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“Julio de Mesquita Filho”

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POTENCIAL TERAPÊUTICO DO ADIPORON E SEUS EFEITOS SOBRE A TRANSIÇÃO EPITÉLIO-MESÊNQUIMA EM CULTURA DE CÂNCER DE PRÓSTATA

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Dissertação apresentada ao Instituto de Biociências, Campus de Botucatu, UNESP, para obtenção do título de Mestre no Programa de Pós-Graduação em Biologia Geral e Aplicada, Área de concentração em Biologia Celular, Estrutural e Funcional.

Prof. Dr. Sergio Luis Felisbino

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RESUMO PARA SOCIEDADE

O câncer de próstata é um dos tipos de câncer mais comuns entre os homens e, em muitos casos, é silencioso, pode se desenvolver por anos sem causar sintomas. O problema é que, quando a doença se torna agressiva, as células cancerosas passam a se mover e invadir outros tecidos do corpo. Para chamar atenção para essa realidade, surgiu o Novembro Azul, uma campanha mundial dedicada à prevenção e ao diagnóstico precoce do câncer de próstata. Durante esse mês, reforça-se a importância de os homens cuidarem da saúde, realizarem exames e discutirem o tema com mais abertura.

Esse processo de disseminação das células do câncer, chamado metástase, ocorre quando células deixam de funcionar como células fixas e estáveis e passam a se mover pelo corpo; assim, elas conseguem se espalhar e causar novos tumores em outros órgãos.

Nos últimos anos, pesquisadores descobriram que uma molécula chamada adiponectina, produzida naturalmente pela gordura do corpo, pode ter efeitos protetores contra o câncer. Porém, nem todos produzem adiponectina em quantidades suficientes, especialmente pessoas com obesidade, condição associada ao aumento do risco de vários tipos de câncer. Pensando nisso, cientistas desenvolveram o AdipoRon, uma molécula sintética que imita a ação da adiponectina.

Neste projeto, estudamos se o AdipoRon pode diminuir a capacidade de invasão e agressividade das células de câncer de próstata cultivadas em laboratório. Em outras palavras, queremos descobrir se essa substância é capaz de fazer com que essas células parem de se mover e se espalhar. Se isso se confirmar, o AdipoRon pode se tornar uma nova opção de medicamento para ajudar a controlar o avanço do câncer, oferecendo tratamentos mais eficazes e com menos efeitos colaterais. Ao entender como o AdipoRon age dentro das células, damos um passo importante para desenvolver novas formas de prevenir e tratar o câncer de próstata, beneficiando a saúde e a qualidade de vida de milhares de homens no futuro.

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LISTA DE ABREVIATURAS

AMPK – Proteína quinase ativada por monofosfato de adenosina

APN – Adiponectina

ADR - AdipoRon

AR – Receptor de andrógeno

CaP (ou PCa) – Câncer de próstata

CPRC – Câncer de próstata resistente à castração

DHT – Dihidrotestosterona

EMT – Transição epitélio-mesênquima

fAg – Adiponectina de comprimento total

gAd – Adiponectina globular

KLKs - Calicreínas

PIA - Atrofia inflamatória proliferativa

PIN – Prostatic intraepithelial neoplasia

PSA - Antígeno prostático específico

PPAR – Receptor ativado por proliferadores de peroxissoma

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RESUMO

O câncer de próstata (CaP) é uma das neoplasias mais prevalentes entre homens e representa uma importante causa de mortalidade em nível global. A progressão tumoral e o desenvolvimento de fenótipos mais agressivos estão associados a múltiplas alterações moleculares, incluindo alterações no metabolismo celular. Nesse contexto, evidências epidemiológicas indicam que a obesidade está relacionada a um pior prognóstico do CaP, sugerindo que adipocinas e vias metabólicas desempenham papel relevante na agressividade tumoral. A adiponectina (APN), uma adipocina com propriedades anti-inflamatórias e antitumorais, destaca-se como um possível elo entre alterações metabólicas e progressão do CaP. Seus efeitos são mediados principalmente pelos receptores AdipoR1 e AdipoR2, os quais podem ser ativados farmacologicamente pelo agonista sintético AdipoRon. Apesar do potencial terapêutico já descrito do AdipoRon em outros tipos de câncer, seus efeitos no CaP ainda não haviam sido investigados. Este estudo buscou avaliar o papel da sinalização da APN na progressão do CaP e investigar os efeitos do AdipoRon sobre o processo de transição epitélio–mesênquima (EMT). Ao integrar os efeitos metabólicos e reprodutivos da APN com seu potencial antitumoral, este trabalho pretendeu elucidar novos mecanismos que conectam metabolismo, regulação hormonal e progressão do CaP. Os resultados demonstraram que o tratamento com AdipoRon levou à modulação significativa da atividade das metaloproteinases de matriz (MMPs), particularmente as envolvidas na degradação da matriz extracelular, concomitantemente com o aumento da expressão e/ou atividade de seus inibidores endógenos, os TIMPs. Esse balanço favorável entre MMPs e TIMPs resultou em uma redução do potencial invasivo das células tumorais de próstata. Além disso, a ativação da via da APN mostrou-se capaz de interferir em marcadores associados à EMT, sugerindo um papel direto dessa sinalização na manutenção de um fenótipo menos agressivo. Em conjunto, esses achados indicam que a ativação dos receptores de APN por AdipoRon exerce efeitos antitumorais relevantes no CaP, apontando essa via como uma promissora estratégia terapêutica. Os resultados também contribuem para a identificação de potenciais biomarcadores de progressão tumoral e podem auxiliar na estratificação de risco e no desenvolvimento de novas abordagens para o tratamento do CaP avançado.

Palavras-chave: adiponectina, obesidade, AdipoRon, MMP, caderinas, transição epitélio-mesênquima.

ABSTRACT

Prostate cancer (PCa) is one of the most prevalent neoplasms among men and represents a significant cause of mortality globally. Tumor progression and the development of more aggressive phenotypes are associated with multiple molecular alterations, including changes in cellular metabolism. In this context, epidemiological evidence indicates that obesity is related to a worse PCa prognosis, suggesting that adipokines and metabolic pathways play a relevant role in tumor aggressiveness. Adiponectin (APN), an adipokine with anti-inflammatory and antitumor properties, is a potential link between metabolic alterations and PCa progression. Its effects are mainly mediated by AdipoR1 and AdipoR2 receptors, which can be pharmacologically activated by the synthetic agonist AdipoRon. Despite the already described therapeutic potential of AdipoRon in other types of cancer, its effects on PCa had not yet been investigated. This study aimed to evaluate the role of APN signaling in prostate cancer progression and investigate the effects of AdipoRon on the epithelial-mesenchymal transition (EMT) process. By integrating the metabolic and reproductive effects of APN with its antitumor potential, this work sought to elucidate new mechanisms connecting metabolism, hormonal regulation, and prostate cancer progression. The results demonstrated that treatment with AdipoRon led to significant modulation of matrix metalloproteinase (MMP) activity, particularly those involved in extracellular matrix degradation, concomitantly with increased expression and/or activity of their endogenous inhibitors, TIMPs. This favorable balance between MMPs and TIMPs resulted in a reduction in the invasive potential of prostate tumor cells. Furthermore, activation of the APN pathway proved capable of interfering with markers associated with EMT, suggesting a direct role of this signaling in maintaining a less aggressive phenotype. Taken together, these findings indicate that the activation of APN receptors by AdipoRon exerts relevant antitumor effects in PCa, pointing to this pathway as a promising therapeutic strategy. The results also contribute to the identification of potential biomarkers of tumor progression and may aid in risk stratification and the development of new approaches for the treatment of advanced PCa.

Keywords: adiponectin, obesity, AdipoRon, MMP, Cadherins, epithelial-mesenchymal transition.

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1. ENUNCIADO DA PROBLEMÁTICA

1.1. Próstata

A próstata humana é um pequeno órgão localizado imediatamente abaixo da bexiga, envolvendo a parte inicial da uretra e situado anterior ao reto (Fig. 1). Anatomicamente, a próstata é dividida em três zonas histológicas: central, de transição e periférica. A zona central circunda os ductos ejaculatórios, enquanto que a zona de transição está próxima à uretra. A zona periférica envolve a região externa da próstata distalmente, constituindo a maior parte do tecido prostático, sendo o local de origem da maioria dos cânceres de próstata [1-5]. Histologicamente, a glândula prostática é composta por alvéolos e ductos inseridos em um estroma fibromuscular, que sustenta o epitélio secretor e mantém o microambiente adequado para sua função [1].

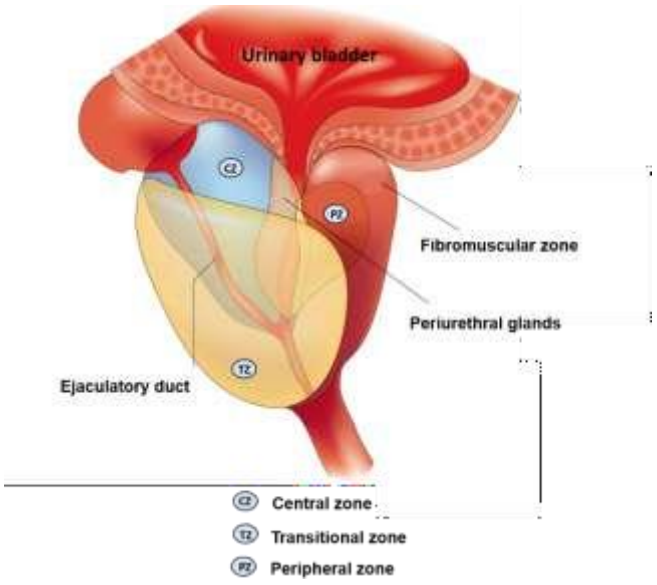

Figura 1. Anatomia da próstata humana. Adaptado de Verze, P. et al., 2016 [1].

A próstata é a principal glândula acessória do sistema reprodutor masculino, responsável pela produção de um fluido levemente ácido (pH 6,4–6,8), que compõe cerca de 15–30% do sêmen. Essa secreção fornece energia, estabiliza e protege os espermatozoides, favorecendo a fertilidade [6]. O líquido prostático contém diversos fatores bioativos, como enzimas, íons e citocinas, que modulam a atividade e a secreção de proteínas pelas glândulas seminais e bulbouretrais. Dentre eles, destacam-se as calicreínas teciduais (KLKs), semenogelinas [1], citrato (metabólito intermediário do ciclo de Krebs) [7] e zinco (Zn^{2+}), armazenado ativamente no citoplasma das células

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