CXCR4 Expression Mediates Hormone Independence and Endocrine Therapy Resistance through Erk1/2 and p38 Signaling


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Chemokine X Receptor 4 (CXCR4) expression is critical to cancer cell invasion and metastasis. Altered expression and activation by its ligand, stromal-derived growth factor 1 (SDF-1), mediates breast carcinoma progression to a more metastatic phenotype. The association of a metastatic phenotype with hormone independence, along with SDF-1 being an estrogen receptor (ER) regulated gene, establishes a link between hormone and chemokine signaling in breast carcinoma. SDF-1-CXCR4 signaling promotes proliferation, cell motility/invasion, and suppresses apoptosis through activation of signaling pathways including mitogen-activated protein kinase (MAPK). Interestingly, MAPKs have been implicated in endocrine therapy resistance. While endocrine therapy holds great promise in treatment of hormone-dependent cancer, many patients display resistance, either acquired or de novo. Resistance primarily occurs through altered signaling cascades leading to ligand-independent activation of estrogen receptor mediated gene expression and hormone independence.

As reported here, a deletion in the COOH-terminal domain confers constitutive activity of CXCR4 leading to enhanced cell growth and metastases in vivo. Furthermore, overexpression of CXCR4 in MCF-7 leads to hormone independence in vivo. Treatment with exogenous SDF-1 negates inhibitory effects of anti-estrogen treatment on MCF-7-CXCR4 tumor growth indicating involvement in endocrine therapy resistance. These effects are correlated with CXCR4 mediated activation of downstream signaling events (Erk1/2, p38) and enhancement of ER-mediated gene expression. These results indicate that, in addition to mediating metastatic potential of ER + breast carcinoma, CXCR4 signaling contributes to hormone independence and endocrine therapy resistance through Erk1/2 and p38 signaling. Better mechanistic understanding of hormone independence/endocrine therapy resistance is paramount to discovery and utilization of novel treatment targets.