Chemokines and Cancer: A Fatal Attraction

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Chemokines are important components of cancer-related inflammation. In this issue of *Cancer Cell*, Chen et al. report that the chemokine CCL18, produced by tumor-associated macrophages, promotes malignant behavior and correlates with metastasis in human breast cancer. Unexpectedly, PITPNM3/Nir1, a molecule unrelated to chemokine receptors, was identified as its elusive receptor.

Recruitment of cells of the monocyte-macrophage lineage is an important step in the cancer-related inflammation orchestrated to a large extent by chemokines. Levels of tumor-associate macrophages (TAMs) are frequently associated with a bad prognosis, as illustrated by recent findings in Hodgkin's lymphoma (Steidl et al., 2010). Chemokines have long been associated with cancer (Mantovani et al., 2010), where they play a key role in orchestrating the recruitment and positioning of leukocytes. Experiments with gene-modified mice have now unequivocally demonstrated that chemokine-orchestrated leukocyte recruitment is a key determinant of carcinogenesis. However, their action is not restricted to their eponymous function (chemotaxis). Chemokines such as CCL2 contribute to polarizing TAMs in a tissue repair/remodeling (M2-like) mode (Biswas and Mantovani, 2010). Chemokines also affect stromal components and tumor cells. In particular, by interacting with endothelial cells and by attracting leukocytes, chemokines promote angiogenesis.

Engagement of chemokine receptors promotes tumor-cell proliferation and survival and guides them to secondary sites to form metastasis. In addition, the chemokine receptor CXCR2 is a reinforcing determinant of cellular senescence. Thus, chemokines mediate cell-autonomous and nonautonomous responses in carcinogenesis (Kulbe et al., 2007; Mantovani et al., 2010). Chemokines act downstream of oncogene activation in transformed cells, but stromal elements can represent an important source of these mediators (e.g., DeNardo et al., 2009). Furthermore, chemokines produced by cancer-associated fibroblasts (CAFs) recruit T regulatory cells (Treg), inducing metastatic progression of breast carcinoma cells (Tan et al., 2011).

In this issue of *Cancer Cell*, Chen et al. (2011) report that TAMs in human breast cancer are the major source of the chemokine CCL18 (Figure 1). CCL18 is induced by IL-4, IL-13 and IL-10 and is therefore part of the chemokine repertoire of M2-like polarized macrophages (Biswas and Mantovani, 2010) that have been shown to drive breast cancer progression and metastasis in preclinical models (DeNardo et al., 2009; Pollard, 2004). Interestingly, the frequencies of $CCL18^{+}$ TAMs correlated with those of infiltrating $CD4^{+}$ T, a finding that may mirror the pivotal role of Th2 cells in M2 polarization in a preclinical setting (DeNardo et al., 2009). High intratumor and circulating levels of CCL18 were also associated with a worse prognosis in a large series of over 500 breast carcinoma patients. CCL18 elicits migration of lymphocytes and monocytes, but in this study, the prime targets were tumor cells and the authors found that CCL18 augmented invasion and metastasis of breast carcinoma cells.

As a general rule, chemokines interact with seven transmembrane-domain G protein-coupled receptors (GPCRs). The CCL18 receptor has long been elusive. Unexpectedly, Chen et al. (2011) now report that CCL18 interacts with and signals through PITPNM3/Nir1, a molecule that belongs to the phosphatidylinositol transfer protein (PITP) family with no apparent structural or functional similarity to conventional GPCRs. Members of the PITP-family contain a phosphatidylinositol transfer protein domain (PIT), an acidic region/Ca^{+2} binding domain, six transmembrane domains, and a C-terminal domain that interacts with PYK2. PITPNM3 and its *Drosophila* homologous rdgB have been implicated in the visual transduction pathway. RdgB functions downstream protein kinase C, rhodopsin and phospholipase C in flies, and mutation in the PYK2-binding domain of PITPNM3 causes autosomal dominant cone dystrophy (CORD5) in humans.

This finding is provocative, but not completely without precedent. Several noncanonical interactions were observed in the chemokine

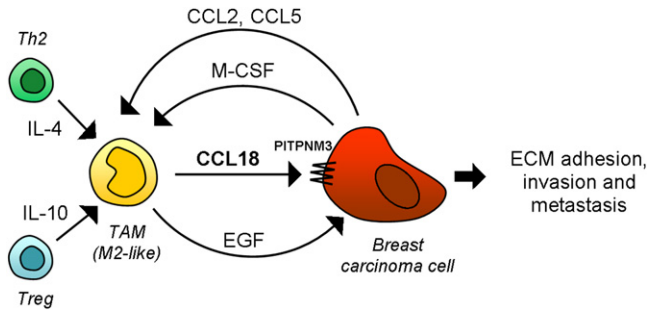

Figure 1. TAMs in Human Breast Carcinoma Have an M2-like Phenotype that Includes the Production of CCL18
CCL18 interacts with a PITPNM3/Nir1-containing complex in tumors to promote their adhesion to extracellular matrix (ECM), invasion, and metastasis. Work in preclinical models supports that IL-4 produced by Th2 cells plays a key role in skewing macrophage polarization. Moreover, chemokines (CCL2 and CCL5) and M-CSF are involved in monocyte recruitment, and TAMs are a source of EGF in the tumor microenvironment.

system. For instance, the chemokine receptors CXCR4 and CCR5 interact with gp120, acting as HIV coreceptors and the chemokine CXCL16 interacts with oxidized LDL. Chemokine receptors can also form heterodimers with other chemokine receptors (Thelen et al., 2010) or with other membrane receptors modulating their function. For instance, CXCR2 and CXCR4 interacting with CD74 become functional receptors for the noncanonical chemokine macrophage migration inhibitory factor (MIF), and one could entertain the possibility that PITPNM3 forms a dimer with a conventional signaling GPCR.

Previous studies (Soria and Ben-Baruch, 2008) have shown that levels of the monocyte-attracting chemokines CCL2 and CCL5 are associated with macrophage infiltration and prognosis. Therefore, a comprehensive "chemokinome" system biology perspective may well be required to explore the clinical significance of chemokine levels in cancer.

The results reported here shed new light on the role of chemokines in cancer and raise important questions. There is no mouse counterpart of CCL18 on which to rely for rigorous genetic approaches to investigate its role in carcinogenesis. CCL18 was found in other human tumors, ovarian in particular. The present findings call for an appraisal of its prognostic significance in these pathologies. The actual structure of the CCL18-recognizing receptor complex will also need to be further investigated. Finally, and no less important, chemokine anticancer therapeutic strategies have entered clinical evaluation. In spite of stumbling blocks (e.g., lack of mouse counterpart, drugability of the receptor), CCL18 may be added to the list of potential therapeutic targets.

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Unswitch-ABL Drugs Overcome Resistance in Chronic Myeloid Leukemia

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ABL inhibitors have revolutionized the clinical management of chronic myeloid leukemia, but the BCR-ABL^{T315I} mutation confers resistance to currently approved drugs. Chan et al. show, in this issue of *Cancer Cell*, that "switch-control" inhibitors block BCR-ABL^{T315I} activity by preventing ABL from switching from the inactive to active conformation.

The BCR-ABL fusion protein is the primary driver oncogene in the majority of chronic myeloid leukemias (CML) and also in about 25% of adult acute lymphoblastic leukemias (ALL) (Druker et al., 2001). This protein is expressed from a fusion gene resulting from a reciprocal translocation between chromosome 9 and 22 (t(9;22)(q34;q11)), the so-called Philadelphia chromosome (Ph+). ABL is a tyrosine kinase and its fusion to BCR causes constitutive activation, driving hematopoietic cell transformation through activation of multiple signaling pathways. The treatment of CML was revolutionized by the development of imatinib, a small molecular-weight drug that inhibits ABL and mediates durable hematologic and cytologic responses in CML patients. The importance of imatinib cannot be underestimated, because as the first tyrosine kinase inhibitor (TKI) to achieve responses in cancer patients, it provided a paradigm shift in cancer treatment.

Although imatinib changed the clinical management of CML, some patients eventually fail on therapy due to acquired resistance. Resistance can be mediated by secondary mutations in BCR-ABL that block imatinib binding through steric hindrance or by switching ABL into the active conformation. Like imatinib, the