POSTER - SYSTEMS BIOLOGY AND MODELING

THE ANTAGONISTIC ROLE OF THE NF-KB INHIBITOR DHMEQ IN BREAST CANCER PROGRESSION

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Breast cancer is the most common type of neoplasia among women in Brazil (Nogueira-Rodrigues et al., 2023). The disease is characterized by genetic and phenotypic heterogeneity and is classified into four main molecular subtypes: luminal A, luminal B, HER2-positive, and triple-negative, according to the expression levels of estrogen (ER), progesterone (PR) hormone receptors, or the transmembrane receptor HER2. The triple-negative breast cancer (TNBC) subtype lacks ER, PR, and HER2 expression, making it the most aggressive form, with poor therapeutic response and high recurrence rates. Different subtypes require specific therapeutic strategies. Therefore, heterogeneity, defined by the presence of cells from different subtypes within the same tumor, is one of the main challenges for treatment, contributing to therapy resistance and recurrence.

Recent results from our group (Lopes et al., 2024) indicate the occurrence of spontaneous phenotypic transitions between the HER2+ and TNBC subtypes

over time. These stochastic transitions appear to be related to sustained activation of the NF-κB signaling pathway. To investigate this hypothesis, we developed a gene regulatory network model, which was converted into a system of ordinary differential equations (ODEs). The model exhibits bistability, suggesting the existence of two stable steady states, separated by a boundary of attraction basins. Calibration of the model using experimental quantitative data on NF-κB expression levels allowed us to associate the two steady states with the HER2+ and TNBC subtypes. Computational simulations suggest that intermittent administration of the DHMEQ inhibitor, followed by its withdrawal, can cause compensatory accumulation of NF-κB, capable of shifting the cell from the HER2+ basin of attraction to the TNBC basin, promoting the phenotypic transition.

This project aims to experimentally validate the model's predictions. In the bioinformatics stage, which has already been completed, we analyzed public transcriptomic datasets (GEO) and identified genes differentially expressed between HER2+ and TNBC subtypes. These genes will be used as transition markers and support the next experimental steps. We will use the HCC-1954 and SK-BR-3 cell lines treated with DHMEQ for different durations, with time-course collections for qRT-PCR analysis of the marker genes. Additionally, immunohistochemistry analyses will be performed to assess HER2 expression and confirm the phenotypic transition. Simultaneously, we will refine the computational model, including sensitivity analysis, stochastic simulations, and identification of critical parameters regulating the transition between steady states. These theoretical and experimental results will be integrated to validate the role of NF-κB in promoting phenotypic heterogeneity in breast cancer.

Palavras-chave: breast cancer; nf-?b; mathematical modeling; her2; tnbc; dhmeq.