CXCR3 Ligands in Cancer and Autoimmunity, Chemoattraction of Effector T Cells, and Beyond

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CXCR3 is a chemokine receptor with three ligands; CXCL9, CXCL10, and CXCL11. CXCL11 binds CXCR3 with a higher affinity than the other ligands leading to receptor internalization. Long ago we reported that one of these chemokines, CXCL10, not only attracts CXCR3+ CD4+ and CD8+ effector T cells to sites of inflammation, but also direct their polarization into highly potent effector T cells. Later we showed that CXCL11 directs the lineage development of T-regulatory-1 cells (Tr1). We also observed that CXCL11 and CXCL10 induce different signaling cascades via CXCR3. Collectively this suggests that CXCR3 ligands differentially regulate the biological function of T cells via biased signaling. It is generally accepted that tumor cells evolved to express several chemokine receptors and secrete their ligands. Vast majority of these chemokines support tumor growth by different mechanisms that are discussed. We suggest that CXCL10 and possibly CXCL9 differ from other chemokines by their ability to restrain tumor growth and enhance anti-tumor immunity. Along with this an accumulating number of studies showed in various human cancers a clear association between poor prognosis and low expression of CXCL10 at tumor sites, and vice versa. Finally, we discuss the possibility that CXCL9 and CXCL10 may differ in their biological function via biased signaling and its possible relevance to cancer immunotherapy. The current mini review focuses on exploring the role of CXCR3 ligands in directing the biological properties of CD4+ and CD8+ T cells in the context of cancer and autoimmunity. We believe that the combined role of these chemokines in attracting T cells and also directing their biological properties makes them key drivers of immune function.

Keywords: CXCR3, chemokines, CXCL10, CXCL9, EAE, cancer, tolerance

INTRODUCTION

Chemokines are small (~8–14 kDa), structurally cytokine-like, secreted proteins that regulate cell trafficking through interactions with a subset of 20 different seven-transmembrane, G protein-coupled receptors (GPCRs) (1). These receptors could be divided into single (mono) receptors, and shared receptors in which a single receptor binds several chemokines. Different chemokines that bind a shared receptor may have different modes of interactions. They may either poses similar biological properties (may explain redundancy), or induce divers signaling cascades and thereby differ in biological properties. This type of biased signaling has been previously observed for beta2-adrenergic receptor (also GPCRs) by the Nobel prize winner Robert J. Lefkowitz (2) and by others (3). Our laboratory was the first to report that such biased signaling is also used by
chemokines to direct the biological properties of CD4+ T cells in controlling effector T cell function vs. tolerance to self (4, 5), and perhaps in controlling anti-cancer immunity (6). The current review focuses on the role of CXCR3 and its ligands: CXCL9, CXCL10, and CXCL11 on the biological function of CD4+ and CD8+ T cells and its translational implications.

Of the three CXCR3 ligands most of the attention has been drawn thus far to CXCL10, as a candidate for cancer immunotherapy. Only recently it has been suggested that CXCL9 is also involved in directing the potentiation of CD8+ T cells in cancer, and that its activity differs from CCL10 (7). Not much is known about the role of CXCL11 in cancer diseases. As for autoimmunity, the role of CXCL10 and CXCL11 has been largely studied by several laboratories including ours, whereas the role of CXCL9 is still elusive (8).

**CXCR3 AND ITS LIGANDS**

CXCR3 is a chemokine receptor that is primarily expressed on CD4+ and CD8+ T cells, and to some extent by other cells, among them, epithelial cells (9). Within the CD4+ subset CXCR3 is mostly abundant on proinflammatory Th1 cells, but notably it is also expressed by FOXP3+ regulatory T cells (Treg) (10–12). Mice express a single isoform of CXCR3 that exclusively bind CXCL9, CXCL10, and CXCL11. In human three isoforms were identified: CXCR3A that is reciprocal to the mouse CXCR3 and also binds CXCL9, CXCL10, and CXCL11, CXCR3-B that binds CXCL9, CXCL10, CXCL11 as well as an additional ligand CXCL4, and CXCR3-al that only binds CXCL11 (13). The CXCR3 ligands share limited sequence homology. Yet, in their structural homology they are more similar to each other than to other non-ELR chemokines. Also all three chemokines are inducible by IFN-γ (14). Together this makes them a well-characterized subfamily of the non-ELR chemokines. CXCL11 is believed to be the dominant CXCR3 agonist, as it is more potent than CXCL10 or CXCL9 as a chemoattractant and in stimulating calcium flux and receptor desensitization (15).

**BIASED SIGNALING VIA CXCR3 DIRECTS THE POLARIZATION OF CD4+ T CELL SUBSETS**

Based on their cytokine profile FOXP3-negative CD4+ T cells fall into different subsets among them IFN-γ\textsuperscript{high}IL4\textsuperscript{low} Th1 cells IFN-γ\textsuperscript{low}IL4\textsuperscript{high} Th2 cells, IL17\textsuperscript{high} + Th17 cells and IL10\textsuperscript{high} T regulatory-1 (Tr1) cells (16). It is generally accepted that the polarization of non-polarized CD4+ T cells (Thnp) into these subsets is directed by the cytokine milieu within their microenvironment (16). Not much attention has been drawn to the role of chemokines in T cell polarization.

Long ago we observed that along the development of two different experimental autoimmune diseases in Lewis rats: Experimental autoimmune encephalomyelitis (EAE), and adjuvant induced arthritis (AA) the immune system generate an autoantibody response (IgG isotype) to pro-inflammatory cytokines and chemokines that are likely to be involved in the pathogenesis of these diseases (17, 18). In these studies we also observed that amplification of these responses by targeted DNA plasmids may restrain the progression of these diseases (17, 18). We further investigated the mechanistic basis of this response and named it “beneficial autoimmunity” (19). While extending these studies to CXCL10 we learned that targeting the function of CXCL10 restrained the development of EAE or AA. Ex vivo analysis of CD4+ T cells subsets indicated for in vivo shift from Th1 to Th2 (20, 21). Independently, others observed that CXCL10 promotes the polarization of human CD4+ T cells into IFN-γ\textsuperscript{high}IL4\textsuperscript{low} Th1 cells (22). The role of CXCL9 in directing effector T cell polarization is yet to be studied. Collectively, this suggests that CXCL10 promotes the polarization of Th1 cells, thus its targeted neutralization restrains autoimmunity. In our studies we could clearly record the effect of CXCL10 neutralization on the Th1/Th2 balance of antigen specific T cells in the periphery (17, 18), and suggested that along the dynamics of each disease these cells are recruited to the inflammatory site, to replace those that undergo apoptosis there (23). The possibility that these antibodies directly enter the CNS to affect T cell polarization there has not been detected.

While further exploring the interplay between CXCR3 ligands, particularly CXCL10 vs. CXCL11 and their role in directing CD4+ T cell polarization we observed that CXCL11 preferentially drives the polarization of IL10\textsuperscript{high} Tr1 cells (4, 5). The underlying signal cascade included signaling via p70 kinase/mTOR in STAT-3- and STAT-6-dependent pathways (4, 5). This differed from CXCL10 that signals via STAT1, STAT4, and STAT5 phosphorylation (4, 5). CXCL11 is believed to be the dominant CXCR3 agonist, as it is more potent than CXCL10 or CXCL9 as a chemoattractant and in stimulating calcium flux and receptor desensitization (15). This suggests that the interplay between CXCL11 and CXCL10 dominates the regulation of CD4+ T cell mediated responses, while favoring active tolerance over effector reactivity. C57BL/6 mice that lack functional CXCL11 due to a shift in the open reading frame of the CXCL11-encoding gene (insertion of two bases after nucleotide 39), resulting in the translation of a chimeric protein lacking the critical CXC motif (24), preferentially induce Th1 oriented response, are highly susceptible to the induction of various Th1-related autoimmune diseases. We observed that these mice are excellent responders to low doses CXCL11-Ig based therapy of EAE in comparison to SJL mice that do not display this open reading frame mutation (4).

The idea of different ligands that differ in their binding site to the same GPCRs receptor also induce different signaling cascade has been primarily investigated by Robert J. Lefkowitz and his team while exploring the Molecular mechanism of beta-arrestin-biased agonism (2, 25, 26). We have explored the relevance of this mechanism for chemokines and T cell regulation.

In summary, we suggest that CXCL11 and CXCL10 plays an opposing role in directing T cell polarization, and as CXCL11 has a higher affinity to CXCR3 it is likely to dominate immune regulation.
THE CONTRADICTIVE ROLE OF CXCR3-CXCL10 AXIS IN NEUROINFLAMMATION

It is largely accepted that CXCL10 promotes the activity of effector CD4+ and CD8+ T cells, and also their recruitment at inflammatory sites (also tumor site) and thus its targeted neutralization could be beneficial in treating various T cell mediated autoimmune diseases among them: psoriasis, rheumatoid arthritis (RA) (27, 28), Inflammatory Bowel Disease (IBD) (29), and type I diabetes (T1DM) (30, 31) (for a recent review also see (32)) (Figure 1B). The role of the CXCL10-CXCR3 axis in neuroinflammation is likely to more complex and controversial (37). The first record that systemic administration of polyclonal antibodies against CXCL10 suppress EAE came from the study of William Karpus and his group in 2001 (39). Independently, and shortly after we reported that targeted DNA vaccines encoding CXCL10 could amplify the production of neutralizing autoantibodies to CXCL10 that could also suppress EAE in Lewis rats (20). Both studies were limited in the use of polyclonal antibodies. Four years later Richard Ransohoff and his group reported that CXCR3 KO mice lacking the CXCR3-CXCL10 interaction develop more severe EAE then WT (40). The absence of CXCR3-CXCL11 interaction could not be taken in account as these were C57BL6 mice lacking functional CXCL11. Klein et al. examined the development of EAE in WT Vs CXCL10 KO mice and observed differences only during sub-optimal induction of disease (41). In another study, Iain Campbell and his group compared the development of EAE in WT and CXCR3KO mice and observed that along the later chronic phase of disease CXCR3KO mice develop a more severe EAE then WT, and that this has been associated with reduced number of FOXp3+ Tregs at the CNS (38). Campbell and his co-authors suggested that perhaps CXCL10 produced by astrocytes at the inflamed CNS mostly direct the recruitment of bone marrow derived cells to the tumor site, and that direct recruitment of bone marrow derived cells that support tumor growth and suppress anti-tumor immunity. Third, chemokine—chemokine receptor interactions are involved in attracting tumor cells to metastatic sites. The key chemokine receptor pathways that directly support tumor development are the CCR2-CCL2 (52–56), CCR4-CXCL12 (48, 57), and CCR5- CCL3/4/5 (58–62) (Table 1). All three pathways are also associated with the recruitment of bone marrow derived cells to the tumor site, and with direct attraction of tumor cells to form metastatic spread. An additional chemokine receptor that recently became of a major interest is CCR8 that is abundant of on FOXp3+ Tregs (63).

Aside of this axis many other chemokine–chemokine receptors are involved in different cancer diseases (for a recent review see (65)). However, the current mini review mostly focuses on CXCR3 and its ligands.

WHAT IS KNOWN ABOUT CXCL10 AND CXCL9 AND IN CANCER IMMUNITY?

Several studies showed that CXCL9 and CXCL10, particularly CXCL10 produced by tumor or host cells can recruit CXCR3+ tumor-infiltrating CD4+ T cells, CD8+ T cells and NK cells that are associated with tumor suppression (33, 66–74). Zumwalt et al. showed active secretion of CXCL10 and CCL5 from colorectal cancer microenvironments in human was associates
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**FIGURE 1**  
CXCL10 directs the biological function of CD4+ and CD8+ T cells in cancer and autoimmunity.  

(A) **The role of CXCL10 in cancer diseases:** CXCL10 directs the accumulation of CXCR3+ effector T cells, in particular effector CD8+ T cells to the tumor site (33) and potentiates their anti-tumor activities, either directly or via the potentiation of effector CD4+ T cells to support their activity. As for tumor cells, it directly suppresses tumor growth (34, 35). Yet, for CNS metastatic spread it had been suggested that CXCL10 produced by astrocytes directs metastatic spread to the brain (36).

(B) **The role of CXCL10 and CXCL11 in inflammatory autoimmunity:** CXCL10 is associated with chemoattraction and potentiation of effector T cells that commence the inflammatory process. Its activity is regulated, in part, by CXCL11 that induces T regulatory-1 (Tr1) cells (4).  

(C) **Neuroinflammation:** In neuroinflammation CXCL10 is likely to hold a dual function. Aside of chemoattraction of effector T cells it selectively induces the accumulation of FOXp3+ Tregs to restrain inflammation (37, 38).

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with Granzyme B+ CD8+ T-cell infiltration (75). It is likely that for CD8+ T cells the CXCR3-CXCL10 axis that is involved in directed migration of these cells to the tumor site also induces their potentiation and proliferation there (7, 33) (Figure 1A). What about CXCL9? Very recently Andy Luster and his group showed that anti-PD-1 efficacy is reduced in CXCR3KO mice, and suggested that the interaction between CXCL9, largely produced by CD103+ dendritic cells (DC) at the tumor site, and CXCR3 on CD8+ T cells enhances anti-PD-1 efficacy (7). The authors also extended this study to humans, suggesting that levels of CXCR3 ligands in the plasma may be used to predict success in anti-PD-1 checkpoint therapy (7). It is yet to be explored whether CXCL9 and CXCL10 induce different signaling cascade via CXCR3 in CD8+ T cells.

WHAT IS KNOWN ABOUT CXCL10 BASED THERAPY OF CANCER DISEASES?

Nineteen years ago, Arenberg et al. showed that intra-tumoral injection of CXCL10 limits non-small-cell lung cancer (NSCLC) in SCID mice by a direct effect on tumor growth (76). Our collaborative study with Israel Vlodavsky was the first to show that systemic administration of CXCL10 (CXCL10-Ig) limits cancer in immunocompetent mice (34). One year later (2015) Peng et al. showed that treatment with epigenetic modulators that increase CXCL9/CXCL10 enhances effector T-cell tumor infiltration, and slows down tumor progression of ovarian cancer (77). At the same year, Barreia da Silva et al. showed that Dipeptidylpeptidase 4 inhibition enhances endogenous CXCL10 levels and suppresses B16/F10 melanoma growth (78). This study also showed a highly effective effect of Dipeptidylpeptidase 4 based therapy if administered in combination with checkpoint blockers (78). It has recently been suggested that in the set-up of multiple myeloma CXCR3 receptor ligands CXCL9 and CXCL10, limits NK cell positioning into the bone marrow by interfering with CXCR4 function (79). It should also be noted that CXCR3 is expressed on Tregs and may be involved in directing their recruitment in cancer and transplantation (11, 12). Collectively this may vote for possible immune-regulating effect. Yet, it has been clearly shown that enhancement of CXCL10 in an in vivo set-up increases anti-tumor immunity and could be effectively used for cancer immunotherapy either as monotherapy, or in combined therapy with immune checkpoint inhibitors (78).

CXCL10 AND BRAIN CANCERS

As discussed above chemokines are involved in cancer diseases by several mechanisms among the direct and indirect effect on anti-cancer immunity, direct and indirect effect on cancer growth, and attracting cancer cells to tumor sites. It is generally accepted that CXCL10 enhances anti-cancer immunity, and by so doing limits cancer development. It has also been observed that CXCL10 directly limits cancer (melanoma) growth in vivo and in vitro (80). Collectively this applies for an anti-cancer property of CXCL10. As for directing metastatic spread Neta Erez and her team very recently suggested that CXCL10 produced by astrocytic cells participates in chemoattraction of tumor cells to the CNS (36). This may give rise to a possible tumor supporting function of CXCL10 in brain metastasis. Nevertheless, as described below many human studies clearly show that in various human cancer diseases low expression/transcription of CXCL10 at tumor sites indicate poor cancer prognosis, whereas high levels of this chemokine are associated with good prognosis.

In summary, CXCL10 is likely to hold anti-cancer property that include: 1. Direct effect on the immune system resulting in enhanced anti-cancer response, effect on epithelial cells surrounding the tumor and direct effect on tumor growth. Its tumor supporting role is by attracting tumor cells to form metastasis, as was recently suggested for brain tumors. We are now using CXCR3KO mice engrafted with CXCR3+ tumor cells to dissect the direct effect of CXCL10-Ig based therapy on tumor growth.

CXCL10 AND CANCER PROGNOSIS IN HUMAN

Ten years ago Jiang et al. reported that low transcription of CXCL10 shows poor prognosis in stage II and III colorectal cancer (81). Later Li et al. showed that in patients with rectal cancer that high expression of CXCL10 may predict better successes in chemoradiotherapy suggesting a synergistic beneficial effect of both (82). Rainczuk et al. showed that high levels of a CXCL10 antagonist in patients with high-grade, serous epithelial ovarian carcinoma (HGSOC) is associated with poor prognosis (83). As for Osteosarcoma (OS), Flores et al. showed better survival in patients with high level of CXCL10 (84). Finally, very recently Zhang et al. showed that in hepatocellular carcinoma (HCC) high levels of CXCL10 are associated with better prognostic and overall survival (85). Several publications challenged this concept (86–88). These studies focused on different cancers: breast cancer,

| Chemokine receptor -chemokine axis | Key pathways | References |
|-----------------------------------|-------------|------------|
| CCR2-CCL2 | Direct support of tumor growth, recruitment of tumor associated macrophages (TAMs) to support tumor growth and suppress anti-tumor immune reactivity | (52–56) |
| CXCR4-CXCL12 | Direct support of tumor growth, metastatic spread, particularly to the bones | (48, 57) |
| CCR5 - CCL3/4/5 | Direct support of tumor growth, recruitment of polymorph nuclear myeloid derived suppressor cells and potentiation of their function at the tumor site. | (58–62) |
| CCR8-CCL1 | CCR8+ Tregs function as master drivers of immune regulation and therefore are key drivers in tumor escape from immune destruction | (63, 64) |
renal cancer and multiple myeloma (86–88). One is that the discrepancy between the studies is because the role of CXCL10 / CXCL9 varies between different cancer disease. If so this should be taken in account as a major criterion in candidate selection for a favorable disease for CXCL10/CXCL9 based therapy.

In summary, CXCL10 is likely to restrict cancer development in many cancers by inducing anti-cancer immune response, and by a direct effect on epithelial cells within the tumor microenvironment and by direct suppression of tumor growth. It is possible that CXCL10 and perhaps pro-cancer function is due to its chemotactic properties for cancer cells.

**CHEMOTRACTION AND BEYOND, CAN WE DIFFERENTIALLY ANALYZE THESE PROPERTIES?**

It is clear that chemotraction of CXCR3+ T cells, and other CXCR3+ cells, to sites of inflammation and tumor sites is an essential feature, and that inhibition of the CXCR3 dependent migration of CXCR3+ T cells to tumor site, or even their adhesion molecule dependent arrest, plays a major role in inflammation and cancer. For example, Mikucki et al. applied adoptive transfer experiments of T cells from CXCR3KO Vs WT mice in a cancer set-up to show that recruitment to the tumor site was markedly inhibited when donor cells came from CXCR3KO mice, and inhibition was comparable to the one achieved by using T cells form WT donors and pertussis toxin (PTX) (33). It is also clear that CXCL10, and probably CXCL9 signaling enhance the effector properties of these cells (7). We believe that what makes CXCR3 and its ligands drivers of immune function is the combination of chemotaxis and direct effect on the biological function (6, 89). Dissecting the direct effect of CXCR3 ligands on cells migration from their ability to affect the biological properties of these cells could be of interest when developing therapeutic tools, such as blocking antibodies or stabilized chemokines for immunotherapy.

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**CONCLUSIONS**

The main take home message of this minireview is that few chemokine receptors, among them CXCR3, are key drivers in directing the immune response as aside of chemotraction they also direct the biological function of immune cells that possess them. CXCR3 is of high interest as each of its three ligands differs in its biological properties via this receptor, and its ability to regulate the biological function of others. For example, CXCL11 with the higher affinity to CXCR3 is likely to hold anti-inflammatory properties and by leading to receptor internalization makes the receptor less accessible to others. Currently much attention is given to CXCL9 and CXCL10 and their role in the potentiation of anti-tumor CD8+ T cells.

Chemokine receptors support tumor development different complementary pathways: First, many of them function as growth/survival factors either by autocrine pathway, and/or by inducing growth factors production by epithelial cells and stromal cells within the tumor microenvironment. Second, several of them direct the recruitment of bone marrow derived cells that support tumor growth and suppress anti-tumor immunity. Third, chemokine—chemokine receptor interactions are involved in attracting tumor cells to metastatic sites. Table 1 indicates the involvement of key chemokine receptors in these pathways.

**AUTHOR CONTRIBUTIONS**

The author confirms being the sole contributor of this work and has approved it for publication.

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