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Chemokines in health and disease

Dayanidhi Raman[1], **Tammy Sobolik-Delmaire**[1], and **Ann Richmond**[1,2,#]

[1]Department of Cancer Biology, Vanderbilt University, School of Medicine, Nashville, TN 37232

[2]VA Medical Center; Nashville, TN 37232

Abstract

Chemokines and their receptors play a key role in development and homeostasis as well as in the pathogenesis of tumors and autoimmune diseases. Chemokines are involved in the implantation of the early conceptus, the migration of subsets of cells during embryonic development, and the overall growth of the embryo. Chemokines also have an important role in the development and maintenance of innate and adaptive immunity. In addition, they play a significant role in wound healing and angiogenesis. When the physiological role of chemokines is subverted or chronically amplified, disease often follows. Chemokines are involved in the pathobiology of chronic inflammation, tumorigenesis and metastasis, as well as autoimmune diseases. This article reviews the role of chemokines and their receptors in normal and disease processes and the potential for using chemokine antagonists for appropriate targeted therapy.

Keywords

chemokines; leukocytes; tumor progression; metastasis; autoimmune diseases

Chemokines or chemotactic cytokines are a family of small molecular weight proteins that promote directional migration of leukocytes, endothelial and epithelial cells. Chemokines are classified into CXC, CC, CX_3C or C chemokines based on the positioning of the conserved cysteine residues [1,2]. Based on their function, chemokines can be homeostatic, inflammatory, or both. Homeostatic chemokines are constitutively expressed and are important for many physiological processes, while the expression of inflammatory chemokines is induced by inflammatory stimuli. These small chemotactic proteins play a vital role in host defense mechanisms through development and maintenance of innate and acquired immunity. In addition to a role in immunity, they also regulate subsets of cells during embryogenesis. Importantly, chemokines are involved in wound healing, angiogenesis / angiostasis and in the development and metastasis of tumors.

This review is organized into two major areas. In the first part of the review, the mechanism by which chemokines/chemokine receptors regulate chemotaxis will be discussed as well as their role in embryonic development, immunity, wound healing and angiogenesis. In the second part, the role of chemokines in inflammation and disease will be discussed.

Corresponding author: Dr. Ann Richmond, Ph. D., Dept. of Cancer Biology, 432 Preston Research Building, 23rd Ave South @ Pierce, Vanderbilt University Medical Center, Nashville, TN 37232, Tel.: 615-343-7777, Fax: 615-936-4687, ann.richmond@vanderbilt.edu.

Chemokines in health

Chemokine receptor signaling, receptor dimerization and chemotaxis

Chemokine receptors are seven transmembrane G-protein coupled receptors (GPCRs) that bind chemokine ligands with high affinity to activate the heterotrimeric $G\alpha_i\beta\gamma$. The exchange of GDP for GTP induces separation of Gα (usually $G\alpha_i$) and Gβγ subunits followed by activation of a series of downstream effectors [3]. A number of adaptor proteins dynamically interact with chemokine GPCRs to facilitate internalization and signal transduction and this dynamic interaction continues during vesicular trafficking where the interactions exhibit both spatial and temporal plasticity. This network of proteins associating with chemokine GPCRs forms a dynamic "chemosynapse" that is vital for chemotaxis [4-7]. Overall, active $G\alpha_i$, Gβγ and the "chemosynapse" facilitate directional sensing, polarization of the cell with the leading edge (pseudopodium) in the front and the formation of a trailing tail (uropod) at the back. Small GTPases Rac, Cdc42 and phosphatidylinositol-3-kinase (PI3K) accumulate at the leading edge with resultant actin polymerization and F-actin formation, leading to stabilization of the lamellipodium. Phosphatase and tensin homolog (PTEN) tyrosine/PIP3 phosphatase resides along the sides and at the posterior end of the migrating cells, Rho GTPase and its effectors accumulate at the trailing edge facilitating actomyosin contraction and tail retraction that result in migration of the cell [8].

Chemokine GPCRs undergo constitutive homo- or hetero-dimerization and the functional impact of such dimerization on the pharmacological properties of the given chemokine receptor appears to be of great significance. Heterodimerization of CCR2 with CCR5 receptor results in negative cooperativity and this is also observed with CCR2/CXCR4 heterodimers. Interestingly, allosteric trans-inhibition with specific antagonists was observed with CCR2/CXCR4 heterodimers. For example, inhibition of CCR2 and CCR5 with TAK-779 or inhibition of CXCR4 with AMD3100, led to functional cross-inhibition of other dimerizing receptors in leukocytes [9]. Interestingly, in a murine air pouch model of inflammation, similar cross-inhibition with specific receptor antagonists was observed. Recently, CCR2, CCR5 and CXCR4 have also been demonstrated to form hetero-oligomeric complexes containing all three receptors [10]. These observations have very important therapeutic implications.

Heterologous transactivation of tyrosine kinase receptors by activated chemokine GPCRs suggests that the cross talk between different receptors can have important physiological consequences. For example, active CXCR4 has been shown to stimulate ovarian cancer cell growth through transactivation of the epidermal growth factor (EGF) receptor [11,12]. Activation of chemokine receptors CXCR4 and CCR5 is reported to transactivate the Jak-STAT pathway as well [13-15].

Devices and methods to study chemotaxis in 2-D and 3-D environment

Microfluidic 2-D devices—To study chemotaxis *in vitro*, 2-dimentional (2D) microfluidic devices have been utilized, wherein a continuous chemokine gradient is generated, allowing cells placed in the device to sense the gradient, polarize and undergo directional migration along the gradient [16,17]. These devices allow visual monitoring of cells during chemotaxis and analysis of molecular pathways contributing to chemotaxis where signaling molecules have been mutated, knocked down, or knocked out. Also, the direction of the chemokine gradient can be reversed quickly to examine the ability of the cells to respond to the change and repolarize quickly.

3-Dimensional matrices—The study of cell migration in 3-dimensional (3D) matrices is very important since many parameters of motility are different in 3D as compared to 2D

migration. A low level of localized Rac activity at the leading edge is critical for cells to undergo persistent migration. Cells migrating in 3D exhibit matrix adhesions all over their surface and are more persistent in directional migration with lower levels of activated Rac at the leading edge [18]. Similarly, experimental evidence in neurons and *C. elegans* also suggested that lower levels of active Rac will promote directionality. 3D cell migration studies are likely to correlate with *in vivo* situations although the extracellular matrix (ECM) present in physiological conditions is far more diverse than that of *in vitro* studies. For example, tenascin, an ECM protein, restrains lymphocyte migration, whereas fibronectin enhances the migration of T lymphocytes compared to using only collagen in the 3D matrix. Thus appropriate replication of the composition and the architecture of the 3D matrix are vital for accurate interpretation of cell migration studies. Two major shortcomings persist in the design of in vitro studies studying cell migration in 3D matrices: 1) the collagen concentrations employed in *in vitro* studies is far lower than what occurs *in vivo*; 2) the more permissive nature of *in vitro* 3D matrices (loose and non-cross-linked or less cross-linked) when compared to compact and highly cross-linked collagenous ECM *in vivo*. Also, cells migrating in 3D matrices lack typical lamellipodium but have pseudopodial protrusions with small flat extensions similar to a lamellipodium [18]. Nevertheless, 3D *in vitro* cell migration studies are thought to be superior to 2D *in vitro* studies. Interestingly, cells migrating in 3D do not form stable focal adhesions with paxillin, focal adhesion kinase (FAK), zyxin, p130-Crk associates substrate (p130CAS) and vinculin but these proteins do regulate cell speed and persistence by modulating pseudopodial protrusion dynamics and matrix deformation [19]. This did not happen in 2D. Similarly, a MEK-cofilin signaling module modulated migration of human T cells only in 3D but not in the 2D microenvironment [20].

Bioreactors—3-D scaffold micro-fabrication technologies are beginning to emerge with designer systems to address the need for creating a 3-D microenvironment for studying cell migration and tumor biology [21-25]. A 3-D reticulated system has been described for T-cell production and an artificial lymph node for studying the interactions between T cells and dendritic cells [22,26]. Micro-scale flows have been created in 3-D microenvironment in order to study autologous chemotaxis as a mechanism for intravasation of tumor cells into the lymphatics [27,28]. This technique was also adapted to investigate the cross-talk between the tumor cell and the lymphatic endothelial cells that lines the lymphatics [28,29]. More work needs to be done to fine tune the 3-D microenvironment so that it better represents the *in vivo* physiological state.

Role of chemokines in embryonic development

Chemokines play a role in the endometrium of the uterus prior to the implantation of the embryo [30]. The chemokine-receptor signaling at the maternal-fetal interface enables human trophoblast (fetal) to migrate and move into the epithelial region of the endometrium [31]. The human trophoblasts express the chemokine receptors CX_3CR1, CCR1, CCR3 and their respective ligands are present in the endometrial microenvironment [31]. The trophoblast also induces the expression of the chemokines CXCL1, CXCL2, CCL8 and the chemokine receptor CXCR4 in the maternal decidualized stromal cells [32]. The bidirectional chemokine mediated signaling between the trophoblast and the maternal endometrium may enable the successful implantation of the embryo.

Chemokines play a functional role in embryogenesis and development of the central nervous system (CNS) in zebra fish and mouse models [33,34]. The chemokine receptors CXCR4 and CXCR7 and their ligand stromal cell derived factor-1α (SDF-1α/CXCL12) influence CNS development through homing of the neuronal precursor cells to their respective target

areas of the developing brain [35-37]. The chemokine CXCL12 is constitutively expressed in both neurons and astrocytes and is involved in axon elongation and path finding [38-41].

The chemokine receptors CXCR4 and CXCR7 and their ligand CXCL12 also mediate and shape the migratory pattern of primordial stem cells [33]. In a Medaka fish model, the transcription factor nanog appears to regulate the primordial germ cell migration by controlling the expression of the chemokine receptor Cxcr4b [42]. Interference with the chemokines or their receptors mis-target the migratory patterns of progenitor cells, resulting in developmental abnormalities [33,43,44].

The CXCL12/CXCR4 axis is also involved in lympho- and myelopoiesis in the bone marrow, hematopoietic stem cell homing to sites of vascular expansion [33,45], and cardiac development [33]. This axis is also involved in murine skeletal muscle development in the limb through the genetic interaction of CXCR4 with Gab1 to direct the progenitor cells to CXCL12-expressing mesenchyme of the limb and the first branchial arch [46].

Role of chemokines in immunity

Chemokines play a pivotal role in innate and adaptive immunity. The innate immune response is mediated by neutrophils, monocytes, dendritic cells (DC) and natural killer (NK) cells. Naïve and memory CD4 and CD8 cells and immature DCs are involved in the adaptive immune response. The constitutive components and conserved products of microbial metabolism form distinct pathogen-associated molecular patterns (PAMP). The PAMPs are recognized by receptors of the innate immune system, pattern-recognition receptors (PRRs), such as NOD1, NOD2 and Toll-like receptors (TLR) [47,48]. The epithelial and dendritic cells release a battery of cytokines as a result of PRR signaling [49]. The TLR signaling trigger distinct biological responses through recruitment of different adaptors MyD88, TIRAP (Mal), TRIF and TRAM. During tissue damage, non-infectious endogenous molecules are released that cause sterile inflammation following activation of TLRs through damage associated molecular patterns (DAMPs) [50]. Recently, adenosine triphosphate (ATP) released from the necrotic cells was shown to activate the Nrlp3 inflammasome. This led to a generation of an intravascular chemokine gradient in order to guide the neutrophils to the necrotic foci. Additionally, formyl-peptide signals released from the necrotic cells also navigated the neutrophils to the sites of sterile inflammation [51]. The cytokines generated through TLR signaling, in addition to their autocrine and paracrine effects, amplify the chemokine release resulting in a polarized cytokine profile (Th1 vs Th2). The adaptive immune response is mediated by both homeostatic and inflammatory chemokines. The chemokines CCL19 and CCL21 activate the chemokine receptor CCR7 present on naïve T cells, B cells, mature DC/Langerhans cells (LC) and $CD56^{bright}$NK cells and induce their migration towards the T cell zone of secondary lymphoid organs (SLO) [52]. Ligands of the sphingosine-1-phosphate (S1P) receptor also modulate the entry and exit of the T cells from SLO [53-56]. The B cells express the chemokine receptor CXCR5 that directs their homing to follicles of the lymph node (LN) that express the chemokine CXCL13, the ligand for CXCR5 [55]. Immature DCs express CXCR1, CCR1, CCR2 and CCR6 and the ligands for these receptors are inflammatory chemokines that recruit these immature DCs to the site of inflammation [55]. Integrins like CD11b have been demonstrated to be a negative regulator of TLR signaling [57]. Loss of negative regulation of TLR signaling and recognition of self-antigens form the basis for pathogenesis of many inflammatory and autoimmune diseases [49]. Toll-like receptors may also link inflammation and angiogenesis. Infiltrated leukocytes at the sites of inflammation can promote oxidative stress by producing carboxyalkylpyrrole protein adducts (CAPs) such as ω-(2-carboxyethyl)pyrrole (CEP). Increased levels of CEP directly promoted pro-angiogenic effects by acting on TLR2 on non-hematopoietic cells that is independent of VEGF [58].

Role of chemokines in cutaneous wound healing

Chemokines are important and vital for proper wound healing. The role of CXC chemokines and their receptors in wound healing has been recently reviewed in detail elsewhere but will be briefly discussed here [59]. Wound healing is a well regulated process with three phases, namely inflammation, proliferation and remodeling. Chemokines are involved in each of these steps [60]. The proliferative phase includes neo-angiogenesis, formation of granulation tissue and ECM, and re-epithelialization. The remodeling phase involves activation of matrix metalloproteinases through the mammalian target of rapamycin (mTOR) pathway. The chemokines CXCL1 and CXCL8 as well as their receptor, CXCR2, are expressed in the human epidermis and are highly involved in wound healing [61]. The role of CXCR2 is wound healing was demonstrated in the study by Devalaraja et al, showing that CXCR2(-/-) mice exhibit impaired recruitment of neutrophils, reduction in migration and proliferation of keratinocytes during epithelialization and also a significant delay in neovascularization and wound closure [62]. Expression of the angiostatic chemokine CXCL10 in the transgenic mice was demonstrated to have an intense inflammatory phase coupled with an extended and disorganized granulation phase. This resulted in impaired neovascularization of the wound bed and delayed wound healing [63]. Ishida *et al* have shown that the chemokine CX_3CL1 and its receptor CX_3CR1 are up regulated at the wound sites [64]. The role of CX_3CR1 in wound healing is further strengthened by the observation that there is reduced macrophage infiltration into the excisional wounds and reduced collagen deposition and neovascularization in CX_3CR1 (-/-) mice [64]. The CC chemokine CCL27 accelerates wound healing through recruitment of bone marrow-derived keratinocyte precursor cells [65]. Prevention of recruitment and activation of natural killer T cell (NKT) to the wound bed leads to enhanced wound healing [66]. Mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK-2 or MK2) gene expression in macrophages is critical in wound healing based upon studies from MK2 knockout mice [67].

Role of chemokines in angiogenesis

ELR^+CXC-chemokines CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8 are pro-angiogenic and ELR^-CXC-chemokines CXCL4, CXCL4L1, CXCL9, CXCL10, CXCL11 and CXCL14 have angiostatic activity [68-74]. The Duffy antigen receptor for chemokines (DARC) sequesters the ELR^+CXC-chemokines and indirectly inhibits angiogenesis [75,76]. The ELR^+CXC-chemokines directly act on the chemokine receptors CXCR2 and CXCR1 in humans and only through CXCR2 in the mouse. These receptors are present on endothelial cells and induce migration, invasion and proliferation of the endothelial cells, resulting in angiogenesis. CXCR2 is the key receptor involved in neo-vascularization as all ELR^+CXC-chemokines bind to and activate CXCR2 but only CXCL6 and CXCL8 can bind to CXCR1. Additionally, only CXCR2 mediates chemotaxis of the endothelial cells and blocking the function of CXCR2 blocks CXCL8 mediated angiogenesis even though CXCL8 is capable of binding to CXCR1 [77-79]. ELR^+CXC-chemokines also serve as a signal for homing of endothelial progenitor cells from the bone marrow to the sites of angiogenesis. Neutralizing antibodies to CXCR2 block endothelial cell migration and genetic ablation of CXCR2 results in profound inhibition of angiogenesis [77]. Thus, CXCR2 exhibits a major role in wound healing. Tumors utilize a similar mechanism to enhance angiogenesis and thus facilitate tumor growth [80-82].

CC chemokines also have a role in angiogenesis. CCL2 mediates neovascularization by acting on CCR2 present on endothelial cells. Plasma membrane anchored membrane type1-matrix metalloproteinase (MT1-MMP) is necessary for this effect on neovascularization. CCL2 that acts on endothelial CCR2 also induces expression of VEGF-A and MCP-1 induced protein, a transcription factor [83]. In addition CCL11 and CCL16 regulate angiogenesis [84,85]. Small molecule agents that either stimulate or inhibit chemokine

mediated angiogenesis will be vital for wound healing and inhibiting tumor growth respectively.

Chemokines in inflammation and Cancer

Chronic inflammatory conditions have often been associated with the development of cancer. Mantovani and colleagues have proposed that inflammation is the seventh hallmark of cancer as it is a key component of the tumor microenvironment. Inflammation and cancer are connected by: 1) the extrinsic pathway, where chronic inflammatory conditions such as ulcerative colitis may predispose to cancer; 2) the intrinsic pathway where genetic events important for transformation promote the production of inflammatory mediators. Prolonged oxidative stress results in the formation of free radicals that contribute to a chronic inflammatory environment. This inflammatory environment in turn predisposes the host to diabetes, cancer, cardiovascular, neuronal and pulmonary diseases. Oxidative stress can lead to activation of several transcription factors including NF-κB, AP-1, p53, HIF-1α, PPAR-γ, β-catenin/Wnt and Nrf2 [86]. This may facilitate the release of a variety of inflammatory mediators. The role of inflammation in tumor progression is elegantly brought out by limiting the inflammation in the tumor microenvironment in a mouse tumor model. Reduced inflammation led to delayed accumulation of myeloid-derived tumor suppressor cells (MDSC) and subsequent reduction in primary and metastatic tumor progression [87]. These MDSCs are thought to link inflammation and cancer [88]. Chemokines and their cognate receptors are involved in the network of inflammatory mediators associated with MDSC recruitment, tumor growth and progression [89-91]. The chemokines also mediate several chronic autoimmune diseases. The CXC chemokine CXCL8, present in the chronic inflammatory site triggers infiltration of macrophages as well as neutrophils in diseases like cystic fibrosis and chronic obstructive pulmonary disease (COPD). The activated neutrophils at the chronic inflammatory site extrude their DNA decorated with antimicrobial peptides. This neutrophil extracellular trap (NET) is increased in chronic inflammation and is called as NETosis [92]. The NET formation by neutrophils is mediated by CXCR2 and is independent of NADPH oxidase activity, but dependent on *Src* family of kinases [93]. Excessive NET formation has been implicated in several autoimmune diseases like preeclampsia, septic shock and autoimmune vasculitis and also in cystic fibrosis [93].

Chemokines in Cancer

Unresolved chronic inflammation leads to tumorigenesis. The tumor progression is influenced by the production of chemokines by tumor and stromal cells. Chemokines and their receptors provide directional cues for leukocytes or tumor cells for migration and metastasis, entry into the circulation, homing and colonization to specific tissues. Many cancer types have up-regulated expression of chemokines and chemokine receptors leading to aberrant chemokine receptor signaling and expression. The amount and type of chemokines released determines the type and extent of leukocyte infiltration into the tumor microenvironment [94]. Reports in the literature demonstrate that most solid tumors are composed of malignant and stromal cells important for growth and metastasis of the tumor. The stromal cells found in tumors are lymphocytes, macrophages, endothelial cells, fibroblasts, eosinophils, granulocytes, B cells, and natural killer cells. It has clearly been shown that the tumor microenvironment is composed of and extensive mix of both CC and CXC chemokine network that is involved in controlling the leukocyte infiltrate into the tumor. The chemokine mediated recruitment of different leukocytes into the chronic inflammatory and tumor microenvironment and their protumorigenic and anti-oncogenic roles will be discussed below.

Cells of the leukocytic infiltrate

Tumor associated macrophages (TAM): Macrophages exhibit different activation states and have the ability to exhibit tumoricidal or protumorigenic activity [95]. In inflammation and cancer two functionally distinct macrophage phenotypes have been described. Macrophages undergo classic activation (a polarized Th1 response that generates M1-macrophages) in response to lipopolysaccharide (LPS) from microbes, exposure to parasites and presence of interferon-γ (IFN-γ). These M1 macrophages are capable of producing reactive oxygen and nitrogen intermediates (ROI and RNI) that endow them with tumoricidal properties. The macrophages associated with the tumor have altered properties as a result of their exposure to an immune-editing microenvironment present in the tumor [96]. These alternatively activated macrophages that support tumor progression and metastasis are called tumor-associated macrophages or TAM or M2-macrophages. TAMs serve to link the chronic inflammatory state and cancer [89,97,98]. The eliciting cytokines IL-4 and IL-13 are associated with M2-macrophages. The cytokine expression profile is a major identification feature for M2 macrophages. Generally, M2 macrophages have a high expression of scavenger mannose receptors, and possess an IL-12^{low}, IL-10^{high}, IL-1 decoy R^{high} and IL-1Ra^{high} phenotype [98]. M2 cells are immunosuppressive and produce anti-inflammatory cytokines IL-10 and TGF-β. They are also involved in angiogenesis, tissue repair, remodeling and metastasis,. M2 cells have been shown to induce the differentiation of regulatory T (T_{reg}) cells and *vice versa*. TAMs also produce TGF-β that may enable clonal expansion of myeloid-derived suppressor cells (MDSCs) that potently suppress the natural T-cell dependent antitumor activity through altered *i*NOS and arginase activity [99]. In addition to TAMs, TGF-β is also produced by effector and regulatory T cells, MDSCs and antigen presenting cells. TGF-β that is secreted is inactive and must be activated by any of the number of molecules including plasmin, matrix metalloproteinases, reactive oxygen species (ROS), thrombospondin 1, αvβ6 and αvβ8 integrins. The precise mechanism and players involved in the activation of TGF-β are still unclear.

Myeloid-derived suppressor cells (MDSC): Myeloid-derived suppressor cells are a heterogeneous population of myeloid progenitor cells normally present in the bone marrow and the spleen. Morphological, phenotypic and functional heterogeneity is a hallmark of MDSCs and the heterogeneity of these cells point to the plasticity of the MDSCs and continuously change in response to the cytokines and chemokines in the tumor microenvironment [100]. MDSCs and TAMs seem to link chronic inflammation and cancer. In the tumor microenvironment, they are in an active state with increased reactive oxygen and nitrogen species (ROS and RNS) production and arginase I [101]. Delano *et al* demonstrate that there is a direct role for toll-like receptor (TLR) signaling through the adaptor MyD88 that leads to expansion of MDSCs in sepsis [102]. MDSCs potently suppress T-cells that have anti-oncogenic activity. MDSCs down regulate the T cell receptor (TCR) associated ζ-chain that occurs in most cancer patients. CD4$^+$ and CD8$^+$ T cells are impaired in their ability to communicate the signals for immune cell activation in the absence of TCR associated ζ-chain [88]. This immunosuppressive activity enables the tumor cells to squelch the immune surveillance. Type I natural killer cells (invariant or *i*NKT) promote tumor rejection while type II NKT cells promote tumor progression by recruiting MDSCs through the release of IL-13 [88]. MDSCs also promote or induce the development of CD4$^+$FOXP3$^+$ regulatory T cells (induced T_{regs}) [103,104]. In mice, the MDSCs have a phenotype CD11b$^+$ Gr1$^+$, whereas in humans the MDSCs lack the mouse homolog Gr1+ and are LIN$^-$HLA-DR$^-$CD33$^+$ or CD11b$^+$CD14$^-$CD33$^+$ [101]. The MDSCs can be distinguished from TAMs by their low expression of F4/80 (F4/80^{low}) and by up-regulated expression of both *i*NOS (not expressed by TAMs) and arginase I. Initially, MDSCs are thought to possess a morphology reminiscent of granulocytes and monocytes/macrophages [101]. Subsequently, these MDSCs were characterized to be CD11b$^+$CD11c$^+$Gr-1$^+$IL4Ra$^+$

inflammatory monocytes [105,106]. In a TGF-β receptor 2 deleted mouse model, there is increased recruitment of MDSCs into tumors through the operation of two chemokine-receptor axes, CXCL5/CXCR2 and CXCL12/CXCR4 [91]. Furthermore, tumor-derived MDSCs mobilize to the pre-metastatic lung long before the tumor cell arrival and increase the level of pro-inflammatory cytokines, decrease IFN-γ production, and promote vascular remodeling [107]. Activated neutrophils and monocytes in the inflammatory microenvironment at the metastatic site release S100 chemokines (S100A8 and S100 A9). S100 chemokines have been shown to be a crucial "calling card" of the metastatic niche, especially the lungs [108,109]. MDSCs from mouse mammary carcinoma have receptors for S100A8/A9 complexes and also secrete S100A8 and S100 A9 [110]. The secreted S100 chemokines can attract additional MDSCs to tumors through a NF-κB dependent pathway resulting in a self-perpetuating MDSC recruitment loop [110]. This may prove deleterious for the host. These chemotactic factors also block the differentiation of myeloid precursors into differentiated DC and macrophages through a STAT3-dependent mechanism [111]. The MDCSs S100A8/A9 $CCL21^{low}$ tumors were defective in recruiting MDSCs, suggesting that this CC chemokine may also play a role in modulation of the tumor microenvironment [112,113]. $CCL21^{high}$ tumors turn on the tolerogenic switch by the CCL21-driven mimicry of the lymph node stroma and are often associated with the recruitment of MDSCs and T_{regs}. Overall, these findings suggest that recruitment of MDSCs along with TAMs link inflammation, tumor progression, and metastasis. S100A8/A9 chemotactic factors appear to be a promising therapeutic target for reducing/eliminating MDSCs and the pathways operating in MDSCs along with reduction or elimination of inflammation. This would delay or reduce the accumulation of MDSCs and that might limit the tumor progression [87,114,115]. MDSCs have also been implicated temporally with the development of cachexia in cancer patients [116].

Neutrophils: Neutrophils have a remarkably short half life of 6-8 h in circulation and are produced at a rate of $5\text{-}10 \times 10^{10}$ cells/day [117]. Increased infiltration of neutrophils has been observed in bronchioalvelolar carcinoma, gastric carcinoma, colon carcinoma, melanoma and myxofibrosarcoma [89]. The neutrophils were recruited by ELR^{+}-chemokines CXCL1, CXCL5, CXCL6 and CXCL8 present in the tumor microenvironment. The presence of neutrophils in the tumor biopsy correlated with poor prognosis and tumor associated neutrophils (TAN) that promote tumor development and growth have been designated as N2 neutrophils with elevated arginase I levels. The neutrophils with anti-tumor activity were designated N1 neutrophils. With blockade of TGF-β, there is infiltration of CD11b(+) / Ly6G(+) tumor-associated neutrophils (TANs) that are hypersegmented and more cytotoxic to tumor cells [118].

Dendritic cells: Dendritic cells are specialized cells for antigen presentation to T cells after migration to secondary lymphoid organs following encounter with non-self antigens like tumor antigens. Dendritic cells are critical for shaping the adaptive immune responses. Mouse monocyte-derived DCs express a specific protein called DC-specific ICAM3-grabbing non-integrin (DC-SIGN). These monocyte-derived DC-SIGN ($CD209^{+}$) cells can up regulate L-selectin and the chemokine receptor CCR7 expression in order to enter secondary lymphoid organs, suggesting that these cells were recruited from the blood directly [119]. DCs cross-present the tumor antigens and activate $CD8^{+}$ T cells. High levels of IFN-γ in the tumor microenvironment combined with *Salmonella typhimurium* infection of tumor cells, or administration of *S typhimurium* bacterial products to the tumor, increased expression of connexin 43 protein in tumor cells and also in adjacent *S typhimurium* unexposed tumor cells. This bacterial pretreatment activated the $CD8^{+}$ T cells through cross-presenting DCs that favored antitumor immunity not only in the tumor but also in its vicinity [120].

The CC chemokine CCL20 is produced in several types of tumors that are heavily infiltrated with dendritic cells (DC) [121-123]. Over-expression of CCL20 facilitates increased recruitment of DCs and in turn activates cytotoxic T cells [124]. The immature DCs reside inside the tumor and the mature DCs occupy the peritumoral regions [125]. Chemokines CCL5, CCL19, and CXCL12 also attract immature DCs [122,126,127]. Tumor induced immune tolerance occurs through defects in DC recruitment, differentiation, maturation and survival [128]. A variety of immunosuppressive factors like GM-CSF, S100A9 (from MDSCs), M-CSF, IL-6, VEGF, TGF-β, IL-10, gangliosides, altered glycosylation products of tumor antigens, ROS, indoleamine 2,3-deoxygensase (IDO) block the recruitment and/or functions of DCs. This primarily occurs through activation of STAT3 transcription factor [129].

Plasmacytoid DCs (pDC) are present in 13% of primary mammary carcinoma and usually predict short progression free survival [127]. In some forms of primary breast cancer, presence of CCL22/CCR4 axis recruited the DC-LAMP$^+$ DCs and T_{regs}. This situation suggests poor prognosis especially if these cells are present at the margins of the tumor [130]. In some tumors, tumor mediated activation of liver-X-receptor-α down regulated the level of CCR7 on dendritic cells, allowing immune escape by tumors [131].

Chemokines from DCs also help recruit cytotoxic T cells (CTL). DCs induce cytotoxic T cell response through cross-priming of tumor antigens. Apparently, DCs require a “license” for cross-priming usually from helper T cells. Utilizing CCR5 ligands, DCs recruit CTLs. Alternatively, “licensing” from natural killer T (NKT) cells that recognize microbial or synthetic glycolipid antigens allows CD8α(+) DCs to secrete CCL17 which then serves as a chemoattractant for CTLs [132].

Natural killer (NK) cells: Infiltration of natural killer (NK) cells is seen in several types of tumors including colorectal carcinoma [133], pulmonary adenocarcinoma [134], gastric carcinoma [135] and squamous cell lung cancer [136] and its increased presence indicates a good prognosis. The chemokines do play a key role in the biology of NK cells [137]. NK cell accumulation into tumors is dependent on the presence of IFN-γ and CXCR3 ligands [138]. Chemokine receptors CXCR3 and CX_3CR1 present on NK cells direct their infiltration into gastric adenocarcinoma. Such tumors expressing chemokines CX_3CL1, CXCL9, CXCL10 show a better prognosis, consistent with murine tumor models [138-140]. NK cells can also induce tumor regression in conjunction with DCs [141].

Tumor-infiltrating lymphocytes (TIL): Tumor-infiltrating lymphocytes (TILs) express high levels of CXCR3 and are attracted to tumors expressing CXCL9 and CXCL10 [142]. They can also be recruited through CX_3CL1 as seen in neuroblastoma [143]. High levels of CX_3CL1 correlated with good prognosis in colorectal carcinoma [144]. In addition, CXCL16 can recruit TILs and its expression correlates with better prognosis in a variety of cancer types [145]. High CXCL16 expression also attracts CD4$^+$ and CD8$^+$ cells. Moreover, ionizing radiation therapy increases the secretion of the chemokine CXCL16 by human and mouse breast cancer cells [145].

CD4$^+$ T cells have been shown earlier to contribute towards tumor regression [146,147]. Very recently in transgenic mouse models of T-cell acute lymphoblastic lymphoma (T-ALL) with conditional oncogene inactivation, it has been shown that CD4$^+$ T cells can mediate cellular senescence and block tumor angiogenesis through the expression of thrombospondin-1 (TSP-1) in immune effectors. This resulted in sustained tumor regression due to “oncogene amnesia” and reinstatement of pathways that would normally induce senescence and cell death [148]. This implies that with a combination of targeted oncogene inactivation along with immunotherapy may work in some forms of malignancies.

The presence of the chemokines CCL17 and CCL22 recruited T_{regs} and polarized Th2 cells, and this correlates with poor prognosis [130,149]. Interestingly, transgenic mice expressing the mDARC decoy receptor in a melanoma tumor model exhibit a heavy infiltration of CD4, CD8 and CD22 lymphocytes, and this correlates with tumor regression [76]. On the contrary, in human melanoma the TILs vary in composition and many times predominate with T_{regs} that down regulate the infiltration of other anti-tumor TILs and hence poor prognosis [150].

B lymphocytes also appear to play a role in progression of the premalignant stage as well as later in the tumor progression. B lymphocytes do not appear to infiltrate the premalignant tissue but indirectly support the premalignant progression through increased deposition of immunoglobulins (Ig). The resultant formation of Ig-antigen complexes and subsequent complement activation or engagement of cell surface multimeric Fc receptors [151]. B lymphocytes that infiltrate prostate tumors secrete lymphotoxin that leads to castration resistant prostate cancer [152].

Role of chemokines in invasion and metastasis

In general, CXCL12/CXCR4 and CCL21/CCR7 axes have been recognized as major factors in invasion and metastasis in several cancer types. The most frequently over-expressed chemokine receptor on tumor cells is the CXC chemokine receptor 4 (CXCR4). A list of tumor types where CXCR4 is over-expressed in given in Table I.

CXCR4 selectively binds the CXC ligand 12 (CXCL12), also known as stromal cell-derived factor-1α (SDF-1α). The interaction between CXCR4 and CXCL12 is a normal process in cell migration. Although multiple pathways contribute to chemokine-induced cell migration such as mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), focal adhesion kinase (FAK), and the Rho family of GTPases [153,154], the general mechanisms in normal cell migration and metastasis are similar. Muller and colleagues demonstrated high levels of CXCR4 expression on breast cancer cells that direct chemotaxis and invasive responses, enabling breast cancer cells to metastasize to other organs [155]. CXCL12 is expressed by stromal fibroblasts within tissues involved in the spread of breast cancer cells such as the lymph nodes, lung, liver, and bone marrow [155,156]. Inhibition of CXCR4 in MDA-MB-231 cells reduced breast cancer metastases to the lung and lymph node after tail vein or mammary fat pad injections [157,158].

Since the discovery of aberrant expression of CXCR4 on breast cancer cells, it has been shown that CXCR4 is up-regulated in more than 20 different tumor types. Other models in which CXCR4 has been suggested to play a role in metastasis are ovarian, prostate, and lung cancers. The CXCL12-CXCR4 axis has been implicated in the migratory behavior of glioma cells. Expression of CXCR1-CXCR5 has been reported in glioblastoma with CXCR4 being the most frequently expressed and associated with cell invasion and poor patient prognosis. [159-162]. CXCR4 has also been identified on cancer stem cells isolated from glioblastoma [160] and pancreatic cancer suggesting that this receptor might provide a key target for therapy [163,164]

Human epidermal growth factor receptor 2 (HER2) up-regulates the expression of the chemokine receptor CXCR4. This occurs through enhanced translation and attenuated degradation of CXCR4 upon activation of HER2. The up-regulation of CXCR4 is required for the breast cancer cells to metastasize to the lungs. Elevated expression of CXCR4 and HER2 in human mammary carcinoma tissues correlates with poor overall survival [165]. CXCL12 activation of CXCR4 has also been shown to transactivate HER2 in lipid rafts in prostate cancer cells and this HER2 activation promotes metastasis to the bone [166]. This

was also shown to occur in breast cancer cells through *src* kinase activation [167]. This functional link between CXCR4 and HER2 or Src deserves attention.

The chemokine CXCL12 also binds to CXCR7, further complicating the role of CXCL12-CXCR4 axis in regulating biological processes. It has been shown that the expression of CXCR7 is higher on transformed cells as compared to non-transformed cells [168]. Additionally, it has been reported that expression of CXCR7 on breast and lung cancer cells correlates with proliferation, metastasis and vascularization [169]. The expression of CXCR7 has been recently shown in mammary carcinoma [169], prostate carcinoma [170] and non-small cell lung carcinoma [171].

Other CXC family members have been identified in other tumor types. Many cancer cells such as melanomas express a number of chemokines including CXCL1 and CXCL8 and its receptors CXCR1 and CXCR2 [82,172-175]. Over-expression of CXCR1 and CXCR2 in melanoma cells leads to aggressive phenotype coupled with increased migration and tumor growth in mice, which can be reversed with antagonists or neutralization of these receptors [176]. Other chemokines involved in melanoma are CXCL1-3, CCL5, and CCL2, which have been implicated in tumor growth and progression. Recent studies have demonstrated organ-specific patterns of melanoma metastasis that correlate with their expression of specific chemokine receptors, including CXCR4, CCR7, CCR9 and CCR10. The expression of CCR9 is associated with intestinal melanoma metastasis [177-179]. CCR9 is expressed on melanoma cells and melanoma cell lines established from small intestinal metastases. These cells were responsive to the CCR9 ligand CCL25, which is selectively expressed in the small intestine and thymus, suggesting an association between expression of CCR9 and organ specific metastasis [177]. In cutaneous melanocytic lesions, CCR10 was found expressed in both benign and malignant lesions. Evaluation of sentinel lymph nodes showed positive lymph nodes had increased CCR10 expression as compared to cases of negative lymph nodes, suggesting a role for CCR10 in human melanoma and its dissemination to lymph nodes [180]

CCR7 expression has been correlated with lymph node metastasis in gastric carcinoma, [181], esophageal squamous cell carcinoma [182], non-small cell lung cancer [183], and colorectal carcinoma [184] and breast cancer [185]. A recent study demonstrated that CCR7 mediates leukemic T cell infiltration into the central nervous system in T-cell acute lymphoblastic leukemia (T-ALL). This study showed that CCR7 expression is regulated in leukemic cells by the T-ALL oncogene Notch1, and silencing of CCR7 or its ligand CCL19 in an animal model of T-ALL inhibits CNS infiltration [186]. Ghadjar and colleagues have shown correlation of CCR6 expression with liver metastasis of colorectal cancer. Evaluation of CCR6 expression by immunohistochemistry verified expression of CCR6 in all 64 primary tumor specimens, 24 of the 64 patients presented with liver metastasis [187]. In colorectal cancer, the predominant organ for metastasis is the liver. CCR6 has one known binding ligand, CCL20 which was originally identified in the liver, and is also expressed in mucosa and lymphoid tissues. The expression of CCL20 in the liver generated interest in the role of CCR6 and its ligand in colorectal cancer and metastatic spread to the liver. Another study demonstrated that patients with colorectal cancer and liver metastasis had higher amounts of CCL20 in their liver compared to controls without metastases [188]. Since CCR6 has been shown to play a role in tumor progression and metastasis, and CCL20 is expressed in the normal prostate, Ghadjar and colleagues used immunohistochemistry to show CCR6 expression was associated with advanced and aggressive prostate cancer [189]. Rubie and colleagues have shown significant mRNA up regulation of CCL20 and CCR6 in samples from patients with pancreatic cancer, additionally, CCL20 expression was strongly associated with advanced T-category (clinical stage) in patients with prostate cancer as compared to normal pancreatic tissue [188].

Expression of CXCR3 has been detected in malignant epithelium from early stage breast cancer patients, and is associated with promotion of lung metastasis in murine mammary tumor model [190]. Silencing of CXCR3 in mammary tumor cell lines inhibited spontaneous lung metastasis and lung colonization from tumor cells implanted in the mammary gland in a murine model [190]. Increased levels of CCL2 expression in breast cancer have been associated with increased levels of tumor associated macrophages, correlating with invasive phenotype and poor prognosis. Myeloid monocytic cells like TAM, MDSC, DC and Tie-2 macrophages are recruited to the tumor through CCL2. Such CCL2 recruited immune cells produce VEGF, PDGF, TGFβ, CXCL8, MMP-2 and MMP-8 [191-193]. These proteins promote tumor angiogenesis and progression and hence poor prognosis. Thus, the chemokine and their cognate receptors play a vital role in the migration of tumor cells from their primary site via the circulation to the preferential sites of metastases.

Decoy receptors sequester chemokines without activating signaling pathways, and generally functions as tumor suppressors [194]. In addition, studies have shown that decreased expression of Duffy antigen receptor for chemokines (DARC) and D6 decoy receptors in breast cancer inversely correlate with lymph node metastases and increased survival rates [195]. The DARC receptor has also been shown to support enhanced chemokine-induced extravasation of leukocytes and thus support the pro-migratory activity of chemokines [196].

Chemokines in autoimmune disorders

Rheumatoid arthritis—Rheumatoid arthritis (RA) is the chronic inflammatory autoimmune disease of the synovia of the joints. The CXC- and CC-chemokines in the inflammatory synovial microenvironment attract the leukocytes that transmigrate through the vascular endothelium and invade the synovia [197]. The inflammatory exudate in the joint cavity along with leukocytes, activated synovial fibroblasts, matrix metalloproteinases and cathepsins, eventually erode the articular cartilage. Bone erosions occur eventually with the signals converging on osteoclast precursors and their subsequent differentiation and maturation [198].

The chemokines CXCL8, CXCL5 and CXCL1 are the most important as well as abundantly expressed in the sera, synovial fluids and membranes [197]. Isolated synovial macrophages constitutively secrete the chemokine CXCL8 *in vitro* [199,200]. The presence of macrophages correlated with the severity of the symptoms of RA [200]. Synovial fibroblasts (SF) secrete CXCL8 in response to inflammatory agents such as IL-1α, IL-1β, lipopolysaccharide (LPS) and tumor necrosis factor (TNF)-α[199]. CXCL8 *per se* is capable of inducing synovial inflammation as evidenced by a single intra-articular injection of CXCL8 into the rabbit knee joint [199] and is present in the synovial fluid of RA patients [201,202]. Leukocyte-derived microparticles or exosomes might activate the synovial fibroblasts and stimulate the release of chemokines CCL1 and CCL2. CCL2, CCL3, CCL18 and CCL20 were detected in the synovial fluid and CCL13 in the articular cartilage of the RA joint [197,203]. XCL1 and CX_3CL1 chemokines are also detected in synovial fluid of RA patients [197]. In addition, the microparticles can stimulate the release of ELR+ CXC chemokines such as CXCL1, CXCL2, CXCL3, CXCL5, CXCL6 and CXCL8 [204-206]. This might augment the angiogenesis in RA joints [203]. Very recently, platelet microparticles are detected in the synovial fluid of the RA patients and they produce the chemokine CXCL7 [197].

T helper 17 (T_h17) cells may be central to synovitis and tissue destruction through its interaction with dendritic cells, macrophages and B cells [198]. CXCL13 is expressed by synovial fibroblasts, endothelial cells and follicular dendritic cells of RA synovia that attracts B cells [207]. Presence of lymphoid follicles suggests that the antigen presentation occurs locally at the synovia and CCL21 has been implicated in the lymphoid neogenesis

within the arthritic synovia [198,208]. The chemokine CXCL16 is also abundant in the RA synovia indicating that CXCR6 mediated pathway is also operating in RA and is involved in leukocyte extravasation into the synovia [209,210].

Chronic obstructive pulmonary disease (COPD)—Chronic obstructive pulmonary disease is due to the chronic inflammatory response of the respiratory system to smoking and/or repeated exposure to noxious pollutants in the air [211]. COPD is characterized by lung infiltration of inflammatory cells of both innate and adaptive immune system and both CC- and CXC-chemokines are involved in this process [211-215]. In COPD patients, several CC chemokines are up regulated including CCL2, CCL3, CCL5 and CCL20. In fact, in CCR5 (-/-) and CCR6 (-/-) mice exposed to nicotine there is reduced accumulation of macrophages, dendritic cells, neutrophils, and CD8+ T-cells in the lung. Furthermore, there is partial protection from developing COPD in these knockout mice [216]. The cytokine IL-17 up regulates several CXC chemokines and neutrophil survival factors in the airway epithelium, including chemokine ligands for CXCR2 [214]. This suggests that CXCR2 antagonists might be beneficial in the treatment of COPD [217]. The neutrophil chemoattractant proline-glycine-proline (PGP) is a biomarker of COPD. PGP is normally degraded by leukotriene A_4 hydrolase (LTA_4H) leading to resolution of the inflammation. Cigarette smoke selectively inhibited LTA_4H that led to an increased accumulation of PGP in the lungs. Elevated levels of PGP led to prolonged presence of neutrophils in the lung leading to the pathogenesis of COPD [218].

Conclusions

Chemokines play a paramount role in physiology and homeostasis as well as in pathogenesis of tumors and their metastasis. Based on what is known currently, a multi-pronged anti-tumor therapeutic approach would be beneficial. This includes reduction or elimination of inflammation, oncogene inactivation, and polarization of immune cells to Th1 type. A variety of approaches are involved in the reduction or removal of the inflammation. It may be lowering of stress level, chronic low dose employment of anti-inflammatory drugs, removal or blocking the accumulation of the chemokines [219], removal or differentiation of MDSCs and conversion of TAMs (M2) to M1 macrophages. If we can reduce chronic inflammation, this could have a huge, positive effect on cancer therapy.

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Table I

Expression of the chemokine receptor CXCR4 in variety of tumors

Breast cancer	[91,153-156]
Lung cancer	[157-159]
Ovarian carcinoma	[11,12,160]
Prostate cancer	[161]
Pancreatic cancer	[162-165]
Colorectal adenocarcinoma	[166-168]
Head and neck squamous cell carcinoma	[169,170]
Human cervical carcinoma	[13]
Melanoma	[171-174]
Renal cell carcinoma	[175-177]
Glioma and Glioblastoma	[178-181]
Multiple myeloma	[182]
B-cell chronic lymphocytic leukemia	[183]
Acute myelogenous leukemia	[184]
Bladder cancer	[185,186]
Esophageal cancer	[187,188]
Rhabdomyosarcoma	[189-191]