Regulation of Breast Cancer Metastasis by Atypical Chemokine Receptors

Commentary on Feng et al., p. 2962

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The interaction between chemokines and their \textit{G}-protein-coupled receptors plays an important role in promoting metastasis of different kinds of human cancers. However, the expression of an atypical chemokine receptor, CCX-CKR, which serves as a decoy receptor to attract chemokines, inhibits the growth and metastasis of breast cancer by sequestration of chemokines.

In this issue of \textit{Clinical Cancer Research}, Feng and colleagues\textsuperscript{(1)} report that CCX-CKR, a novel chemokine decoy receptor, is a negative regulator of growth and metastasis in breast cancer.

Chemokines are small proteins known mostly to be involved in cell migration, but they have also been found to be involved in other activities such as angiogenesis, proliferation, and apoptosis\textsuperscript{(2, 3)}. They, in cooperation with their receptors, have also been implicated in the progression of many different cancers, affecting survival, proliferation, and metastasis. One well-studied example is the chemokine CXCL12 and its receptor, CXCR4, which have been shown to be involved in many cancers. CXCR4 is expressed in organs, such as lung, liver, bone, and lymph nodes, where metastases are commonly located\textsuperscript{(4)}. Additionally, CXCR4 has been reported to be required for HER2-mediated metastasis\textsuperscript{(5)}. Other chemokine-receptor pairings, such as CCR7-CCL19, CCR9-CCL25, and CXCR5-CXCL13, have also been shown to play a role in cancer. "Silent" or atypical chemokine receptors comprise a three-member subfamily of chemokine receptors: Duffy antigen receptor for chemokines (DARC), D6, and ChemocentryX chemokine receptor (CCX-CKR). Among them, CCX-CKR is the most recently discovered. These receptors differ from other chemokine receptors in that the signaling elements of traditional chemokines are not conserved, and they are able to bind a broader spectrum of chemokines. To date, there are no known signaling cascades activated by them\textsuperscript{(3)}. It has been suggested that they might act as decoy receptors to compete for ligand binding, to control the availability of ligands in a particular environment, or that they might mediate transcellular transport of chemoattractants\textsuperscript{(2)}. The authors have previously shown that both DARC and D6 play a negative role in breast cancer\textsuperscript{(6, 7)}, and in this issue, they further examine the effect of CCX-CKR in breast cancer. CCX-CKR has been found to bind CCL19, CCL21, CCL25, and CXCL13, which are involved in migration to secondary lymphoid organs, thymocyte migration, and leukocyte migration\textsuperscript{(2, 8)}. Additionally, CCX-CKR-expressing cells are able to efficiently uptake CCL19 and mediate its degradation\textsuperscript{(2, 3)}. However, many questions regarding the functionality and expression of CCX-CKR still remain. Although the importance of secreted chemokines in attracting migrating cells bearing specific chemokine receptors is well established, how these atypical receptors work is still poorly understood. As mentioned above, it has been proposed that atypical receptors may work in several ways: (a) to compete for ligand binding and hence inhibit the migration of cells bearing typical receptors; (b) to internalize and degrade ligands and therefore deplete chemokine levels in a particular microenvironment to reduce the recruitment of cells to that site; (c) in the transcytosis of chemokines to, in turn, transfer ligands across certain barriers; or (d) to retain or present chemokines\textsuperscript{(2)}.

In this issue of \textit{Clinical Cancer Research}, Feng and colleagues report for the first time that CCX-CKR is a negative regulator of growth and metastasis in breast cancer\textsuperscript{(1)}. Overexpression of CCX-CKR in breast cancer cells inhibited the proliferation and invasion \textit{in vitro}, as well as the tumor growth and lung metastasis \textit{in vivo}. In their 98-case breast cancer study, a significant correlation between CCX-CKR expression and lymph node metastasis was observed. Higher CCX-CKR expression was negatively correlated with lymph node metastasis; furthermore, CCX-CKR was found to be associated with longer patient survival. In a multivariate analysis by the Cox risk proportion model, CCX-CKR status was determined to be an independent prognostic factor for disease-free survival in breast patients.

Feng and colleagues also show that CCX-CKR can decrease CCL19, CCL21, CCL25, and CXCL13 protein levels in xenograft tumors and significantly inhibit tumor growth and lung metastasis, and that mRNA expression of the ligands in CCX-CKR-transfected cells is not significantly changed \textit{in vitro}, suggesting that CCX-CKR mediated the internalization and degradation of chemokine proteins, similar to those shown in...
previous publications (1). It should be mentioned that those ligands are not expressed predominantly by tumor cells, but by stromal cells and endothelial cells in the microenvironment; thus, it would be interesting to see whether CCX-CKR in tumor cells might affect the ligand secretion from stromal and endothelial cells. Moreover, the authors demonstrate that, over time, CCX-CKR-expressing cells are capable of depleting large quantities of extracellular chemokines; consequently, intratumoral neovascularity was inhibited in CCX-CKR-transfected xenografts (Fig. 1). The correlation is interesting, and it would also be worthwhile to further provide a causal relationship between the depletion of extracellular chemokines and the decreased neovascularity. This issue is important, as it has been reported that activation of the CCR7 receptor on fibroblast-like synoviocytes (FLSs) by CCL19 results in an enhanced VEGF secretion (9), yet VEGF expression was not changed in the supernatant of CCX-CKR transfectants in this study.

The results presented by Feng and colleagues raise many interesting questions (1). For example, it remains to be determined why the expression of CCX-CKR inhibits angiogenesis. How is the expression of CCX-CKR itself regulated? What is the relationship between the expression of CCX-CKR and typical chemokine receptors? Coexpression of the typical and atypical chemokine receptors in the motile cells raises the interesting question of whether the typical receptors like CCR7, CCR9, and CXCR5 are also coexpressed with the atypical receptors like CCX-CKR. Can CCX-CKR also deplete the chemokines at the secondary sites, e.g., in lymph node and lung? If so, can it serve the chemokine-chemokine receptor axis at the secondary site, and therefore reduce the recruitment of migrating cells to the secondary sites? Additionally, because atypical chemokine receptors cannot transduce signals, can the expression of atypical receptors inhibit the adherence and growth of the tumor cells in the metastatic site and therefore reduce the formation of the secondary tumor? Will the combination of CCX-CKR and typical chemokine receptors be a better prognostic factor for breast cancer patients? Is CCX-CKR expressed in human tumors other than breast cancer, and, if so, does it contribute in the same way? And, finally, is it possible that CCX-CKR might be a new therapeutic avenue for cancer treatment? Answering all of these questions will increase our understanding of how CCX-CKR regulates the chemotactic networks and human tumors, and whether it may be a potential cancer intervention in the near future.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.
References


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