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Recent Advances in Discovering the Role of CCL5 in Metastatic Breast Cancer

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Abstract

The most common cause of mortality in cancer patients is metastasis. Therefore, a variety of therapeutic strategies are currently under investigation to develop effective drugs that can target and inhibit factors that promote tumor invasion. Considerable emphasis has been placed on studying cancer as an inflammatory process that proceeds in a dynamic microenvironment. In fact, the tumor microenvironment has been implicated to contribute considerably to metastasis. For instance, chemokine C-C motif ligand 5 (CCL5) produced by cells in the tumor microenvironment has been established as an important contributor to metastatic disease. Recently, the role of CCL5 in breast cancer invasion has been extensively studied. This review summarizes the recent developments in regards to this chemokine, including the conditions that increase the generation of CCL5 and the effects mediated by this signaling pathway. Moreover, the potential use of CCL5

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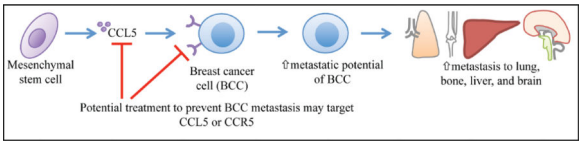
CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

and its receptor chemokine C-C motif receptor 5 (CCR5) as a target for treating and/or preventing breast cancer metastasis is also discussed.

Graphical Abstract



Keywords

Breast cancer; CCL5; CCR5; mesenchymal stem cells; metastasis; triple-negative breast cancer

INTRODUCTION

In the year 2000, Hanahan and Weinberg categorized the acquired properties of cancerous tissues into six hallmarks, one of which was metastasis and tissue invasion [1]. Indeed, metastatic lesions are considerably difficult to treat and are typically the main cause of death for cancer patients. Notably, 10–15% of breast cancer patients present with metastases within three years after their first diagnosis [2]. Moreover, breast cancer patients run a lifetime risk of developing metastases, as they can appear ten or more years after diagnosis [2]. Common sites for breast cancer invasion include the lungs, brain, bones, and liver [3]. In light of this information, it is crucial to understand the basis of metastasis and what could be done to prevent and/or treat it. There have been extensive studies that also attempt to explain metastasis in the context of the complex and dynamic tumor microenvironment, consisting of cells, blood vessels, extracellular matrix (ECM), cytokines, and chemokines [4]. In particular, inflammatory processes mediated by the tumor microenvironment have been emphasized in breast cancer progression [5]. An example of a chemokine that has been linked to aggressive breast cancer is chemokine C-C motif ligand 5 (CCL5), which is also known as RANTES (Regulated upon Activation, Normal T-cell Expressed and Secreted) [6].

In humans, the CCL5 gene is found at the chromosome location 17q11.2-q12 [7] and the 8 kDa protein has significant roles in multiple physiological processes. For instance, CCL5 can be expressed by platelets, endothelial cells, bronchial epithelial cells, and cells of the immune system (e.g. macrophages, monocytes, natural killer cells, and dendritic cells) [8]. Kruppel-like factor 13 (KLF13) controls the transcription of CCL5 in T lymphocytes [9]. In particular, CCL5 mediates migration and chemotaxis of cells, including memory T lymphocytes [10], monocytes [10a], dendritic cells [11], eosinophils [12], basophils [12], and mast cells [12].

CCL5 has three different chemokine C-C motif receptors (CCRs): CCR1, CCR3, and CCR5 [13]. In 2006, CCL5 was also discovered to bind G protein-coupled receptor 75 (GPR75) [14]. Elevated levels of CCL5 and CCR5 have been detected in more than 58% of basal breast cancer and ERBB2+ breast cancer patients [6d]. In addition to the migratory effects mediated by CCL5, other CCR5 ligands also trigger the migration of Th1 cells, natural killer

(NK) cells, and macrophages [15]. Besides playing a role in breast cancer progression, CCL5 expression has also been detected in ovarian cancer [16], prostate cancer [17], pancreatic cancer [18], and melanoma [19]. In 2014, the structure of the CCL5-CCR5 complex was derived [20]. Structural information of this complex represents an important advancement for elucidating interactions that can antagonize the effects of CCL5-CCR5 signaling.

This review summarizes recent studies that reveal the role of CCL5 in breast cancer metastasis.

THE SOURCE OF CCL5 AND ITS EFFECT IN CANCER LESIONS

Mesenchymal stem cells (MSCs) are multipotent progenitor cells that are required for the regeneration of tissues such as cartilage, bone, adipose, and muscle [21]. These cells are found largely in the bone marrow, but are also present in other tissues [22]. It is known that breast cancer cells under hypoxic conditions release certain factors, such as placental growth factor (PGF) [23] and chemokine C-X-C motif ligand 16 (CXCL16) [24], that recruit MSCs to the tumor microenvironment. Notably, when breast cancer cells were co-cultured with MSCs *in vitro,* it was found that the latter cells produce CCL5 [25]. However, breast cancer cells may also secrete this chemokine, although the proportion of CCL5 derived from cancer cells may not have a major impact on cancer propagation [26]. The secretion of MSC-derived CCL5 is driven by a positive-feedback loop. Namely, CCL5 and hypoxia stimulate breast cancer cells to secrete colony-stimulating factor 1 (CSF1), which in turn promotes the increased production of CCL5 from MSCs [24]. It has been demonstrated that breast cancer cells need to be closely associated with MSCs in order to stimulate the secretion of CCL5 [25]. CSF1 also recruits tumor-associated macrophages (TAMs) (Fig. 1) and myeloid-derived suppressor cells (MDSCs) to the tumor microenvironment [24]. In addition, CSF1 promotes secretion of TAM-derived epidermal growth factor (EGF), which acts on breast cancer cells to increase their metastatic potential [24]. Moreover, *in vivo* studies have demonstrated that the secretion of CCL5 promotes breast cancer metastasis [25]. PGF and CXCL16 released by breast cancer cells stimulate the MSCs to secrete CXCL10, which reinforces the action of CCL5 by promoting invasiveness (Fig. 2a) [23, 24]. An additional factor that is involved in mediating the release of CCL5 from MSCs is cancer cell-derived osteopontin (Fig. 2b) [27]. Osteopontin, which is a glycosylated phosphoprotein that acts as a cytokine, also mediates cell adhesion [28], and has previously been associated with breast cancer metastasis [29]. Osteopontin causes increased gene expression of CCL5 by binding to integrin on the surface of MSCs, subsequently causing activation of activator protein-1 (AP-1), which is a transcription factor for CCL5 [27]. Osteopontin has also been shown to trigger the differentiation of MSCs by increasing their expression of cellular markers that are typical of cancer-associated fibroblasts (CAFs) [27]. CAFs are known to contribute to angiogenesis and cancer cell proliferation in tumors [30]. Furthermore, CAFs also promote the onset of epithelial to mesenchymal transition (EMT) in cancer cells [31]. Further support for the role of osteopontin in breast cancer invasiveness comes from studies demonstrating that an RNA aptamer that inhibits the activity of osteopontin causes reduced metastasis [27]. In essence, several intertwined feedback loops between cancer cells and cells in the tumor microenvironment serve to increase the metastatic potential of breast cancer cells.

In a study where breast cancer cells were made to overexpress CCL5, it was found that the chemokine enhances metastasis by increasing the motility and extravasation of cancer cells from the blood to a distant site in the body [25]. The same study also demonstrated that the CCL5-induced metastatic phenotype is reversible, since cells that have already formed metastatic lesions do not display enhanced invasiveness. Additionally, CCL5 was also shown to promote metastasis by inducing the secretion of metalloproteinases (MMPs) that break down surrounding ECM proteins, thereby facilitating the movement of tumor cells (Fig. 2d) [32]. In the normal murine mammary gland (NMuMG), the secretion of both CCL5 and CCL9 by MSCs enhanced the invasion of injected 4T1 mammary tumor cells through the production of MMP 9 and/or MMP 13, and MMP14 [32]. These MMPs can be produced by both cancer cells and cells in the microenvironment [33].

In addition to promoting invasiveness, CCL5 has also been shown to increase the proliferative potential of MDA-MB-231 human breast cancer cells (triple-negative) [34]. Moreover, other studies using the MCF-7 cell line (estrogen receptor positive) with MSC xenografts have also revealed that CCL5 promotes proliferation [25, 35]. The effect of CCL5 on breast cancer proliferation was demonstrated in an *in vivo* study as well using a mouse tumor model with co-grafted MSCs and MDA-MB-231 cells [27]. However, these results are contradicted by other studies claiming that CCL5 improves the metastatic potential of cancer cells, but does not affect cell replication. In particular, the inhibition of CCL5 and CCR5 binding did not affect the growth of MDA-MB-231 cells [6d]. Similarly, it was shown that the overexpression of CCL5 or the presence of MSCs does not affect tumor growth kinetics in MDA-MB-231 cells [25]. These discrepancies could potentially be explained by differences in experimental techniques. For example, the latter study used subcutaneous tumor models, whereas the study linking CCL5 to enhanced proliferation used orthotopic models. It is possible that an orthotopic environment provides additional factors or characteristics that work along with CCL5 to promote breast tumor cell proliferation. In general, it is thought that MSCs only promote the proliferation of estrogen receptor positive breast cancer cell lines, which typically display limited production of autocrine IL-6, thus rendering them more sensitive to paracrine IL-6 [36]. Accordingly, MSCs can provide these cell lines with a continuous source of IL-6 [37], which has been shown to promote replication of breast cancer cells [36b].

In summary, CCL5, which is mainly produced by MSCs, promotes metastasis by triggering MMP production and improving cancer cell motility through a complex network of interacting factors and positive feedback loops (Fig. 3).

HYPOXIA INCREASES CCL5 EXPRESSION

Hypoxia inducible factor-1 (HIF-1) is a transcriptional activator that consists of HIF-1α and HIF-1β components. HIF-1β is expressed continuously, whereas HIF-1α is increased in response to low levels of oxygen. Since the activation of HIF-1 requires both components to be present, the protein becomes functional upon HIF-1α stabilization [34]. The activation of HIF-1 enables binding to hypoxia-responsive element (HRE), consequently initiating the transcription of target genes that respond to hypoxia. Hypoxia is a significant contributor of tumor progression, and until recently, the effects of hypoxia on the CCL5-CCR5 axis had

not been evaluated. Currently, it is known that HIF-1α contributes to increased expression of CCR5 and CCL5, along with enhanced motility of the cancer cells [24, 34]. Recently, HIF-binding regions in the CCR5 gene have also been identified [24].

HIF is also correlated with the recruitment of MDSCs to the mammary tumor microenvironment [24]. A recent study demonstrated that CCL5 secreted by cells originating from the bone marrow (e.g. T cells, platelets, and macrophages) is crucial for the growth of MDSCs [26b]. MDSCs have been shown to indirectly reduce the numbers of antitumor CD8+ T cells, which are needed for host-derived tumor suppressive responses [26b]. The same study has also shown that in the absence of CCL5, MDSCs develop a phenotype that does not suppress antitumor CD8+ T cells.

CCL5 INDIRETLY PROMOTES EMT OF BREAST CANCER CELLS

In addition to MSCs, TAMs can also enhance metastasis through interactions with breast cancer cells. Indeed, macrophages in the tumor microenvironment largely possess the M2 phenotype that propagates pro-oncogenic functions, such as cell division, metastasis, and survival of tumor cells [38]. Therefore, the recruitment of TAMs to the tumor microenvironment has been connected to adverse outcomes in breast cancer patients [39]. Correspondingly, low numbers of TAMs at the tumor site has been linked to decelerated tumor progression [40]. The recruitment of monocytes from the blood stream is driven by CCL5 [41], CCL2 [41b], and CSF1 [40] in the tumor microenvironment (Fig. 1). The secretion of CSF1 by breast cancer cells is induced by CCL5 and hypoxia [24]. Once the monocytes have arrived at the tumor site, the breast cancer cells promote their differentiation into TAMs [42]. This process is mediated by granulocyte macrophage-colony-stimulating factor (GM-CSF), which is secreted by mesenchymal-like cancer cells [42]. Furthermore, lactate, which is a common metabolic product of cancer cells, also contributes to macrophage differentiation [42]. Thereafter, the fully differentiated TAMs secrete CCL18 that binds to the PITPNM3 receptor on cancer cells to trigger downstream calcium signaling, which promotes EMT [39]. A positive-feedback loop is formed, as cancer cells that have recently acquired a mesenchymal phenotype will further promote macrophage transformation into TAMs (Fig. 1). In essence, CCL5 does not directly stimulate EMT, rather this process is indirectly driven by CCL5, CCL2, and CSF1, which recruit monocytes to the cancer lesion (Fig. 1).

FURTHER INTERACTIONS WITH CCL5 IN THE TUMOR MICROENVIRONMENT

Interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), CCL5, and CCL2 (also known as monocyte chemoattractant protein, MCP-1) act synergistically to promote breast cancer progression [43]. The expression of all four factors is enhanced in breast tumors as compared to normal breast tissue [43]. Together these factors act in a spatiotemporally controlled manner to promote malignancy. In fact, IL-1β and TNF-α stimulate the secretion of CCL5 and CCL2 from breast cancer cells (Fig. 2c) [43], while CCL2 elaborates the exocytosis of CCL5 from breast cancer cells [44]. Additionally, TNF-α is involved in triggering actin cytoskeleton rearrangements and the onset of EMT, thus promoting

metastasis [43]. The same study has also shown that IL-1β also triggers tumor progression through EMT, although to a lesser extent than TNF-α. Accordingly, patients displaying relapse from invasive ductal carcinoma have increased levels of TNF-α and IL-1β [43]. CCL5 also acts as a mediator that promotes shedding of microparticles containing the S100A4 protein from the outer membranes of various cells, including fibroblasts [45]. Once released, S100A4 increases CCL5 and fibronectin expression, and enhances cellular migration and overall metastatic potential [45]. Together, CCL5 and S100A4 increase invasiveness by inducing the recruitment of cells that belong to the tumor stroma and immune system [45]. These cells collectively contribute to the growth of tumor cells in a location distant from the primary tumor.

An additional signaling molecule that affects CCL5 production in the tumor microenvironment is transforming growth factor-β (TGF-β). TGF-β is known to contribute to breast cancer progression by promoting EMT and metastasis [31, 46]. Serum CCL5 has been positively correlated with TGF-β1 [47]. Notably, it has been shown that in colon cancer, the CCL5/CCR5 axis promotes production of TGF-β in T regulatory cells (Tregs), which subsequently causes apoptosis of antitumor CD8+ T cells [48]. Antitumor CD8+ T cells are needed for an efficient immune response against cancer. In the 4T1 mammary tumor model, we observed a significant decrease in tumor-infiltrating Tregs in the absence of CCL5 [26b], suggesting that a similar CCL5-mediated increase in Tregs is involved in breast cancer progression.

Furthermore, there exists a negative correlation between serum levels of CCL5 and estradiol [47], indicating that the systemic levels of CCL5 rise and fall cyclically in premenopausal women. In fact, circulating CCL5 levels fall significantly during the mid-follicular phase [47]. Moreover, a negative correlation between serum levels of CCL5 and progesterone has also been found [47].

BLOCKING CCL5/CCR5

The CCL5/CCR5 axis is enhanced in basal breast cancers and ERBB2+ breast cancers [6d, 49]. In a primary breast tumor population, only a small proportion of cancer cells are positive for CCR5 expression [6d]. On the contrary, the *in vivo* analysis of secondary breast tumors that have metastasized to a distant site has revealed an eight-fold increase in the cell population that is positive for CCR5 [6d]. This observation could potentially be due to enhanced invasiveness of cells that express CCR5, or elaborated CCR5 expression promoted by the secondary tumor environment. *In vitro*, CCR5+ basal breast cancer cells are 40-fold more invasive than their CCR5-counterparts [6d], indicating that increased invasive ability is the reason for the higher fraction of CCR5+ cells in secondary lesions.

Maraviroc, a US Food and Drug Administration (FDA)-approved anti-viral drug, is known to prevent the function of CCR5 [49]. In particular, the human immunodeficiency virus (HIV) can bind to CCR5 through the gp120 viral surface protein, thereby mediating viral entry into target cells [49–50]. Indeed, systemic administration of maraviroc proved useful in reducing breast cancer metastasis to the lungs, providing further evidence for the importance of CCL5 for metastatic dissemination [49]. Notably, maraviroc does not affect

the proliferation of the cancer cells, indicating that a reduction in metastasis is not due to a drug-induced anti-proliferative effect [6d]. However, CCR5 has also been shown to promote adaptive immune responses that suppress tumor progression, through the activation of T cells that have antitumor functions [51]. It has also been shown that in ovarian cancer, CCL5 secreted by CD4+ T cells attracts CCR5+ dendritic cells (DCs) to the cancer lesion, subsequently activating them. The DCs then prime CD8+ T cells, which also have antitumor functions [52]. Therefore, it has been postulated that therapeutically it may be more beneficial to stimulate CCR5 than to inhibit this receptor. It is yet to be seen whether blockage of CCR5 impairs the antitumor adaptive immune response to such an extent that the resulting enhancement of cancer progression outweighs the benefits of blocking CCR5.

Additionally, the blockage of CCR5 will also affect the function of other ligands that bind to this receptor, including CCL3 (macrophage inflammatory protein-1α, MIP-1α), CCL4 (MIP-1β), CCL5, CCL8 (monocyte chemotactic protein 2, MCP-2), and CCL3L1 (MIP-1α/LD78β) [51, 53]. For instance, the interactions between DCs and CD4+ T cells are mediated by CCL3 and CCL4, which also have the ability to recruit CD8+ T cells [54]. Therefore, it may be more advantageous to therapeutically suppress CCL5 as opposed to CCR5, in order to retain immunological antitumor function. Moreover, the choice of whether to block the receptor or the ligand should also be based on the corresponding cell types, i.e. CCL5 is mainly produced by MSCs and CCR5 is present on breast cancer cells. In this regard, it may be easier to use MSCs as a therapeutic target as they are typically present in smaller quantities than cancer cells [55], thereby requiring less therapeutic agent to achieve complete blockage of the signaling pathway. Furthermore, since the genome of cancer cells is relatively unstable [56], these cells are more likely to undergo mutations that render them resistant to therapy. On the contrary, non-cancerous cells in the tumor microenvironment are presumed to be genetically stable, potentially making them a more suitable therapeutic target [57].

FUTURE CONSIDERATIONS

The metastatic properties of breast cancer cells mediated by CCL5 are only transiently upregulated and the metastatic phenotype is reversible [25]. Consequently, it has been proposed that it could be challenging to detect temporary expression of molecules and phenotypes that propagate breast cancer. Accordingly, whereas many studies have reported elevated CCL5 levels in breast cancer patients [6b, 58], one study reported similar levels of circulating CCL5 in healthy women and women with breast cancer [47]. The lack of difference in CCL5 levels between healthy individuals and breast cancer patients could be due to variations in CCL5 levels during different stages of the menstrual cycle [47]. Hence, future studies with human subjects should control for menstrual cycles while analyzing plasma CCL5 levels in breast cancer patients.

In the context of therapeutics, the use of maraviroc to antagonize CCR5 function has shown promising results in terms of reducing breast cancer metastases to the lungs [49]. Alternatively, small interfering RNA (siRNA) against CCL5 or CCR5 could be used to specifically suppress the expression of these proteins. In fact, siRNA has been used extensively *in vitro* and *in vivo* to reduce the levels of various oncogenes [59]. Since the

delivery of naked siRNA is challenging due to rapid degradation and low intracellular uptake, the use of biocompatible nanodelivery systems could provide the means for achieving therapeutic efficacy [60]. The CCL5-CCR5 axis may prove to be an especially useful target for triplenegative breast cancer, as this disease has limited treatment options in comparison to breast tumors expressing estrogen, progesterone, and/or epidermal growth factor receptors [61]. Importantly, CCL5 does not play a crucial role in other biological functions indicating that CCL5 inhibition should not produce adverse side effects. In fact, CCL5-knockout mice appear to undergo normal development and growth stages, and their ability to resist various infections remains mostly unchanged [62].

In essence, CCL5 represents a potentially efficacious target for preventing breast cancer metastasis. Nevertheless, the impact of impairing or stimulating CCL5 signaling should be carefully evaluated in the context of this disease. It is likely that the effect of CCL5 signaling will be different depending on the breast cancer type and stage of disease, suggesting that precision medicine and the appropriate design of dosage regimens could be crucial for obtaining therapeutic efficacy.

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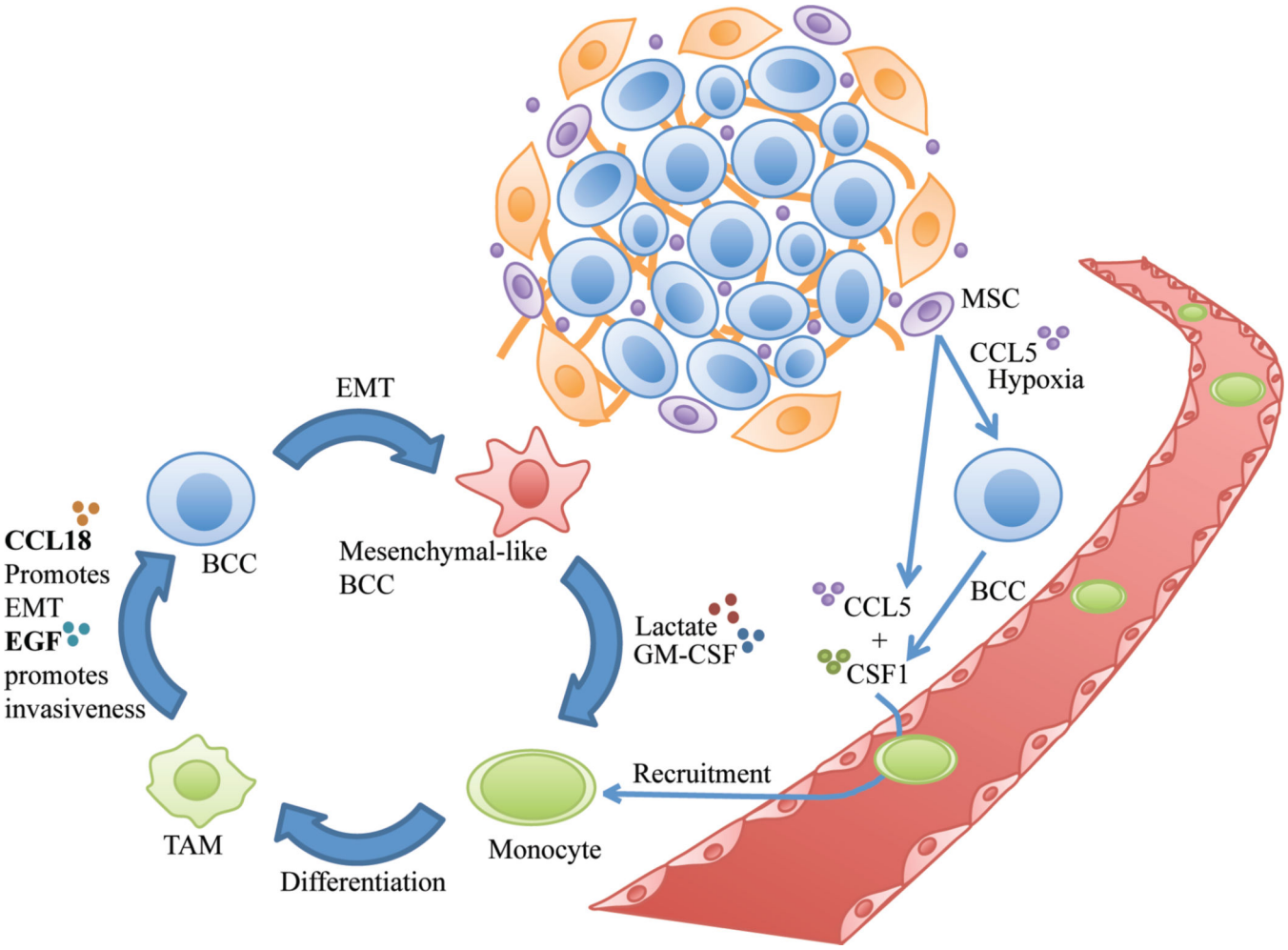

Figure 1.

Mesenchymal stem cells (MSCs) secrete chemokine C-C motif ligand 5 (CCL5) in the breast tumor microenvironment. CCL5, combined with hypoxia, stimulates breast cancer cells (BCCs) to secrete colony-stimulating factor 1 (CSF1). CSF1 and MSC-derived CCL5 promote monocyte recruitment. CCL2 (not shown here) also helps recruit monocytes from the blood. Monocytes in the tumor microenvironment differentiate to form tumor-associated macrophages (TAMs). CSF1 from BCCs also stimulates TAMs to release epidermal growth factor (EGF), which enhances BCC invasiveness. TAMs also secrete CCL18, which initiates the epithelial to mesenchymal transition (EMT) in tumor cells. BCCs that have undergone EMT then release lactate and granulocyte macrophage-colony stimulating factor (GM-CSF). These factors promote monocyte differentiation into TAMs, which propel further EMT in BCCS by secreting CCL18.

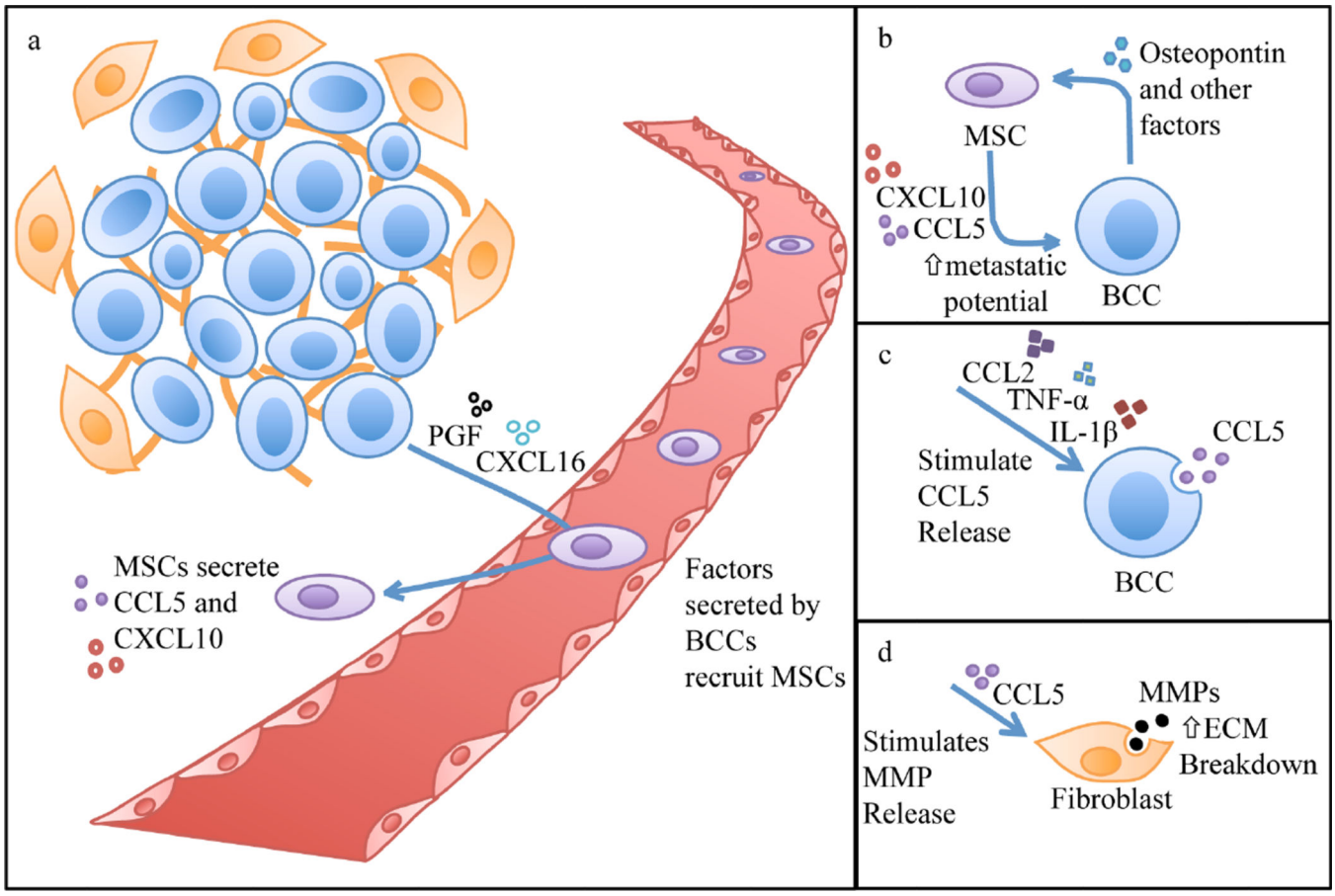

Figure 2.

(a) Under hypoxic conditions, BCCs release placental growth factor (PGF) and chemokine C-XC motif ligand 16 (CXCL16), which recruit MSCs to the site of the primary breast tumor and trigger their secretion of CXCL10 and CCL5. (b) Osteopontin released by BCCs stimulates MSCs to release CCL5. In addition, MSCs also secrete CXCL10 upon stimulation by BCC-derived PGF and CXCL16. CCL5 and CXCL10 enhance the metastatic potential of BCCs. (c) Factors such as CCL2, tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β) stimulate CCL5 secretion by BCCs. (d) CCL5 stimulates BCCs (not shown) and stromal cells such as fibroblasts to secrete metalloproteinases (MMPs). MMPs break down the proteins of the extracellular matrix (ECM), which enhances metastasis of BCCs.

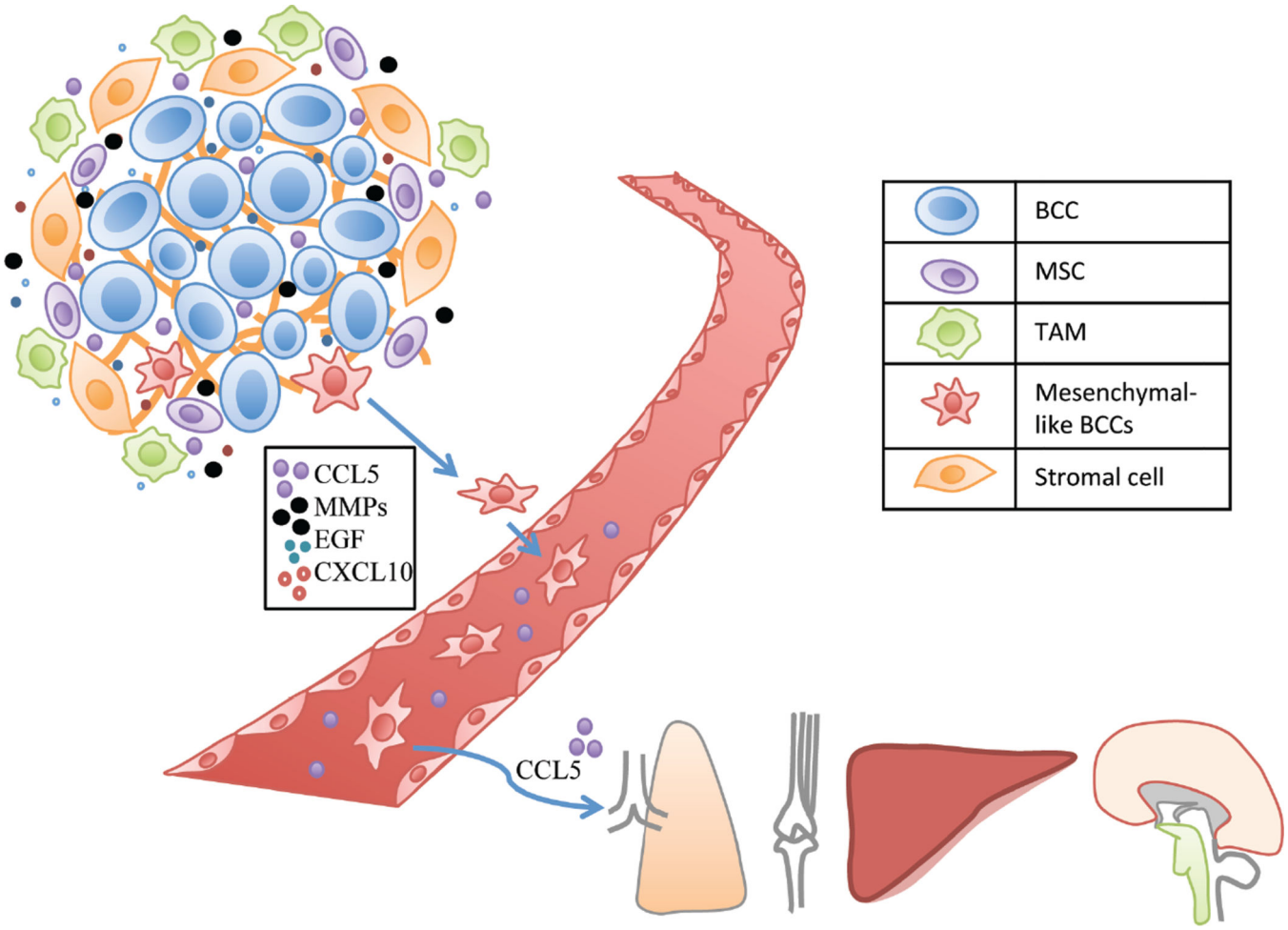

Figure 3.

CCL5, epidermal growth factor (EGF), and CXCL10 improve the invasiveness and motility of cancer cells. MMPs break down the surrounding ECM, thereby facilitating BCC motility. MSCs, monocytes and stromal cells, such as fibroblasts, are recruited to the microenvironment. Monocytes differentiate into TAMs. CCL5 also promotes the later steps of metastasis, by aiding extravasation from blood vessels to the metastatic niche. Breast cancer cells mainly metastasize to the lungs, bones, liver, and brain.