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UNIVERSIDADE ESTADUAL PAULISTA
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Instituto de Biociências
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ÁCIDOS GRAXOS DERIVADOS DE GELEIA REAL COMO FONTE DE INIBIDORES DE DESACETILASES DE HISTONAS HUMANAS: PERSPECTIVAS PARA A TERAPIA EPIGENÉTICA DO CÂNCER DE MAMA

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Palavras-chave: 10-HDA; Câncer de mama triplo negativo; Geleia real; HDAC; Terapia epigenética.

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Epígrafe

“Life is not easy for any of us. But what of that? We must have perseverance and above all confidence in ourselves. We must believe that we are gifted for something and that this thing must be attained”.

– Marie Curie

“A vida não é fácil para qualquer um de nós. Mas e aí? Devemos perseverar e acima de tudo, confiar em nós mesmos. Devemos crer que temos talento para alguma coisa e buscar alcançá-la”.

Tradução livre e recorte de:
https://www.mariecurie.org.uk/who/our-history/marie-curie-the-scientist

Resumo

O câncer consiste em um conjunto de doenças heterogêneas, responsáveis for notória mortalidade e morbidade no mundo, sendo a segunda maior causa de morte antes dos 70 anos de idade no Brasil. Particularmente, o câncer de mama é o segundo tipo mais incidente e o mais prevalente entre as mulheres (excluindo-se o câncer de pele do tipo não melanoma). O câncer de mama é uma doença complexa que envolve diversas alterações genéticas e epigenéticas. A desregulação epigenética tem um papel essencial no desenvolvimento e progressão tumoral, bem como na aquisição de resistência à quimioterapia. A terapia epigenética é uma ferramenta promissora para o tratamento ou sensibilização de tumores aos protocolos clássicos, melhorando sua eficiência. Dentre as diferentes estratégias para a terapia epigenética, as desacetilases de histonas (HDACs) são os alvos mais estudados em ensaios clínicos, geralmente em combinação com radioterapia ou quimioterapia citotóxica/genotóxica, imunoterapia, hormonioterapia ou direcionadas a alvos específicos. Dados prévios do nosso grupo de pesquisa indicam o potencial de que o ácido 10-hidróxi-2-decenóico (10-HDA), derivado da geleia real, seja um possível inibidor de desacetilases de histonas (HDACi). Neste contexto, o presente estudo foi delineado com o objetivo de identificar novos HDACi dentre os ácidos graxos derivados da geleia realO estudo será apresentado em duas partes (capítulos). O primeiro capítulo apresenta as bases teóricas da terapia epigenética, seu potencial uso no câncer de mana e a evidências sobre o 10-HDA como um potencial HDACi. O segundo capítulo corresponde à versão premilinar do manuscrito contendo: a análise de expressão diferencial determinada por RNA-Seq dos genes codificadores de *HDAC*s recuperados do projeto *The Cancer Genome Atla*s (TCGA Research Network: https://www.cancer.gov/tcga); a descrição dos ácidos graxos derivados da geleia real quanto suas características estruturais, físico-químicas e principais componentes compartilhados entre as moléculas (chamados de *cores*); *in silico screening* com os ácidos graxos derivados da geleia real por meio do método *docking* molecular para determinar as possíveis interações com a proteína humana modelo HDAC2, comparada com o inibidor conhecido, ácido hidroxâmico suberoilanilida (SAHA). Globalmente, os resultados indicam que os ácidos graxos da derivados da geleia real podem ocupar o domínio catalítico da HDACs de modo semelhante ao inibidor conhecido (SAHA) e indicam as melhores moléculas candidatas para os estudos futuros baseados em ensaios bioquímicos de inibição de HDACs, bem como ensaios funcionais *in vitro* para investigar o potencial efeito de ácidos graxos na sensibilização de linhagens celulares resistentes à quimioterápicos comumente utilizados na prática oncológica.

Palavras-chave: 10-HDA; Câncer de mama triplo negativo; Geleia real; HDAC; Terapia epigenética.

Abstract

Cancer consists of a heterogenous group of diseases, responsible for notorious mortality and morbidity worldwide, considered the second main cause of death before 70 years old in Brazil. Particularly, breast cancer is one of the most incidents and more prevalent among women (excluding non-melanoma skin cancer). Breast cancer is a complex disease that involves several genetic and epigenetic alterations. The epigenetic dysregulation has an essential role in tumor development and progression, as well as chemotherapy resistance acquisition, therefore epigenetic therapy of cancer is promising tool for treatment or sensitization of tumors to the classical therapeutic protocols, increasing efficacy of response. In the different possible strategies for epigenetic therapy of cancer, the histone deacetylases (HDACs) are the most studied targets in clinical trials, usually combined with radiotherapy or cytotoxic/genotoxic chemotherapy, immunotherapy, hormonal therapy or targeted therapies. Previous data of our research group indicates the potential of the 10-hydroxy-2-decenoic acid (10-HDA), derived from royal jelly, as a possible new HDAC inhibitor (HDACi). This present work is composed of two parts (chapters). The first is an introduction to the theorical basis of epigenetic therapy of breast cancer and its possible use in breast cancer, the current evidence regarding 10-HDA as a potential HDACi. The second chapter is the preliminary version of the manuscript that is yet to be finished and submitted, with our preliminary data: differential expression analysis (RNAseq data) of HDAC coding genes in human cancers from *The Cancer Genome Atlas* (TCGA Research Network: https://www.cancer.gov/tcga); structural and physicochemical description of royal jelly derived fatty acids and their core structures; *in silico screening* with the fatty acids using the *molecular docking* method to determinate the possible interactions with human HDAC2 model, with a well-stablished inhibitor, suberoylanilide hydroxamic acid (SAHA). Overall, the results show that the royal jelly derived fatty acids might occupy the catalytic domain of HDACs, similarly to the known inhibitor (SAHA) and suggest candidate molecules for future assays based on biochemical inhibition of HDACs, as well as functional assay in vitro in order to investigate the potential effects of royal jelly derived fatty acids in sensitization of breast cancer cell lines resistant to chemotherapeutical agents routinely used in oncological practice.

Keywords: 10-HDA; triple negative breast câncer; royal jelly; HDAC; epigenetic therapy.

Summary

3. Conclusions

By using *in silico* approaches, the present study contributed to the scientific literature with new insights in drug development and discovery from products of natural origin. Overall, the findings suggest that fatty acids derived from royal jelly can inhibit human HDACs.

Among the differentially expressed genes encoding HDACs, there is a trend of the ubiquitous HDACs (class I) to be up-regulated in most cancers. *HDAC2* gene is one of most frequently overexpressed in human cancer, including breast cancer.

Fatty acids derived from royal jelly are very similar to the 10-HDA, its major and unique fatty acid, which suggests that they may have similar biological functions in royal jelly, notably considering the analysis of core structures that indicated three key clusters: 3-hydroxydecanoic acid and Methyl 3-hydroxydecanoate in the first; Trans-10-acetoxydec-2-enoic acid and 10-hydroxy-2-decenoic acid in the second; and Octanoic acid and 2-decene-1,10-dioic acid in the third cluster. .

Using this information, it was demonstrated that these fatty acids might interact with the catalytic domain of human HDAC2, similar to suberoylanilide hydroxamic acid (SAHA), a well-known HDACi. The aforementioned data strengths the hypothesis of an additive effect of these fatty acids in royal jelly.

These findings support the design of future experimental approaches devoted to validating the inhibitory activity of fatty acids on HDACs and the potential use of this chemical compounds in pre-clinical studies for the identification of new drugs for epigenetic therapy.

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5. Conclusions

Royal jelly is a promising source of bioactive molecules for biomedical interest. Specifically, its fatty acids such as the 10-HDA and other similar molecules may be useful for new histone deacetylase inhibitors design. Our *in silico* data suggests that 10-HDA could interact with human HDAC2 and that it is a potential target for human carcinomas since it is up-regulated in various tumor types.

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