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TITLE

Inhibition of Axl signaling pathway as a novel therapeutic strategy to impair tumor cell dissemination

HYPOTHESIS:

Axl signaling promotes cell migration and invasion and hence targeting this signaling pathway offers a novel therapeutic approach to prevent the dissemination of tumor cells.

BACKGROUND/AIMS:

Cancer is the second leading cause of death in the United States with approximately 90% of cancer-related deaths resulting from metastatic disease. In tumor cells, upregulation of certain signaling pathways promote metastatic phenotypes characterized by enhanced invasion, migration, survival, proliferation and induction of angiogenesis. One pathway of considerable interest involves the receptor tyrosine kinase Axl that is expressed in a variety of tumor types and is associated with poor prognosis and metastasis. Furthermore, Axl's ligand, Growth arrest specific 6 (Gas6) protein, previously was shown to pathways that activate a number of downstream signaling promote metastatic phenotypes. Thus, the purpose of the current study was to characterize Axl and Gas6 in a number of human tumor cell lines and to determine the effect of Axl suppression on the metastatic potential.

METHODS:

A panel of human tumor cell lines, including prostate, breast, colorectal, renal, and osteosarcoma, were characterized for Axl expression by Western blot and qPCR. Gas6 expression was characterized by qPCR and secretion by collecting conditioned media and determining the concentration by ELISA. Axl was genetically inactivated by shRNA in prostate (DU145) and breast cancer (MDA-MB-231) cell lines. The efficiency of knockdown was determined by Western blot and the phenotypic effect of Axl knockdown on migratory and invasive potentials of these cell lines was evaluated by transwell migration and invasion assays.

RESULTS & CONCLUSIONS

Axl-expressing tumor cells also expressed and secreted its ligand Gas6, suggesting that Axl is coexpressed with Gas6, and may be mediated by autocrine regulation. Axl expression was suppressed via shRNA in breast and prostate cancer cell lines, MDA-MB-231 and DU145, respectively. Genetic inactivation of Axl in these cell lines inhibited cell migration and invasion in both of the cell lines. Further studies are ongoing to characterize Gas6 expression and secretion in Axl knockdown cell lines. Future experiments will utilize knockdown Axl cell lines as well as pharmacologic suppression with the Axl targeting agent R428 to determine the effects on Axl signaling and metastatic phenotype.