Role of cancer-associated fibroblasts in breast cancer metastasis and investigation of potential therapeutic targets

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Background: The mechanisms behind lung metastasis development in breast cancer is still under extensive investigation. Various signaling pathways involving cancer cells and tumor microenvironment (TME) cells, especially cancer-associated fibroblasts and related signaling pathways (i.e., PDGF and FGF receptors), are crucial. Currently, preclinical and clinical trials aiming to block breast cancer metastasis by targeting epigenetic mechanisms, promoting cancer cells dormancy , activate the immune response, and modify the TME.
Emerging therapeutic approaches, including tyrosine kinase inhibitors (TKIs), Polo-like kinase (PLK) inhibitors, and NADPH oxidase (NOX) inhibitors, have shown significant potential in experimental models. This study investigated the in vivo and in vitro effects of Nilotinib and Nintedanib (TKIs), Volasertib (PLK inhibitor), and Setanaxib (NOX inhibitor) on metastatic breast cancer by targeting primary tumors in animal models and in vitro models.

Methods: Multiple in vivo metastatic models, using the highly metastatic mouse 4T1 cell line, have been used to evaluate the anti-metastatic efficacy of Nilotinib, Nintedanib, and Setanaxib. Furthermore, 3D and 2D in vitro models were used to characterize Nilotinib, Nintedanib, volasertib, and Setanaxib properties to confirm the in vivo results.

Results: Our results demonstrated that Nintedanib significantly reduced 4T1 primary tumor size and lung metastasis. Furthermore, in adjuvant therapy settings and experimental metastasis models, Nilotinib and Nintedanib prevent lung metastasis development. In vitro experiments demonstrated that Nilotinib and particularly, Nintedanib and Volasertib decreased 3D growth of 4T1 and 4T1/fibroblast spheroids by reducing cell viability and inducing cell death. Moreover, we observed that in vitro treatment with Setanaxib reduced
4T1 cell adhesion to ECM. Finally, Setanaxib also reduced the ability of 4T1 cells to perform anchorage-independent growth in agar assays and lung metastasis in tail vein experimental models of metastasis.

Conclusions: These promising results suggest that Nintedanib, Volasertib, and Setanaxib could be effective strategies for the treatment of metastatic breast cancer.