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Instituto de Biociências de Botucatu - Unesp

CARACTERIZAÇÃO DO TRANSCRITOMA CODIFICADOR DA METÁSTASE CEREBRAL DE CÂNCER DE PULMÃO

VANESSA DAS GRAÇAS PEREIRA DE SOUZA

BOTUCATU – SP

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CANDIDATA: VANESSA DAS GRAÇAS PEREIRA DE SOUZA

ORIENTADORA: PROFª DRª PATRICIA P. REIS

Tese apresentada ao Instituto de Biociências, Câmpus de Botucatu, UNESP, para obtenção do título de Doutora no Programa de Pós-Graduação em Ciências Biológicas (Genética).

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ATA DA DEFESA PÚBLICA DA TESE DE DOUTORADO DE VANESSA DAS GRAÇAS PEREIRA DE SOUZA, DISCENTE DO PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS BIOLÓGICAS (GENÉTICA), DO INSTITUTO DE BIOCIÊNCIAS - CÂMPUS DE BOTUCATU.

Aos 21 dias do mês de fevereiro do ano de 2024, às 09:00 horas, no(a) Unidade de Pesquisa Experimental (UNIPEX), Botucatu, SP., realizou-se a defesa de TESE DE DOUTORADO de VANESSA DAS GRAÇAS PEREIRA DE SOUZA, intitulada **Caracterização do transcritoma codificador da metástase cerebral de câncer de pulmão**. A Comissão Examinadora foi constituida pelos seguintes membros: Profa. Dra. PATRICIA PINTOR DOS REIS (Orientador(a) - Participação Presencial) do(a) Departamento de Cirurgia e Ortopedia / Faculdade de Medicina de Botucatu Unesp, Profa. Dra. ERICA NISHIDA HASIMOTO (Participação Presencial) do(a) Departamento de Cirurgia e Ortopedia / Faculdade de Medicina de Botucatu - Unesp, Profa. Dra. SARAH SANTILONI CURY (Participação Presencial) do(a) Departamento de Biologia Estrutural e Funcional / Instituto de Biociências de Botucatu - UNESP, Profa. Dra. LETÍCIA FERRO LEAL (Participação Virtual) do(a) Centro de Pesquisa em Oncologia Molecular / Hospital de Câncer de Barretos, Profa. Dra. MÁRCIA MARIA CHIQUITELLI MARQUES SILVEIRA (Participação Virtual) do(a) Centro de Pesquisa em Oncologia Molecular / Hospital de Câncer de Barretos. Após a exposição pela doutoranda e arguição pelos membros da Comissão Examinadora que participaram do ato, de forma presencial e/ou virtual, a discente recebeu o conceito final: APROVADA . Nada mais havendo, foi lavrada a presente ata, que após lida e aprovada, foi assinada pelo(a) Presidente(a) da Comissão Examinadora.

Profa. Dra. PATRICIA PINTOR DOS REIS

Dedicatória

Dedico este trabalho à minha família, aos amigos que sempre estiveram ao meu lado, e especialmente aos pacientes e seus familiares, cujas generosas contribuições de amostras foram fundamentais para a realização deste estudo. A colaboração de vocês foi essencial para o avanço da pesquisa nas metástases cerebrais de câncer de pulmão. Muito obrigada por tornar isso possível.

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Epígrafe

"Ninguém educa ninguém, ninguém se educa a si mesmo, os homens se educam entre si, mediatizados pelo mundo."

Paulo Freire

Sumário

Resumo

O câncer de pulmão é uma das fontes mais frequentes de metástases cerebrais (MC). Para câncer de pulmão de células não pequenas (CPCNP), cerca de 7 a 10% dos pacientes apresentam MC no momento do diagnóstico, e 20 a 40% dos pacientes desenvolvem MC durante o curso da doença. Apesar das estratégias de tratamento atualmente disponíveis, o prognóstico dos pacientes permanece desfavorável, com uma sobrevida média de 15 meses para pacientes tratados. Diante desse cenário desafiador, torna-se evidente a necessidade de estudos moleculares em larga escala, visando identificar biomarcadores clinicamente aplicáveis para melhorar o desfecho da doença e o prognóstico dos pacientes. Este trabalho oferece uma visão abrangente do estado da arte no estudo das MC abordando eventos-chave na formação da MC, a influência do microambiente tumoral e determinantes moleculares da progressão. Além disso, a integração de dados de sequenciamento de RNA total (RNA-Seq), microarray e sequenciamento de RNA de célula única (scRNA-Seq), juntamente com ferramentas avançadas de bioinformática, foi realizada com o objetivo de identificar os mecanismos subjacentes à formação da MC no adenocarcinoma de pulmão, o subtipo histológico mais incidente de CPCNP. A combinação de RNA-Seq e microarray identificou um conjunto de 20 genes associados a MC do adenocarcinoma pulmonar, principalmente relacionados a vias do sistema imune, destacando a importância do sistema imunológico na formação da MC. Adicionalmente, o uso do scRNA-seq permitiu elucidar o microambiente tumoral da MC e de tumores primários de diferentes estadios de progressão, revelando diferenças na infiltração de células imunológicas. Células T foram identificadas como predominantes em tumores primários, enquanto as microglias predominaram nas MC. A análise de enriquecimento de vias revelou que as microglias apresentam uma marcada upregulação da via de sinalização COX, associada à regulação da resposta inflamatória, indicando um potencial papel da inflamação no desenvolvimento das MC. A infiltração de células supressoras mieloides derivadas de polimorfonucleares (PMN-MDSCs) em MC reforça a importância da infiltração de células imunossupressoras na inflamação crônica associada a essas metástases. A interação entre microglias ativadas, células dendríticas CD163+ CD14+, Th17 e PMN-MDSCs sugere um ambiente inflamado imunossupressor nas MC, com implicações na progressão do tumor. A pesquisa também destaca a interligação entre a sinalização JAK-STAT, interleucina-23 (IL-23) e a produção de interleucina 17 (IL-17), mediadas por microglia ativada, células dendríticas CD163+ CD14+ e Th17, evidenciando uma complexa rede molecular e imunológica na formação das MC. Em resumo, este estudo propõe uma abordagem abrangente, integrando dados de sequenciamento de RNA e ferramentas computacionais para compreender as MC de adenocarcinoma de pulmão. A identificação de biomarcadores, a compreensão das vias moleculares e a análise do microambiente tumoral fornecem *insights* valiosos para o desenvolvimento de terapias mais eficazes e direcionadas, abrindo caminho para avanços significativos no tratamento das metástases cerebrais do câncer de pulmão.

Palavras-chave: Adenocarcinoma; Câncer de pulmão; Microambiente tumoral; Transcriptoma.

Abstract

Lung cancer is one of the most frequent sources of brain metastases (BM). For non-small cell lung cancer (NSCLC), approximately 7 to 10% of patients present with BM at the time of diagnosis, and 20 to 40% of patients develop BM during the course of the disease. Despite currently available treatment strategies, the prognosis for patients remains unfavorable, with an average survival of 15 months for treated patients. Faced with this challenging scenario, the need for large-scale molecular studies becomes evident, aiming to identify clinically applicable biomarkers to improve disease outcomes and patient prognosis. This study provides a comprehensive overview of the state of the art in BM studies, addressing key events in BM formation, the influence of the tumor microenvironment, and molecular determinants of progression. Additionally, the integration of total RNA sequencing (RNA-Seq), microarray, and single-cell RNA sequencing (scRNA-Seq) data, along with advanced bioinformatics tools, was performed to identify the underlying mechanisms of BM formation in lung adenocarcinoma, the most incident histological subtype of NSCLC. The combination of RNA-Seq and microarray identified a set of 20 genes associated with lung adenocarcinoma BM, primarily related to immune system pathways, highlighting the importance of the immune system in BM formation. Furthermore, the use of scRNA-Seq elucidated the tumor microenvironment of BM and primary tumors at different stages of progression, revealing differences in immune cell infiltration. T cells were identified as predominant in primary tumors, while microglia predominated in BM. Pathway enrichment analysis revealed that microglia showed a marked upregulation of the COX signaling pathway, associated with the regulation of the inflammatory response, indicating a potential role of inflammation in BM development. The infiltration of myeloid-derived suppressor cells (PMN-MDSCs) in BM reinforces the importance of immune suppressor cell infiltration in the chronic inflammation associated with these metastases. The interaction between activated microglia, CD163+ CD14+ dendritic cells, Th17, and PMN-MDSCs suggests an immunosuppressive inflammatory environment in BM, with implications for tumor progression. The research also highlights the interconnection between JAK-STAT signaling, interleukin-23 (IL-23), and interleukin-17 (IL-17) production, mediated by activated microglia, CD163+ CD14+ dendritic cells, and Th17, demonstrating a complex molecular and immune network in BM formation. In summary, this study proposes a comprehensive approach, integrating RNA sequencing data and computational tools to understand lung adenocarcinoma BM. The identification of biomarkers, understanding molecular pathways, and analyzing the tumor microenvironment provide valuable insights for the development of more effective and targeted therapies, paving the way for significant advances in the treatment of brain metastases from lung cancer.

Keywords: Adenocarcinoma; Lung cancer; Tumor microenvironment (TME); Transcriptome.

1. Introdução

1.1 Epidemiologia e fatores de risco associados ao desenvolvimento do câncer de pulmão

O câncer de pulmão é a causa mais comum de mortalidade por câncer em ambos os sexos em todo o mundo (SUNG *et al.*, 2021). A mortalidade por câncer de pulmão é maior do que as mortes por câncer de estômago, pâncreas e próstata combinados (SUNG *et al.*, 2021). Aproximadamente 2,1 milhão de novos casos são diagnosticados a cada ano, em todo o mundo, e sua incidência está aumentando, principalmente nos países em desenvolvimento (BRAY *et al.*, 2018; SUNG *et al.*, 2021). No Brasil, os dados de incidência estimam mais de 32.560 novos casos para cada ano do triênio de 2023 a 2025, a maioria (~ 18.020) em homens, de acordo com o Instituto Nacional do Câncer (INCA, 2023).

O câncer de pulmão é classificado em dois tipos histológicos principais; o câncer de pulmão de células não pequenas (CPCNP, da sigla, em inglês, NSCLC, *Non-Small Cell Lung Cancer*) e câncer de pulmão de células pequenas (CPCP, da sigla, em inglês, SCLC, *Small-Cell Lung Cancer*). Estes carcinomas diferem histologicamente e molecularmente, mostrando mutações e alterações moleculares específicas de cada subtipo. O CPCNP é responsável pela maioria (~85%) dos casos de câncer de pulmão (INAMURA, 2017) e é classificado em diferentes subtipos histológicos, sendo os mais comuns o adenocarcinoma (AD) (~40% dos cânceres de pulmão), carcinoma de células escamosas (CCE) (~25%) e carcinoma de grandes células (~10%) (INAMURA, 2017).

O tabagismo é um dos principais fatores de risco associados ao desenvolvimento do câncer de pulmão. Mais de 90% dos casos estão associados à exposição crônica ao tabaco (HERBST; MORGENSZTERN; BOSHOFF, 2018). Considerando que cerca de metade dos novos pacientes com câncer de pulmão são ex-fumantes, ou indivíduos que pararam de fumar há mais de 10 anos, o câncer de pulmão continuará sendo um grave problema de saúde por muitos anos em vários países, incluindo o Brasil. Além disso, o câncer de pulmão também ocorre em indivíduos que nunca fumaram, muitas vezes devido à exposição passiva aos carcinógenos do tabaco e poluentes ambientais; esta doença é considerada uma doença clínica e molecular distinta em comparação ao câncer de pulmão que surge em fumantes (KORPANTY *et al.*, 2018; SUN; SCHILLER; GAZDAR, 2007).

A incidência de câncer de pulmão entre nunca fumantes apresentou aumento nas últimas décadas. Em Taiwan por exemplo, mais de metade dos casos de câncer de pulmão ocorrem em indivíduos que nunca fumaram (CHIEN *et al.*, 2020). Nos Estados Unidos estima-se que 10% a 15% dos casos de câncer de pulmão ocorrem em nunca fumantes (OFFICE OF THE SURGEON GENERAL (US); OFFICE ON SMOKING AND HEALTH (US), 2004). No Brasil, apesar das políticas de saúde pública terem levado ao declínio do consumo de tabaco nos últimos anos, o câncer de pulmão – sem considerar os tumores de pele não melanoma – é o quarto tipo de câncer mais incidente entre mulheres (14.540) e o terceiro entre homens (18.020); e a segunda causa de morte por câncer no país em homens e mulheres (INCA, 2023). Até 2040, a incidência e mortalidade por câncer de pulmão, no Brasil, são projetadas com aumento para mais de 73 mil casos novos com aproximadamente 65 mil óbitos relacionados à doença (FERLAY *et al*., 2020).

As estratégias terapêuticas para o câncer de pulmão apresentaram avanços substanciais nos últimos anos e incluem ressecção cirúrgica, quimioterapia, radioterapia, terapêuticas com alvos moleculares e imunoterapias (MITHOOWANI; FEBBRARO, 2022). Em geral, pacientes com estadiamento inicial são submetidos à cirurgia, enquanto os pacientes com doença localmente avançada ou metastática são submetidos a terapias sistêmicas (MITHOOWANI; FEBBRARO, 2022). Apesar das opções terapêuticas, o câncer de pulmão ainda tem um prognóstico ruim com sobrevida em 5 anos de 7 a 26% (LU *et al.*, 2019). ***Uma das principais razões para o prognóstico desfavorável reside no diagnóstico tardio da doença, devido à inespecificidade dos sintomas principalmente nos estágios iniciais de desenvolvimento da doença*** (MIRANDA-FILHO *et al.*, 2021)***. Aproximadamente 79% dos pacientes com câncer de pulmão apresentam doença localmente avançada ou metastática (estadios III e IV, respectivamente), reduzindo as possibilidades terapêuticas e, consequentemente, a sobrevida dos pacientes*** (BADE; DELA CRUZ, 2020). Aproximadamente 47% dos pacientes com CPCNP apresentam metástases à distância no momento do diagnóstico, sendo osso, pulmão e cérebro os sítios metastáticos mais comuns (BARTA; POWELL; WISNIVESKY, 2019).

6. Conclusões

Este trabalho fornece análises detalhadas do microambiente tumoral (TME) das MC de adenocarcinoma de pulmão e revela insights importantes sobre os mecanismos subjacentes à formação das MC e estratégias terapêuticas potenciais. No primeiro estudo, identificamos 102 genes com expressão alterada no ambiente cerebral, associados a moléculas de adesão celular, sinalização de quimiocinas e vias de diferenciação celular. Destacaram-se como genes-chave *CD69* e *GZMA*, relacionados à regulação imunológica. O segundo estudo analisou o TME tanto no tumor cerebral metastático quanto no tumor primário, destacando perfis únicos de infiltração imunológica. Células T predominaram nos tumores primários, enquanto as microglia foram proeminentes no ambiente cerebral metastático. A inflamação crônica foi associada às células dendríticas CD163 + CD14+, enfatizando os papéis interconectados da microglia, células T e MDSCs na inflamação. A análise de comunicação intercelular identificou interações importantes entre microglia, células endoteliais e oligodendrócitos, sugerindo potenciais alvos terapêuticos. A regulação negativa de genes HLA na MC indica um mecanismo potencial de evasão imunológica. No geral, essas descobertas ressaltam a importância do sistema imunológico na MC de adenocarcinoma de pulmão, e abordar o sistema imunológico surge como uma estratégia promissora para o tratamento da MC. Além disso, os resultados deste trabalho fornecem informações valiosas sobre os mecanismos moleculares envolvidos na formação da MC em adenocarcinoma de pulmão. Futuramente, esperamos que nossos dados contribuam com o desenvolvimento de novas estratégias de tratamento e detecção precoce da MC.

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