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REPOSICIONAMENTO DE FÁRMACOS NO CÂNCER DE COLO UTERINO: Análise *In Silico* com Software MOE para Identificação de Candidatos Terapêuticos

DRUG REPURPOSING STRATEGIES IN CERVICAL CANCER: In Silico Analysis with the MOE Software for Identification of Therapeutic Candidates

Larissa Paula Carvalho Ferreira
Laboratório de Bioinformática e Análises Moleculares, Universidade Federal de Uberlândia, 38702-178, Patos de Minas, MG, Brasil.
http://orcid.org/0009-0007-4198-2644
E-mail: larissacarfe@ufu.br

Angelo Borges de Melo Neto
Laboratório de Bioinformática e Análises Moleculares, Universidade Federal de Uberlândia, 38702-178, Patos de Minas, MG, Brasil.
https://orcid.org/0000-0003-0978-2355
E-mail: angelo.melo@ufu.br

Bruna Custódio Dias Duarte
Laboratório de Bioinformática e Análises Moleculares, Universidade Federal de Uberlândia, 38702-178, Patos de Minas, MG, Brasil.
https://orcid.org/0000-0002-6628-7185
E-mail: bruna.custodio@ufu.br

Laurence Rodrigues do Amaral
Laboratório de Bioinformática e Análises Moleculares, Universidade Federal de Uberlândia, 38702-178, Patos de Minas, MG, Brasil.
https://orcid.org/0000-0003-4681-5451
E-mail: laurence@ufu.br

Fábio Ribeiro Queiroz
Laboratório de Pesquisa Translacional em Oncologia, Instituto Mário Penna, 30380-490, Belo Horizonte, MG, Brasil.
https://orcid.org/0000-0003-0238-5787
E-mail: fabio.queiroz@mariopenna.org.br

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ABSTRACT

1. INTRODUCTION

Cervical cancer (CC) remains one of the leading causes of cancer-related death among women, particularly in low- and middle-income countries. One of the main therapeutic challenges is resistance to chemoradiotherapy, often associated with specific molecular alterations. Strategies such as drug repurposing, the use of approved medications for new indications, have shown success in other malignancies and emerge as a promising alternative in CC. Previous studies identified the

PNMA3 and *RASSF2* genes as differentially expressed in non-responsive patients, suggesting their involvement in resistance mechanisms[1].

2. OBJECTIVES

To investigate whether a functional interaction exists between PNMA3 and RASSF2 proteins in CC patients. If confirmed, to explore the therapeutic potential of repurposed drugs capable of modulating this interaction as a strategy to overcome therapeutic resistance.

3. MATERIALS AND METHODS

Protein sequences of PNMA3 and RASSF2 were retrieved from the UniProt database. Their 3D structures were refined and prepared using the Molecular Operating Environment (MOE) software. Functional domains were defined based on UniProt annotations and active site analysis using the Site Finder module. A total of 179 approved drugs were selected from the ChEMBL database based on bioactivity, AlogP, molecular weight, and clinical status, prioritizing compounds with previously reported activity against oncological targets and favorable drug-likeness profiles. Molecular docking assays were conducted using the *induced fit* protocol in MOE, applying the MMFF94x force field with London dG scoring for initial placement and GBVI/WSA dG for final rescoring. The docking protocol was previously validated by redocking the HIV-1 protease (PDB: 1HVR), with RMSD calculation. The most relevant interactions were subjected to 100 ps molecular dynamics simulations. Comparative graphs were generated to distinguish drugs exclusive to each protein or shared between both.

4. RESULTS

Structural analysis suggested that PNMA3 may associate with the SARAH domain of RASSF2, potentially blocking its interaction with MST1/MST2 kinases, key elements of the Hippo pathway, and apoptotic regulation. Among the evaluated drugs, compounds such as Avanafil, Netarsudil, and Sacubitril exhibited strong binding affinity for both PNMA3 and RASSF2, indicating a non-selective interaction profile. In contrast, Nebivolol hydrochloride demonstrated high and exclusive affinity for PNMA3

(S = −9.42 kcal/mol), with no significant interaction detected with RASSF2 across any tested structural region (including the SARAH and RAS domains), indicating relevant functional selectivity. Redocking with HIV-1 protease confirmed protocol reliability (S = −9.14 kcal/mol, RMSD = 1.19 Å)[2].

5. DISCUSSION

The data support the hypothesis that PNMA3 may functionally inhibit RASSF2 by preventing its binding to MST1/MST2, thereby impairing Hippo pathway activation and apoptosis. The docking results reinforce this model: compounds with high affinity for PNMA3 but not for RASSF2, such as Nebivolol, are consistent with a PNMA3-binding mechanism that selectively disrupts the PNMA3–RASSF2 interaction without directly occupying the RASSF2 active site. Drug distribution across the targets reinforces this model, especially with the identification of selective compounds such as Nebivolol, which showed no interaction with RASSF2. These findings are consistent with previous reports describing RASSF2 as a K-Ras-specific effector involved in apoptotic regulation through Hippo signaling[3]. These observations provide a rationale for functional validation of the PNMA3–RASSF2 interaction as a therapeutic target and for the rational repurposing of drugs as a strategy to overcome resistance in CC.

6. CONCLUSION

A possible functional interaction between PNMA3 and RASSF2 was observed, suggesting that PNMA3 may negatively regulate the pro-apoptotic activity of RASSF2. Rational drug repurposing identified candidate compounds with selective affinity for PNMA3, particularly Nebivolol hydrochloride. These findings support the potential of a novel therapeutic target for treatment-resistant cervical cancer and justify further experimental validation, including in vitro and in vivo assays to confirm the functional PNMA3–RASSF2 interaction and assess the therapeutic efficacy of the candidate compounds.

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NOTAS

CONFLITOS DE INTERESSE

Não há conflitos de interesse.

CONTRIBUIÇÃO DOS AUTORES

Indicar a autoria com baseado em contribuições substanciais: (a) Concepção e elaboração do manuscrito, (b) Coleta e Análise de dados, (c) Discussão dos resultados, (d) Revisão e aprovação final do artigo.

Larissa Paula Carvalho Ferreira: A-B-C-D.
Angelo Borges de Melo Neto: A-B-C.
Bruna Custódio Dias Duarte: B-D.
Matheus de Souza Gomes: D.
Paulo Guilherme de Oliveira Salles: B-D.
Laurence Rodrigues do Amaral: C-D.
Letícia da Conceição Braga: C-D.
Fábio Ribeiro Queiroz: A-B-C-D.

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