CXCR4 and CCR7 interact to form functional dimeric receptor and to promote cancer metastasis

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CXCR4 and CCR7 chemokine receptors have been assigned major roles in advancing metastatic dissemination of various tumours, however, the fundamental biochemical and cellular mechanisms that underpin the critical role of chemokine receptors in metastasis are unknown.

Latest paradigm suggests that chemokine receptors exist as homo- or heterodimers. We have discovered that native chemokine receptors CXCR4 and CCR7 physically and functionally interact in breast and colon cancer cells and this interaction is a prerequisite for the cell metastatic potential. Using a variety of methods we have demonstrated the presence of heterodimeric CXCR4/CCR7 chemokine receptors in cancer cell lines as well as mouse and human primary tumours. Importantly, we have also correlated the formation of this novel chemokine receptor dimer with the receptor activation and cells’ metastatic phenotype. Thus the dimeric CXCR4/CCR7 receptors are only detected on highly metastatic cells and tumours. Moreover, activation of both CXCR4 and CCR7 can be induced by their respective ligands only in highly invasive cells. However in benign or non-invasive cancer cells, while individual receptors are still expressed on the cell surface the CXCR4/CCR7 heterodimer is not present and both receptors are silent. We have further shown that CXCR4 and CCR7 are functionally inter-dependent in metastatic cells, as inactivation of either receptor is sufficient to almost completely abrogate the activation of the other and to alter the cells’ metastatic phenotype both in vitro and in vivo. These novel findings may potentially have far-reaching implications for fundamental chemokine receptor biology, cancer research and cancer therapeutics.