meio da ativação do microRNA-19a (Ren et al. 2016).

6. CONCLUSÕES

Diante dos objetivos colocados, este estudo trouxe as seguintes conclusões:

- Pacientes com implante de stent apresentaram maior frequência do genótipo GG e do alelo G do polimorfismo *MMP-9 Arg279Gln (G>A)* e do genótipo CC do *MMP-9 (-1562 C>T)* podendo este estar relacionado a maior risco de doença coronariana;
- A avaliação dos níveis de citocinas inflamatórias não é considerada um bom marcador para a reestenose;
- Pacientes com reestenose *intra-stent* apresentam maiores níveis de danos no DNA de células mononucleares do sangue periférico do que aqueles sem reestenose;
- Pacientes com reestenose apresentam transcriptoma de células mononucleares do sangue periférico diferente daqueles sem reestenose;
- Pacientes com implante de *stent*, com ou sem reestenose, apresentam transcriptoma de células mononucleares do sangue periférico diferente daqueles com obstrução coronariana < 20%;
- Pacientes com reestenose apresentam transcriptoma mais próximo ao dos com obstrução coronariana < 20% que os sem reestenose.
- Hiperexpressão do gene *c-REL* pode estar relacionada ao processo de reestenose *intra-stent*

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