Suppression of Metastatic Spread of Breast Cancer by DN10746-mediated Inhibition of Axl Signaling

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Abstract

Breast cancer is the most common malignant disease among women, contributing to a substantial proportion of the global cancer burden. In these patients, not the primary tumor, but metastasis is the main cause of breast cancer-related deaths Metastasis, Axl belongs to the TAM receptor tyrosine kinase (RTK) family, a recently identified class of the RTK subfamily that also includes Tyro-3 and Mer. It has been demonstrated that Axl and its major ligand Gas 6 are upregulation in a wide variety of cancer cell lines as well as cancer patient samples including breast cancer, acute leukemia, colorectal cancer, lung cancer, melanoma, ovarian cancer, prostate cancer and other. Moreover, Axl activation has been shown to be correlated with poor prognosis, promotion of increased invasiveness/metastasis, the EMT phenotype and resistance to chemotherapy as well as targeted anti-cancer therapies. In this study, we report a previously unidentified activity of DN10764 against Axl, resulting in the suppression of metastatic development of breast cancer. In breast cancer cells, we found that DN10764 inhibits cell proliferation and Gas6-mediated Axl signaling pathways, consequently resulting in the suppression of migration and invasion. In addition, DN10764 induced caspase3/7-mediated apoptosis in breast cancer cells and inhibited tube formation of HUVEC cells. Considering multiple roles of Axl in tumor progression and recurrence, therapeutic strategies targeting Axl in combination with systemic therapies will improve response to anti-cancer therapies and to reduce breast cancer recurrence and metastases.