CXCR4 expression reflects tumor progression and regulates motility of bladder cancer cells.

Abstract:

Transitional cell carcinoma of the urinary bladder remains life threatening due to the high occurrence of metastases. Emerging evidence suggests that chemokines and their receptors play a critical role in tumor metastases. In our study, we performed a systematic analysis of the mRNA and protein expression levels of all 18 chemokine receptors in normal urothelium and bladder cancer. CXCR4 was the only chemokine receptor whose mRNA expression level was upregulated in bladder cancer cell lines as well as in invasive and locally advanced bladder cancer tissue samples (pT2-pT4). In contrast, superficial bladder tumors (pTa and pT1) displayed low CXCR4 expression levels and normal urothelial cells were negative for CXCR4. Immunohistochemistry of a bladder cancer tissue microarray (TMA) confirmed that a subgroup of invasive bladder cancers revealed a high CXCR4 protein expression, while superficial bladder tumors showed low immunoreactivity. To investigate the functional significance of CXCR4 expression, we performed migration and invasion assays. Exposure of CXCR4-positive bladder cancer cells to CXCL12 in a Boyden chamber type assay provoked a significant increase in migration as well as invasion across a Matrigel barrier. Enhanced migration and invasion were inhibited by a CXCR4-specific blocking antibody. In contrast, normal urothelial cells did not
respond to CXCL12 and lacked chemotactic migration. In conclusion, bladder cancer cells express CXCR4 progressively with advanced tumorigenesis and this receptor interacts with CXCL12 to mediate tumor chemotaxis and invasion through connective tissue. These properties identify CXCR4 as a potential target for the attenuation of bladder cancer metastases.