



## Targeting metastasis through the inhibition of interleukin 6 and 8

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“Enhancing our ability to treat breast cancer with improved patient outcomes will require the development of novel combination strategies that simultaneously target both tumor growth and metastasis”

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Metastasis is a complex, multistep process involving the spread of cancer cells from a primary tumor to distal sites throughout the body via the circulatory or lymphatic systems [1]. Breast cancers typically arise from a host of genetic aberrations [2,3] that influence both disease progression and the therapeutic approaches utilized by physicians to combat the disease [4]. With the exceptions of estrogen receptor (ER), HER2, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, PIK3CA, and AKT1, validated oncogenic drivers of breast cancer remain elusive. Directly targeting metastasis is essential with regards to therapeutic interventions and could have major medical and societal implications, as mounting scientific evidence shows that metastasis accounts for 90% of the cancer-related deaths [5]. Although targeting metastasis itself may seem a daunting task scientifically and logistically, progressive improvements in our knowledge of the disease is providing novel and innovative approaches.

Many chemokines and cytokines (mainly interleukins) play critical roles in the metastatic process, from influencing epithelial to mesenchymal transition (EMT) [6] and facilitating the detachment of tumor cells from the primary tumor mass, to regulating cell migration [7], promoting seeding by circulating tumor cells (CTCs) [8] and stimulating proliferation [9]. Recent studies have demonstrated that interleukins cooperatively regulate aspects of metastasis. For instance, IL-6 and IL-8 co-regulate tumor cell proliferation and migration and the seeding of CTCs [10–13]. Since tumor cells rely on coordinated interactions with different cell populations within the microenvironment (both malignant and stromal cells) for fitness and survival during tumorigenesis [14], it is logical that they would also rely on the synergistic interplay of secreted proteins, particularly employing interleukins to successfully metastasize.

Tumor cells autonomously produce IL-6 and IL-8 which synergistically attracts CTCs and promotes the self-seeding of breast, colon and melanoma tumors [13]. Furthermore, these cytokines enhance tumor cell migration through cell-autonomous paracrine mechanisms driven in part by the increase in local cell density [10,11]. Interestingly, this signaling is unique to tumorigenic metastatic cells but not normal or non-metastatic cancer cells. IL-6 and IL-8 promote cell migration within collagen rich extracellular matrices through downstream signaling via WASF3 and Arp2/3 complex and increases the formation of dendritic protrusions. Furthermore, pharmacological inhibition of the binding of these interleukins to their cognate receptors using tocilizumab (a humanized monoclonal antibody that targets the IL-6 receptor) and reparixin (a small molecule that targets the IL-8 receptor) decreases effective metastasis to the lungs, liver and lymph nodes in preclinical breast cancer models [10].

Breast cancers, particularly triple negative breast cancers (TNBCs), lacking the expression of the estrogen receptor, progesterone receptor (PR) and HER2, are largely treated with chemotherapeutics [15]. Paradoxically, studies suggest that chemotherapies currently used in the clinic for treating primary triple negative breast cancers may induce breast cancer metastasis [16]. Considering this, strategies that target both tumor growth and tumor-specific signals that trigger and/or promote migration may be more efficacious than chemotherapies alone, or targeted therapies that primarily inhibit cell growth.

Combination therapy is a promising strategy to combat the ails of monotherapy and realizing the goal of a bitherapeutic strategy to target both cell growth and cell migration. The amalgamation of two or more therapeutic agents working synergistically or additively typically provides superior clinical benefits through the effective reduction of drug resistance or enhanced efficacy via the targeting of complimentary cellular mechanisms [17]. For instance, the combination of standard chemotherapy regimens with bevacizumab significantly prolongs the survival of patients with metastatic cancers of the colorectal, breast and lung [18–20]. Considering the evidence that suggests that the synergistic signaling of IL-6 and IL-8 plays a critical role in the metastatic cascade [10–13], the simultaneous use of tocilizumab and reparixin with other anticancer therapeutics could greatly decrease tumor growth and metastatic capacity of breast cancer cells.

Enhancing our ability to treat breast cancer with improved patient outcomes will require the development of novel combination strategies that simultaneously target both tumor growth and metastasis. However, it is also critical that we develop our understanding of how malignant cells co-opt these long-range (mainly chemical) and short-range (mainly biophysical) signaling mechanisms within the tumor microenvironment.

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