UNIVERSIDADE FEDERAL DE UBERLÂNDIA
INSTITUTO DE BIOTECNOLOGIA
PÓS-GRADUAÇÃO EM GENÉTICA E BIOQUÍMICA

Sinalização de Anexina A1: Papel das Vias De EGFR E IL-6 nos Cânceres de Próstata e Mama

Aluna: Sara Teixeira Soares Mota

Orientador: Drª. Thaise Gonçalves de Araújo

Co-Orientador: Drª. Lara Vecchi

UBERLÂNDIA – MG

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Tese apresentada à Universidade Federal de Uberlândia como parte dos requisitos para obtenção do Título de Doutora em Genética e Bioquímica (Área Genética)

UBERLÂNDIA – MG

2021

UNIVERSIDADE FEDERAL DE UBERLÂNDIA
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ATA DE DEFESA - PÓS-GRADUAÇÃO

Programa de Pós-Graduação em:	Genética e Bioquímica				
Defesa de:	Doutorado Acadêmico - 02/2021 - PPGGB.				
Data:	Quatro de novembro de dois mil e vinte e um	Hora de início:	08:30h	Hora de encerramento:	13:00
Matrícula do Discente:	11723GBI009				
Nome do Discente:	Sara Teixeira Soares Mota				
Título do Trabalho:	Sinalização de Anexina A1: papéis das vias de EGFR e IL-6 nos cânceres de próstata e mama.				
Área de concentração:	Genética				
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Aos quatro dias do mês de novembro de dois mil e vinte e um, às 08:30 horas, reuniu-se via web conferência pela Plataforma *Microsoft Teams*, em conformidade com a Portaria nº 36, de 19 de março de 2020 da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – CAPES e Resolução de nº 06/2020 do Conselho de Pesquisa e Pós-graduação pela Universidade Federal de Uberlândia, a Banca Examinadora, designada pelo Colegiado do Programa de Pós-graduação em Genética e Bioquímica, assim composta: Profª. Drª. Tatiana Martins Tilli, Profª. Drª. Adriana Freitas Neves, Profª. Drª. Fernanda de Assis Araújo, Profª. Drª. Vivian Alonso Goulart e Profª. Drª. Thaise Gonçalves de Araújo, orientadora da candidata e demais convidados. Iniciando os trabalhos a presidente da mesa, Profª. Drª. Thaise Gonçalves de Araújo, apresentou a Comissão Examinadora e a candidata, agradeceu a presença do público, e concedeu à Discente a palavra para a exposição do seu trabalho. A duração da apresentação da Discente e o tempo de arguição e resposta foram conforme as normas do Programa de Pós-graduação em Genética e Bioquímica. A seguir a senhora presidente concedeu a palavra, pela ordem sucessivamente, aos examinadores, que passaram a arguir a candidata. Ultimada a arguição, que se desenvolveu dentro dos termos regimentais, a Banca, em sessão secreta, atribuiu os conceitos finais. Em face do resultado obtido, a Banca Examinadora considerou a candidata:

APROVADA.

Esta defesa de Tese de Doutorado é parte dos requisitos necessários à obtenção do título de Doutor. O competente diploma será expedido após cumprimento dos demais requisitos, conforme as normas do Programa, a legislação pertinente e a regulamentação interna da UFU. Nada mais havendo a tratar foram

encerrados os trabalhos. Foi lavrada a presente ata que após lida e achada conforme foi assinada pela Banca Examinadora.

Documento assinado eletronicamente por **Thaise Gonçalves de Araújo**, **Presidente**, em 04/11/2021, às 13:12, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do Decreto nº 8.539, de 8 de outubro de 2015.

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COMISSÃO EXAMINADORA

Presidente: Profa. Drª. Thaise Gonçalves de Araújo

Examinadores: Profa. Drª. Vivian Alonso Goulart
Profa. Drª. Fernanda de Assis Araújo
Profa. Drª. Adriana Freitas Neves
Profa. Drª. Tatiana Martins Tilli

Data da defesa:

As sugestões da Comissão Examinadora e as Normas PPGGB para o formato da Tese foram contempladas.

_____

Orientador

"Por isso mesmo, empenhem-se para acrescentar à sua fé a virtude; à virtude o conhecimento; ao conhecimento o domínio próprio; ao domínio próprio a perseverança; à perseverança a piedade; à piedade a fraternidade; e à fraternidade o amor."

2 Pedro 1:5-7.

Dedicatória

A Deus.

A gente sonha Deus realiza!

A todos que me ajudaram ao longo desta caminhada.

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SUMÁRIO

CAPÍTULO III

APRESENTAÇÃO

A Anexina A1 (AnxA1) é uma proteína de 37 KDa que se liga a fosfolipídios de membrana de maneira cálcio-dependente, sendo responsável por regular a inflamação, a organização de membranas celulares e o tráfico vesicular. AnxA1 é expressa principalmente no citoplasma, onde apresenta uma atividade anti-inflamatória. Já no núcleo está envolvida em regular a transcrição e, portanto, o funcionamento gênico. AnxA1 também pode ser clivada proteolicamente gerando um fragmento de 33-KDa e liberando seu peptídeo clivado N-terminal, que é biologicamente ativo. Tanto o peptídeo quanto a proteína de comprimento total podem ser secretados para o meio extracelular, onde são capazes de ativar Receptores de Peptídeos Formilados (FPRs), desencadeando, assim uma sinalização autócrina.

O eixo de sinalização autócrina AnxA1/FPR1 está envolvida nas propriedades pró-invasivas e pró-tumorais, principalmente de tumores em estágios mais avançados, como o câncer de mama triplo negativo (CMTN) e o câncer de próstata resistente à castração (CRPC). AnxA1 desempenha papéis relevantes na transformação maligna, ativando oncogenes e inativando genes supressores de tumor, induzindo a proliferação e invasão celulares e a formação de metástases. Por isso, investigar a via sinalização da AnxA1, bem com a interação com outras moléculas nos diversos tipos de tumores, se mostra imprescindível para elucidar as particularidades dessa proteína e, assim, desenvolver novas estratégias de diagnóstico e terapêuticas para as diferentes neoplasias malignas.

Em tumores, a Anxa1 desempenha atividade pró-inflamatória, induzindo um microambiente tumoral (TME) favorável com a promoção do crescimento e circulação de células malignas. Portanto, no Capítulo I, revisamos o papel da AnxA1 no estabelecimento do microambiente tumoral, com foco nas atividades imunossupressora e imunomoduladora. Primeiramente, descrevemos como células cancerosas suprimem as atividades do sistema imunológico, favorecendo a malignidade e a disseminação do câncer. Em seguida, apresentamos as principais características do TME e que a presença de algumas células imunológicas em sua composição cria um ambiente altamente imunossupressor, o que favorece o crescimento e a progressão do tumor. Retratamos a estrutura e características da

Anxa1, bem como os seus papeis na transformação maligna. Por fim, evidenciamos como a AnxA1 promove a supressão tumoral pela interação com o receptor do fator de crescimento epidérmico (EGFR), desencadeando um mecanismo de escape imunológico pelas células do câncer.

No segundo capítulo, mostramos que a AnxA1 ativa uma sinalização autócrina em células CRPC por meio do FPR1. Além disso, no CRPC, observamos que a sinalização autócrina de AnxA1 promove a localização nuclear no EGFR. Já foi descrito previamente que, uma vez no núcleo, EGFR é associado à progressão do câncer de próstata para o fenótipo resistente à castração. Quando inibimos o FPR1 utilizando Ciclsoporina H, a localização nuclear do EGFR e sua sinalização a jusante nas linhagens CRPC foram bloqueadas. Sugerimos, então, que a inibição da sinalização autócrina de AnxA1 e, consequentemente, da localização nuclear de EGFR pode ser uma estratégia relevante para o tratamento de CRPC

No último Capítulo, demonstramos uma interação entre as vias de sinalização de AnxA1/FPR1 e da Interleucina-6 (IL-6) e STAT3 (Fator de transcrição ativado por tirosinas quinases 3) no CMTN. Os nossos resultados mostraram que nas linhagens de CMTN, MDA-MB-231 e MDA-MB-157, a cascata de sinalização de IL-6 modula a ativação do eixo autócrino AnxA1/FPR1. Ao tratar camundongos fêmeas atímicas transplantadas com células MDA-MB-231 com Tocilizumabe, um anticorpo monoclonal humanizado que atua bloqueando os receptores de IL-6, observamos a redução do crescimento do tumor e a inibição da formação de metástases. Por último, mostramos que as vias IL-6 /STAT3 e AnxA1/FPR1 influenciam o TME, alterando a motilidade de fibroblastos. Sugerimos que a inibição de IL-6 pode ser usada como uma possível intervenção terapêutica e/ou uma nova terapia adjuvante para melhorar o resultado clínico de pacientes com CMTN ao bloquear a sinalização autócrina de AnxA1, retardando a progressão tumoral.

Por fim, demostramos que a AnxA1 estimula um microambiente tumoral favorável o que leva o escape imunológico pelas células do câncer. E em tumores de próstata mais agressivos, como CRPC, a via de sinalização autócrina da AnxA1 e FPR1 promove a localização nuclear de EGFR, e que esta localização desempenha um papel importante na sobrevivência celular e agressividade das células CRPC. Já em tumores de mama triplo negativos a via de IL-6 mostrou-se um mecanismo compensatório da sinalização de do eixo AnxA1 e FPR1 e essas

vias além de apresentarem um papel importante na agressividade do CMTN, também influenciam a TME, reduzindo a motilidade de fibroblastos. Portanto, este trabalho contribuiu de forma eficaz para a comunidade científica demostrando que o Anexina A1 desempenha diferentes papeis na progressão tumoral e que estudos mais aprofundados sobre essa molécula, e, em especial na via de sinalização autócrina AnxA1/FPR1, mostram se relevantes para uma maior compreensão dos tumores mais agressivos, bem como, possíveis estratégias terapêuticas.

Palavras-chave: Anexina A1, câncer de mama, câncer de próstata, microambiente tumoral, EGFR, IL-6, STAT3, ciclosporina e Tocilizumab.

Capítulo 1

Annexin A1 as a regulator of immune response in cancer

cells

MDPI

Review

Annexin A1 as a Regulator of Immune Response in Cancer

Thaise Gonçalves Araújo [1,2], Sara Teixeira Soares Mota [1,2], Helen Soares Valença Ferreira [1], Matheus Alves Ribeiro [1], Luiz Ricardo Goulart [2] and Lara Vecchi [2,*]

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Abstract: Annexin A1 is a 37 kDa phospholipid-binding protein that is expressed in many tissues and cell types, including leukocytes, lymphocytes and epithelial cells. Although Annexin A1 has been extensively studied for its anti-inflammatory activity, it has been shown that, in the cancer context, its activity switches from anti-inflammatory to pro-inflammatory. Remarkably, Annexin A1 shows pro-invasive and pro-tumoral properties in several cancers either by eliciting autocrine signaling in cancer cells or by inducing a favorable tumor microenvironment. Indeed, the signaling of the *N*-terminal peptide of AnxA1 has been described to promote the switching of macrophages to the pro-tumoral M2 phenotype. Moreover, AnxA1 has been described to prevent the induction of antigen-specific cytotoxic T cell response and to play an essential role in the induction of regulatory T lymphocytes. In this way, Annexin A1 inhibits the anti-tumor immunity and supports the formation of an immunosuppressed tumor microenvironment that promotes tumor growth and metastasis. For these reasons, in this review we aim to describe the role of Annexin A1 in the establishment of the tumor microenvironment, focusing on the immunosuppressive and immunomodulatory activities of Annexin A1 and on its interaction with the epidermal growth factor receptor.

Keywords: Annexin A1; tumor microenvironment; immune-suppression; cancer aggressiveness

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1. Introduction

Neoplastic transformation and progression encompass multiple unknown or poorly described events. In this context, Hanahan and Weinberg proposed different hallmarks that, despite being interrelated, define the principles of tumorigenesis. These hallmarks include the resistance to cell death mechanisms, uncontrolled proliferation, induction of angiogenesis, invasion potential, metastasis formation and immune escape [1]. Cancer cells acquire these hallmarks by modifying the extracellular matrix (ECM) and modulating the behavior of different cell types that surround the tumor. In this way, cancer cells create a unique environment, called the tumor microenvironment (TME), that strongly favors malignancy and cancer dissemination [2]. Unfortunately, the appearance of metastasis profoundly worsens the prognoses of patients, since no efficient therapies are available [3]. It is therefore essential to study the factors that are involved in the establishment of the TME in order to design new therapeutic strategies that could help to avoid cancer spreading and manage metastatic cancer patients. Of particular interest is the understanding of how cancer cells create a TME that favors immune evasion. In this context, it is important to unravel the immunomodulatory role of the protein Annexin A1 (AnxA1), which is the purpose of this review.

2. Anticancer Immune Response and Cancer Immune Escape

The immune system recognizes antigens expressed on the surface of transformed cells, leading to their destruction, thus hampering tumor progression. Remarkably, both

Treg	regulatory T cell
Trp	tryptophane
VCAM 1	vascular cell adhesion molecule 1
VEGF	vascular endothelial growth factor

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Capítulo 2

Annexin A1 promotes the nuclear localization of the epidermal growth factor receptor in castration-resistant prostate cancer

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Annexin A1 promotes the nuclear localization of the epidermal growth factor receptor in castration-resistant prostate cancer

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ABSTRACT

Epidermal growth factor receptor is a cancer driver whose nuclear localization has been associated with the progression of prostate cancer to the castration-resistant phenotype. Previous reports indicated a functional interaction between this receptor and the protein Annexin A1, which has also been associated with aggressive tumors. The molecular pathogenesis of castration-resistant prostate cancer remains largely unresolved, and herein we have demonstrated the correlation between the expression levels and localization of the epidermal growth factor receptor and Annexin A1 in prostate cancer samples and cell lines. Interestingly, a higher expression of both proteins was detected in castration-resistant prostate cancer cell lines and the strongest correlation was seen at the nuclear level. We verified that Annexin A1 interacts with the epidermal growth factor receptor, and by using prostate cancer cell lines knocked down for Annexin A1, we succeeded in demonstrating that Annexin A1 promotes the nuclear localization of epidermal growth factor receptor. Finally, we showed that Annexin A1 activates an autocrine signaling in castration-resistant prostate cells through the formyl peptide receptor 1. The inhibition of such signaling by Cyclosporin H inhibits the nuclear localization of epidermal growth factor receptor and its downstream signaling. The present work sheds light on the functional interaction between nuclear epidermal growth factor receptor and nuclear Annexin A1 in castration-resistant prostate cancer. Therefore, strategies to inhibit the nuclear localization of epidermal growth factor receptor through the suppression of the Annexin A1 autocrine loop could represent an important intervention strategy for castration-resistant prostate cancer.

1. Introduction

Prostate cancer (PCa) represents the second most common type of cancer in men and the second leading cause of cancer death among males in the USA and Brazil (Rawla, 2019). In 2018, 1,276,106 new cases of PCa worldwide were reported (Bray et al., 2018). It is well-known that PCa is a highly heterogeneous disease whose subtypes are poorly understood, so far (Kaffenberger and Barbieri, 2016). Patients

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Capítulo 3

Interleukin-6 signaling in triple negative breast cancer cells elicits the Annexin A1/Formyl peptide receptor 1 axis and af-fects the tumor microenvironment

cells

MDPI

Article

Interleukin-6 signaling in triple negative breast cancer cells elicits the Annexin A1/Formyl peptide receptor 1 axis and affects the tumor microenvironment

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Abstract: Annexin A1 (AnxA1) is a pleiotropic protein that exerts essential roles in breast cancer (BC) growth and aggressiveness. In our previous work, we described the autocrine signaling of AnxA1 through Formyl Peptide Receptor 1 (FPR1) in the triple-negative (TN) BC cell line, MDA-MB-231. Here we aimed to describe the interaction between the AnxA1/FPR1 and the Interleukin-6 (IL-6) signaling pathways and their role in the tumor microenvironment (TME). First, we demonstrated that AnxA1 and IL-6 expression levels are correlated in BC tissue samples. In three TNBC cell lines, overexpression of both AnxA1 and IL-6 was also identified. Next, we inhibited FPR1, the IL-6 receptor and STAT3 in both MDA-MB-231 and MDA-MB-157 cells. The FPR1 inhibition led to increased levels of IL-6 and secreted AnxA1 in both cell lines. On the other side, inhibition of the IL-6 receptor or STAT3 led to the impairment of AnxA1 secretion, suggesting the essential role of the IL-6 signaling cascade in the activation of the AnxA1/FPR1 autocrine axis. Finally, we described the interaction between IL-6 and the AnxA1/FPR1 pathways and their role on the TME by analyzing the effect of supernatants derived from MDA-MB-231 and MDA-MB-157 cells under inhibition of FPR1 or IL-6 signaling on fibroblast cell motility.

Keywords: Annexin A1, autocrine signaling, Breast cancer, Formyl Peptide Receptor, IL-6, STAT3;

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1. Introduction

Breast cancer (BC) is the most common cancer worldwide being a major cause of morbidity and mortality in women [1, 2]. The expression of Estrogen Receptor (ER) and Progesterone Receptor (PR) - that are collectively named hormone receptors (HR) -, Human Epidermal Growth Factor Receptor 2 (HER2) and of the proliferation marker, Ki67, defines BC subtypes which are categorized into: Lumina A (HR+, HER2-), Luminal B (HR+, HER2+ or HR+, HER2-; Ki67 high), HER2-enriched (HR-, HER2+), and Triple-Negative (TN: HR-, HER2-). The majority of TNBCs belongs to the basal-like subtype and displays a highly aggressive phenotype with poorer overall survival and high relapse

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