

Preface

The chemokine receptors are a diverse family of seven-transmembrane G-protein-coupled receptors binding a large family of ligands. Chemokine receptors were first identified on leukocytes and mediate directed migration of many host cells to sites of ligand expression. It is now well established that most malignant cells also express one or more chemokine receptor. This volume will summarize the growing body of evidence that several chemokine receptors contribute to tumor behavior.

There is abundant evidence that CXCR4, which is widely expressed in many malignancies, contributes to the ability of tumor cells to metastasize to sites of ligand expression. Evidence for regulation of CXCR4 by hypoxia is described. Like CXCR4, both CCR7 and CXCR3 function to promote tumor cell homing and metastasis of melanoma, breast and colon cancers. Several chemokine receptors also function to support the survival and proliferation of tumor cells either directly or through transactivation by tyrosine kinase-coupled growth factor receptors.

While chemokine receptors expressed on tumor cells generally support tumor growth and dissemination, expression of these receptors on host cells has both pro-tumor and anti-tumor functions. Both angiostatic and angiogenic functions of CXC chemokines acting on endothelial cells have been described. The CXCR3 receptor expressed on malignant cells promotes metastasis but CXCR3 + Th1 cells and NK cells play a protective role in several tumor models. Data demonstrating the potential therapeutic potential of CXCR3 ligand overexpression acting on host immune and endothelial cells are also summarized. The CCR5/CCL5 axis has a complex role in tumor behavior with induction of an early protective T-cell response that is ultimately overridden by a tumor growth-promoting role of CCL5.

There are also several chemokine receptors that act as decoy receptors, binding ligands with high affinity. Although these receptors do not transduce signals that mediate intracellular responses, ligand binding does contribute to tumor behavior. For example, the D6 receptor may act as a biological sink to reduce the bioavailability of pro-angiogenic chemokines. Differences in decoy receptor expression in different populations may contribute to disparities in cancer incidence and outcome.

The therapeutic potential and challenges of targeting chemokine receptors in cancer is also discussed. Based on promising preclinical data, antagonists of CXCR4 are currently being evaluated in clinical trials. Initial studies have indicated that inhibition of several other chemokine receptors, expressed on the malignant cell, shows promise; however, this approach is complicated by the fact that many protective host cells express the same receptors. In summary, the study of chemokine receptors in cancer has rapidly expanded since the initial description, in 2001, of CXCR4 and CCR7 in cancer cells. Many studies attest to the importance of chemokine receptors as determinants of tumor behavior. The current challenge is to understand the mechanisms underlying these functions and to more effectively target these receptors therapeutically.

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