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CXCR3 ligands: redundant, collaborative and antagonistic functions

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Abstract

CXCR3 is a chemokine receptor that is rapidly induced on naïve T cells following activation, and preferentially remains highly expressed on type-1 helper (Th1)-type $CD4^+$ T cells, effector $CD8^+$ T cells and innate-type lymphocytes, such as natural killer (NK) and NKT cells. CXCR3 is activated by three interferon (IFN)-γ-inducible ligands CXCL9 (monokine induced by gamma-interferon), CXCL10 (interferon-induced protein-10) and CXCL11 (interferon-inducible T-cell alpha chemoattractant). Although some studies have revealed that these ligands have redundant functions *in vivo*, other studies have demonstrated that the three CXCR3 ligands can also collaborate and even compete with each other. Differential regulation of the three ligands at specific times in defined anatomically restricted locations *in vivo* likely participates in the fine control of T-cell trafficking over the course of an immune response. Among the differences in regulation, CXCL10 is induced by a variety of innate stimuli that induce IFN-α/β as well as the adaptive immune cell cytokine IFN-γ, whereas CXCL9 induction is restricted to IFN-γ. In this review, we will discuss how the balance, timing and pattern of CXCR3 ligand expression appears to regulate the generation of effector T cells in the lymphoid compartment and subsequent migration into peripheral sites of Th1-type inflammation in which the CXCR3 ligands also then regulate the interactions and migratory behavior of effector T cells in an inflamed peripheral tissue.

Keywords

CXCR3; CXCL9; CXCL10; chemokines; T-cell trafficking

One of the fundamental questions in chemokine biology has been the apparent redundancy of chemokine ligands. We now know that there are approximately 50 chemokines and 20 chemokine receptors. Many chemokine receptors therefore have multiple chemokine ligands. *In vitro* assays have revealed that multiple chemokines can have similar binding affinities for the same receptor, and induce a similar signaling cascade and a similar chemotaxis profile through the same receptor. Thus, the question arises as to why have multiple ligands for the same receptor? The CXCR3 receptor and its ligands represent a complex chemokine system whereby one receptor has three interferon (IFN)-γ-inducible ligands, CXCT9, CXCT10 and CXCL11.

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CONFLICT OF INTEREST
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CXCR3 is an inflammatory chemokine receptor whose expression is associated with $CD4^+$ Type-1 helper (Th1) and $CD8^+$ cytotoxic lymphocytes (CTLs) (Table 1).[1–4] Early studies found that T cells, recovered from inflamed peripheral tissues in human autoimmune disease, were highly enriched in CXCR3 surface expression relative to T cells found in the blood.[2,5,6] This observation coupled with finding that the CXCR3 ligands were highly expressed in these same diseased tissue, indicated a specific role for CXCR3 and its ligands in the recruitment of T cells into these otherwise restricted sites (Table 2). CXCR3 is absent on naïve T cells, but is rapidly upregulated following dendritic cell (DC)-induced T-cell activation.[3,7,8] $CXCR3^+$ cells make up between 60 and 90% of CD8+ memory T cells[9,10] and 40% of $CD4^+$ memory T cells.[11,12] T-bet, the master transcription factor of Th1 and CTL commitment, directly transactivates CXCR3 and other genes important for Th1 and CTL cell function, thus allowing these cells to infiltrate into the inflamed tissues.[13–16] The tight correlation between CXCR3 expression and Th1 and CTL differentiation led to the hypothesis, subsequently verified in mouse models, that CXCR3 and its ligands regulate the migration of Th1 cells into sites of Th1-driven inflammation[8,17,18] (Table 2).

In addition to CXCR3 expression on effector $CD4^+$ and $CD8^+$ T cells, CXCR3 is also highly expressed on innate lymphocytes, such as natural killer (NK) cells and NKT cells in which it is thought to participate in the localization of these first-line defenders at sites of infection and inflammation.[5,19] Further, CXCR3 is expressed on plasmacytoid DCs and subsets of B cells in which it may have a role in the migration of these cells in the inflamed lymph node (LN).[20,21]

CXCR3 through binding of its chemokine ligands has been shown to coordinate inflammation in the periphery.[22] CXCR3 binds three chemokines: CXCL9 (also known as monokine induced by gamma-interferon, MIG), CXCL10 (interferon-induced protein of 10kDa, IP-10), CXCL11 (interferon-inducible T-cell alpha chemoattractant, I-TAC) to induce migration.[1,2,23,24] Although CXCL9, CXCL10 and CXCL11 all bind CXCR3 and elicit migration of CXCR3-expressing cells *in vitro*, inflammatory models demonstrate that chemokine redundancy may not be operative *in vivo*. As we will discuss, CXCL9, CXC'L10 and CXCL'11 have been shown to work redundantly, synergistically collaboratively and, in some instances, apparently antagonistically *in vivo*. Thus, understanding the balance, timing and expression pattern of this chemokine system *in vivo* will be important for understanding the respective roles of the three CXCR3 ligands in the generation and delivery of an immune response.

CXCR3 LIGAND INDUCTION

As their original names suggest, IFN-γ Type II interferon mediates the induction of all three CXCR3 ligands (Table 1).[23,25,26] However, unique promoters control the distinct pattern of expression of each CXCR3 ligand. The CXCL10 promoter contains a functional IRSE and nuclear factor kappa Bl (NF-κBI) element,[27–29] whereas the CXCL9 promoter contains an γIRE-1 element and a weak NF-κB2 element.[29–31] The CXC11 promoter is more similar to the CXCL10 promoter, and contains an IRSE site and an NK-κB2 site.[32] For CXCL11 expression, a STAT3-STAT1 heterodimer, and not the classical STAT1–STAT2 heterodimer, binds to the *CXCL11* promoter subsequent to IFN stimulation. In addition, the NF-κB family member p65 and IFN-regulatory factor 1 also binds to the CXCL11 promoter.[33] As such, the CXCR3 ligands are differentially regulated. CXCL10 is strongly induced by IFN-γ as well as by the Type I interferons IFN-α//β, and weakly induced tumor necrosis factor, although tumor necrosis factor synergizes strongly with the IFNs for CXCL10 induction.[34,35] CXCL9 is strongly induced by IFN-γ but not induced by IFN-α/β, and whereas tumor necrosis factor does not induce CXCL9 expression alone, it does synergizes with the IFN-γ in inducing CXCL9 transcription.[34,36] CXCL11 is induced by

IFN-γ and by IFN-β but surprisingly not by IFN-α[37] As with the other two CXCR3 ligands, tumor necrosis factor synergizes with IFN-γ in inducing CXCL11 transcription. Thus, although CXCL9 is completely dependent on IFN-γ for its induction, CXC10 and CXCL11 are not.[22,38] In addition, as CXCL10 is induced by IFN-α, it is also induced by innate sensors, such as the toll-like receptors and the RNA helicases (for example, RIG-I and MAD-5), through activation of IFN-regulatory factor 3 and the release of IFN-α.[39] Autocrine signaling of IFN-α and activation of Stat1 activates the *CXCL10* gene.[40] CXCL10 is also preferentially induced by hypoxia-reperfusion injury by NF- κB activation, independent of p50, and has been shown to have an early role in the hypoxia-induced inflammation associated with solid-organ transplantation, such as the heart and lung.[38,41] Thus, owing to different regulatory elements on their promoters, CXCR3 ligands have different temporal and spatial patterns of expression, regulated by different stimuli and expressed by distinct cell types during the course of an immune response.[38,42] These differences undoubtedly account for the unique role of the CXCR3 ligands in regulating the fine control of T-cell trafficking *in vivo*.

Receptor binding

In addition to different expression profiles, CXCR3 ligands display unique binding characteristics toward their shared receptor. This may result in these ligands transducing slightly different signals to CXCR3-expressing cells, which may also contribute to the unique roles of the three CXCR3 ligands *in vivo*. There is a hierarchy of affinity for CXCR3, with CXCL11 binding to CXCR3 having the highest affinity followed by CXCL10 having intermediate affinity and then CXCL9 having the lowest affinity for CXCR3.[43–45] Concordant with their affinity, CXCL11 induces calcium mobilization and chemotaxis at lower doses than CXCL9 and CXCL10.[23,46] Different regions of the CXCR3 receptor enact binding, activation and internalization by each protein. CXCR3 is sulfated on its N-terminus and that sulfation is required for binding and activation by all three ligands, whereas the proximal 16 amino acid residues of the N terminus are required for CXCL10 and CXCL11 binding and activation but not CXCL9 activation.[47] Two distinct domains control internalization of CXCR3.[48] The carboxyl-terminal domain and beta-arrestin-1 binding domain are predominantly required for CXCL9- and CXCL10-directed internalization, whereas third intracellular loop is required by CXCL11.[48] Structure-activity studies with CXCR3 ligands have identified unique regions in each protein, which are important for their binding to CXCR3 and to heparin, further explaining their differential effects on the receptor.[49–51] These differences in protein-receptor binding and protein structure can potentially be exploited to develop new therapeutics, with enhanced functional properties, which has been demonstrated for a CXCL10-CXCL11 chimeric protein that had greater antitumor activity than the parent chemokines.[52]

The CXCR3 ligands also enact their functions through the binding of other chemokine receptors as well as glycosaminoglycan (GAG)-containing molecules, such as proteoglycans. At high concentrations, all three ligands are thought be natural antagonists for CCR3, a chemokine receptor normally expressed on eosinophils.[53] Therefore, differential expression of CCR3 may also alter the function of these chemokines. In addition, CXCL11 but not CXCL9 and CXCL10 binds to CXCR7.[54,55]

The CXCR3 ligands are basic proteins that bind avidly to negatively charged GAG molecules, both on the surface of cells and in the extracellular matrix.[50,51,56] GAG binding is thought to be important for the retention and presentation of chemokines to their chemokine receptors *in vivo*. Although the *in vitro* chemotactic activity of CXCL10 and CXCL11 was shown to be independent of GAG binding, the ability of these chemokines to induce CXCR3-dependent T-cell migration *in vivo* was shown to be dependent on their

ability to bind GAGs.[51,57] Although it is not the focus of this review, the ability of CXCL0 to influence the behavior of certain non-immune cells, such as endothelial cells and fibroblasts, that do not express CXCR3, is a function of the ability of these chemokines to bind to cell surface GAGs.[58–63]

LIGAND-DEFICIENT COMPLEXITY

A further piece of information adding to the confusion surrounding the CXCR3 ligand system is that wild-type C57BL/6 mice, which are most commonly used for mouse experimentation, contain a point mutation and a single-base deletion in the leader sequence, resulting in a reading frame shift that introduces a stop codon early within the *Cxcl11* gene, making these mice deficient for CXCL11. The C57BL/6 mice are still capable of responding to injected CXCL11 in a CXCR3-dependent manner.[18] This observation, further confounds the interpretation of results, as both the *Cxcl9*$^{-/-}$ and *Cxcl10*$^{-/-}$ mice were generated using 129 embryonic stem cells, and subsequently backcrossed onto the C57BL/6 background.[64,65] The close linkage of these chemokine genes means that both *Cxcl9*$^{-/-}$ and *Cxcl10*$^{-/-}$ mice have an intact *Cxcl11* gene, so there is a discrepancy between *Cxcl9*$^{-/-}$ and *Cxcl10*$^{-/-}$ and their wild-type controls. Owing to this added complexity, caution must be taken when interpreting results from *Cxcl9*$^{-/-}$ and *Cxcl10*$^{-/-}$ mice on a C57BL/6 background. It will be important for future studies to investigate the expression of CXCL11 in these knockout mice, to determine whether some observed affects are because of the difference in CXCL11 production. Ultimately, it will be important to generate *Cxcl9*$^{-/-}$ and *cxcl10*$^{-/-}$ mice using C57BL/6 embryonic stem cells.

LIGAND REDUNDANCY

In an *in vivo* model of cell recruitment, each of the CXCR3 ligands are equally efficacious at recruiting activated effector CD4^{+} and CD8^{+} T cells into the lung.[18] However, this T-cell recruitment model does not consider the complexity of ligand induction as discussed above. Surprisingly, even during an immune response in which the ligands are differentially expressed and regulated, there appears to be significant chemokine redundancy in this system.[38] In a murine model of obliterative bronchiolitis, CXCL9 and CXCL10 are differentially regulated and they together coordinate CXCR3^{+} T-cell infiltration into the airways. Early after an allogenic transplant, CXCL10 is expressed in a manner that is independent of IFN-γ, p50 and STAT1.[38] This CXCL10 expression was the result of an oxidant-sensitive pathway, possibly involving other NF- κB family members. However, later in the course of transplant rejection, CXCL9 and CXCL10 were both induced in an IFN-γ- and STAT1-dependent manner. Although CXCR3 deficiency reduced airway obliteration in this model, neither *Cxcl9*$^{-/-}$ or *Cxcl10*$^{-/-}$ mice showed any decreased rejection. These results suggest that despite their different induction, the loss of one chemokine is compensated for by the presence of the other, and that either of the ligand is required for the recruitment of allograft-reactive CXCR3-expressing cells.[38]

LIGAND DOMINANCE

In some inflammatory models, the requirement of one CXCR3 ligand dominates, and its deficiency cannot be compensated for by the presence of the other ligands. Some infections in the brain show an importance of CXCL10 over the other CXCR3 ligands. In dengue virus infection, *Cxcr3*$^{-/-}$ mice have higher viral loads than those of wild-type mice because of reduced trafficking of CD8^{+} effector cells into the brain. Although CXCL9, CXCL10 and CXCL11 are all induced by dengue virus infection, the latter two could not compensate for the absence of CXCL10 in *Cxcl10*$^{-/-}$ mice.[66] Similarly, in West Nile virus infection, CXCL10 is expressed by neurons and directs the migration of CD8^{+} T cells into the brain.[67]

Cxcr3$^{-/-}$ and *Cxcl10*$^{-/-}$ mice are protected from meningitis during central nervous system lymphocytic choriomeningitis virus infection.[68] Whether the predominant importance of Cxcl10 during these infections is particular to the brain or to viral infections is unknown, as this CXCR3 ligand also appears to dominate in other non-brain viral responses and non-viral central nervous system infections.[17,64]

In a model that uses acute lymphocytic choriomeningitis virus infection of transgenic mice that express the glycoprotein of lymphocytic choriomeningitis virus in the cells of the islets of Langerhans, all CXCR3 ligands are upregulated in the pancreas.[69] Although CXCL9 immunohistochemistry showed limited expression around the outer aspects of islet, CXCL10 stained throughout the infiltrated islet.[70] *Cxcr3*$^{-/-}$ mice showed delayed onset of insulitis in this model, seemingly because of an impaired T-cell infiltration into the islet through CXCL10. This was also seen in mice treated with CXCL10-neutralizing antibodies, whereas CXCL9 neutralizing antibodies had no affect on disease progression.[69,70] In a small-bowel allograft rejection model, CXCR3^{+} T-cell infiltration of the graft lamina propria was primarily because of CXCL10, as either using neutralizing CXCL10 or using grafts from *Cxcl10*$^{-/-}$ mice significantly delayed rejection.[71,72] Further, in the interleukin-10 null inflammatory bowel disease model, CXCL10 and CXCR3 were highly expressed at sites of colitis, and CXCL10 neutralization attenuated the severity of colitis.[73,74]

In contrast, *Cxcr3*- and *Cxcl9*-deficient, but not *Cxcl10*-deficient, Murphy Roth Large/lpr mice were protected from autoimmune lupus-like inflammation of the kidney[75] Interestingly in this model, *Cxcr3* deficiency blocked the infiltration of not only Th1 cells but also interleukin-17-secreting cells into the kidney[76] Few studies have investigated the role of *Cxcl11 in vivo*. However, in a model of acute skin allograft inflammation, *Cxcl11* was the most highly elevated chemokine. Treatment with a CXCL11-neutralizing antibody reduced the number of CXCR3^{+} cells in the skin allograft and prolonged graft survival.[77] Although it may appear from this review that CXCL10 is the dominant CXCR3 ligand in most immune responses, it is worth noting that this chemokine is the most highly studied, and multiple studies evaluate only this single chemokine. Further studies of these models may reveal unappreciated roles for CXCL9 and CXCL11.

LIGAND COLLABORATION

As mentioned above, several models of T-cell inflammation in the brain and spinal cord have shown a dominance of CXCL10 as the primary CXCR3 ligand responsible for ‘inviting’ effector T cells into this otherwise restricted site. In contrast, in other models, cooperation between CXCL9 and CXCL10 is required for full T-cell infiltration. CXCR3 is required on CD8^{+} cells for infiltration into the brain during *Plasmodium berghtei* ANKA infection for the development of cerebral malaria symptoms.[42,78] The *Cxcr3*$^{-/-}$ mice are protected from cerebral malaria because of reduced CD8^{+} CTL sequestration in the brain. This protection is mediated equally by CXCL9 and CXCL10, as each mouse deficient in one of these ligands showed partial disease protection.[42,79] This cooperation between CXCR3 ligands appears to be because of the differential expression of the ligands by different cell types. Immuno-histochemistry of *P. berghei*-infected mice revealed that CXCL9 was predominantly expressed by endothelial cells and CXCL10 was predominately expressed by neurons explaining the non-overlapping roles of these two CXCR3 ligands in the pathogenesis of cerebral malaria.[42] Similarly, in a mouse model of herpes simplex virus-2 infection, expression of both CXCL9 and CXCL10 was necessary for optimal recruitment of NK cells and CTLs into the spinal cord.[80] During the course of the disease in the ligand-deficient mice, the RNA levels of the alternate ligand were significantly diminished. These data suggest that each CXCR3 ligand contributes to the expression of other CXCR3 ligands

in this model. This regulation is likely to be indirect because of increased IFN-γ levels in the local environment provided by the first wave of recruited NK and CTL cells into the spinal cord.[22,80] Unfortunately, this study did not investigate cell type-specific expression of the CXCR3 ligands, however, it is likely that each chemokine ligand is expressed by different cells in the spinal cord and brain, as was seen in the model of cerebral malaria.[42,80]

Differences in temporal or tissue-specific expression of the CXCR3 ligands have also been shown to collaborate to choreograph the movement of CXCR3-expressing T cell from the lymphoid compartment to the peripheral inflamed tissue. This was demonstrated in a murine model of granulomatous liver disease induced by *Propioni-bacterium acnes*.[81] In this model, LN DCs produced CXCL10, whereas hepatic granuloma cells in the liver parenchyma produced CXCL9. Neutralization of either CXCL9 or CXCL10 gave different results, leading to the hypothesis that CXCL10 instructs $CD4^+$ Th1 cells to stay in the LN interacting with DCs, whereas CXCL9 expression in the periphery drives the recruitment of these cells out of the LN and into the liver.[81] Therefore, the transient switch in expression of CXCL9 and CXCL10 is critical during the disease to allow the progression of a Th1 cell responses.

The collaboration of CXCR3 ligands during immune responses coordinates T-cell infiltration in the periphery. Multiple studies have demonstrated that recruitment of effector T cells and inflammation drives further recruitment and inflammation. This likely involves both CXCR3-dependent and a CXCR3-independent amplification loops. The CXCR3-dependent amplification of immune responses involves the collaboration of the different CXCR3 ligands, which are regulated differentially during the course of an inflammatory response that moves from innate stimuli (for example, IFN-α/β) to adaptive stimuli (for example, IFN-γ)[22,38] (Figure 1). This CXCR3-dependent inflammatory loop potentially may not only increase recruitment of CTLs into peripheral tissues but also may enhance the generation of CTLs,[82] and promote increased effector responses through STAT1 signaling.[83] This CXCR3-dependent inflammatory loop also has been shown to spark CXCR3-indendent inflammation. This has been observed in the context of CXCR3-dependent inflammation whereby CXCR3-dependent T-cell recruitment permits the entry of CXCR3 negative and *Cxcr3*$^{-/-}$ T cells into immune-privileged sites.[42,76]

Although the concept of an IFNγ-CXCR3-chemokine-dependent inflammatory loop is firmly established, interesting questions about the cellular sources of the ligands in different types of inflammation still remain unanswered. Whether the cells upregulating CXCR3 ligands are peripheral dendritic cell subsets and/or non-immune structural cells in the site of inflammation remains to be determined. In addition, it is not clear whether the T cells involved in this amplification loop directly contact cells that upregulate CXCL9 and CXCL10, or whether soluble chemokine gradients dispersed throughout the inflamed tissue recruit more effector cells.

APPARENT LIGAND ANTAGONISM

As was mentioned for the *P. acnes* model of liver granuloma above, inhibition of the individual CXCR3 chemokine ligands has on some occasion given apparent opposite results. This was recently demonstrated in a model of allograft heart transplant rejection. In this model, CXCL9 produced by allograft DCs promote the priming of host $CD8^+$ and $CD4^+$ cells towards CTL and Th1 IFN-γ-producing T cells.[84] DC-produced CXCL9 was induced by NK cell-derived IFN-γ. Deficiency in *Cxcl9*, specifically in the passenger DCs from the allograft, reduced the priming of graft-reactive CTLs and Thl cells in the spleen of mice receiving heart transplants. CXCL10 was also produced in the spleen with a similar kinetics as CXCL9. Surprisingly, CXCL10 appeared to have the opposite effect on T-cell priming, in

which a deficiency of *Cxcl10* resulted in increased IFN-γ-producing $CD8^+$ T cells, although this study did not dissect whether the *Cxcl10* deficiency in the recipient or the allograft was responsible for this effect.[84] The treatment of $Cxcl10^{-/-}$-transplanted mice, with CXCL9-neutralizing antibody reduced the numbers of IFN-γ-producing $CD8^+$ T cells to that observed in wild-type-transplanted mice, suggesting that the *Cxcl10* deficiency increase in IFN-γ-producing was because of CXCL9 increased expression.[84]

Observations of opposing ligand function have also been detailed in a model of ocular immune response to herpes simplex virus-1 infection using $Cxcl9^{-/-}$ and $Cxcl10^{-/-}$ mice. $Cxcl10^{-/-}$ mice showed an increased sensitivity to ocular virus and elevated virus titer in the tear film and corneal tissue. In comparison, there was a significant reduction in $CD4^+$ T-cell infiltration into the cornea in *Cxcl9*-deficient mice, illustrating opposing functions of these chemokines *in vivo*.[85] These observations of opposing ligand function may explain studies in which *Cxcr3* deficiency or antagonism results in only a modest decrease in T-cell entry, despite high expression of CXCR3 receptor and ligands in target tissue.[86]

Whether these findings of opposing *in vivo* functions represent true antagonistic function of the CXCR3 ligands or actually represent collaborative functions of these ligands that appear opposing when analyzed in different tissues at different time points, as was seen in the *P. acnes* model discussed above,[81] remains to be determined.

Further complexity in the system is now appreciated with the finding that CXCR3 is expressed on a Th1-specific $CD4^+$ T-regulatory cell.[87] It is also therefore possible that concomitant inhibition of CXCR3-expressing T-regulatory cells may also partially explain studies in which *Cxcr3* deficiency or antagonism results in only a modest decrease in T-cell entry, despite high expression of CXCR3 receptor and ligands in the target tissue. Although the trafficking requirements of $CXCR3^+$ T-regulatory cells remain to be determined, it is possible that they may be more responsive to one CXCR3 ligand, allowing for differential trafficking of effector and T-regulatory cell CXCR3-expressing cells during T-cell priming and inflammation. It will be interesting to observe whether this direct competition between CXCR3 ligands occurs in other models. Whether these ligands have differential effects on different T-cell subsets remains to be resolved.

At present it is not clear why in some instances different results have been obtained when examining CXCR3 ligand function in similar models. For example, in various allograft models a single pattern of CXCR3 ligand function has not emerged. As discussed, CXCR3 ligands have been shown to directly antagonize each other in one model of heart transplant,[84] whereas in another CXCL10 function was shown to be dominant and upstream of the other CXCR3 ligands[41] and in a third model CXCL9 was shown to be the dominant CXCR3 ligand.[88] In a model of lung transplant rejection, CXCL9 and CXCL10 were shown to be redundant,[38] whereas in another study they were shown to be cooperative.[89] In one model of skin allograft rejection, CXCL9 was shown to be the dominant CXCR3 ligand,[90] whereas in another skin allograft model CXCL11 was shown to be the dominant chemokine involved in the infiltration of $CXCR3^+$ T cells into the inflamed tissue.[77] Difference in the cellular sources and the timing of CXCR3 ligand expression in these models may explain the apparent differential requirements for the three ligands in seemingly related inflammatory models, although this clearly needs to be studied in more detail.

CONCLUDING COMMENTS AND FUTURE DIRECTIONS

In the last few years, much has been learned of the involvement of the CXCR3 chemokine system during inflammation. Yet there remain many questions that still need to be answered. How precisely the chemokines are regulated, both temporally and in a cell type-specific

manner, needs to be further investigated. Other factors, in addition to members of the IFN family that induce the CXCR3 ligands during the initiation of the immune response as well as during peripheral T-cell trafficking may be found. Indeed, some studies have identified ligand expression that cannot be fully explained by our current understanding of chemokine regulation.[38]

Despite the demonstration of their importance in multiple disease models, surprisingly few studies have investigated in detail the specific cellular sources of CXCR3 ligand production during inflammation. Much of the work in this area has been done using quantitative PCR on total inflamed organs. Although this method confirms timing and tissue expression, it obscures the fine local temporal and spatial control of CXCR3 ligands, and it offers little information about the types of cells that elicit effector T-cell recruitment, and the molecules that induce this expression. It is likely that the cell types responsible for ligand expression greatly influence the outcome of CXCR3-expressing cell responses, for instance CXCR3 ligand expression in priming or regulatory DC subsets may induce differential responses by Thl $CD4^+$ T cells.[40] In addition, investigation of the location of CXCL9 and CXCL10, by way of immunohistology staining, may not fully answer questions of which cell produce these chemokines. An interesting question in the future will be to answer whether the same cells that present these chemokines in LN and in the periphery, are the same cells that produce them, or whether CXCL9 and CXCL10 are secreted by one cell and taken up by others to present to T cells. It may be that this presentation or the activation state of the cells presenting CXCL9, CXCL10 and CXCL11 will determine the outcome of CXCR3-mediated responses.

Finally, several studies look exclusively at one ligand by expression or blocking to explain the regulation of CXCR3-dependent mechanisms. In the future, greater detail of all the ligands of CXCR3 should be investigated as, in all probability, further analysis of these systems will highlight additional circumstances of collaboration or conflicting functions of CXCR3 ligands exist. These inquiries will be particularly necessary to dissect in diseases in which CXCR3 and its ligands have been suggested as therapeutic targets.

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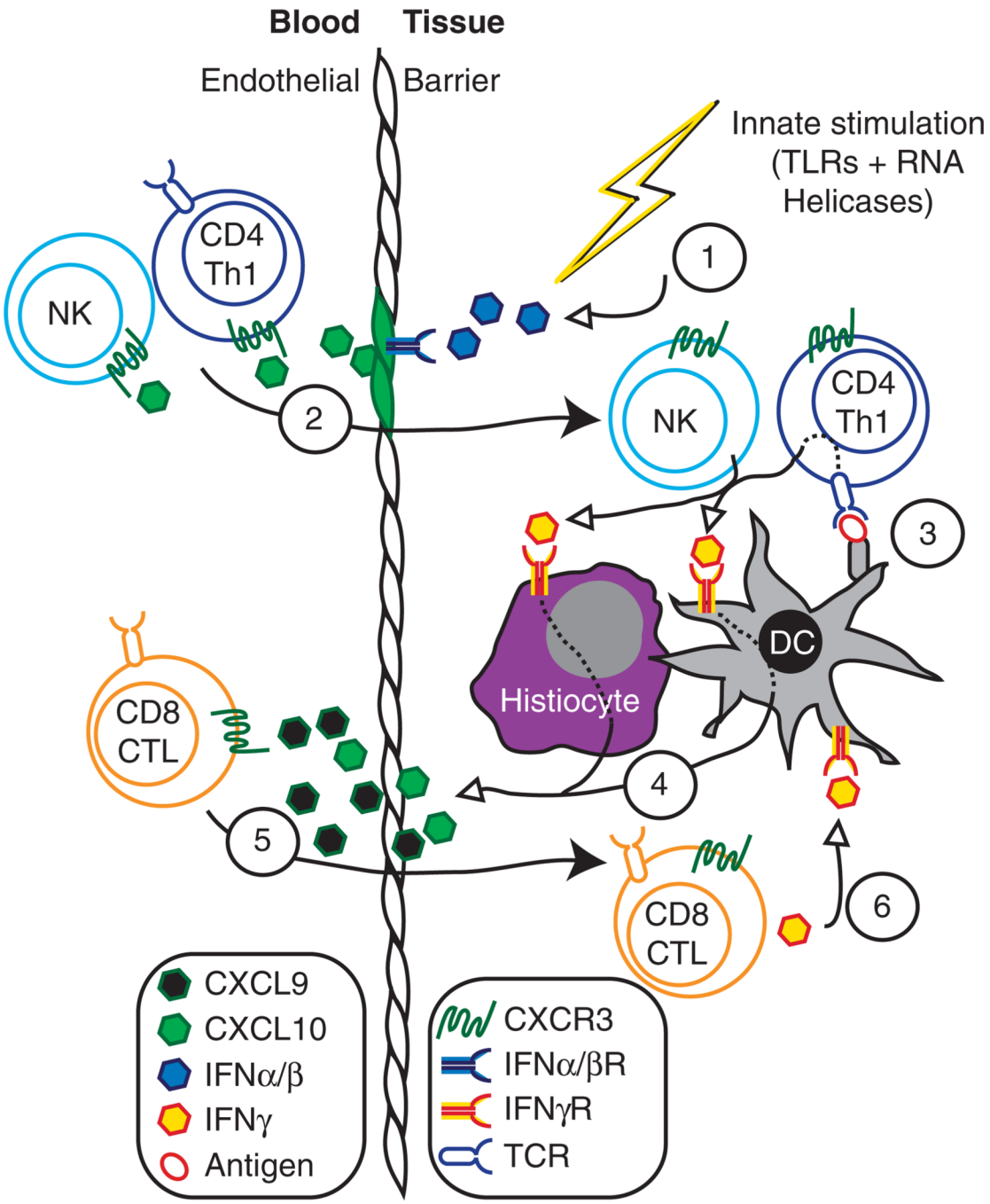

Figure 1.

Collaboration between CXCR3 ligands coordinates effector immune responses. This model describes the sequential events from top (1) to bottom (6) involving Type I and Type II interferon induction of the CXCR3 ligands, CXCL9 and CXCL10, and how this defines their respective roles in the recruitment of effector T cell and NK cell populations into inflamed tissues. CXCL11 also likely contributes to this process but currently less is known how this CXCR3 ligand contributes to this cascade. Open arrowheads indicate cytokine/chemokine secretion and closed arrowheads indicate cellular movement. (1) Innate immune activation, such as bacterial or viral infection, activates TLRs and RNA helicases leading to the release of IFN-α/β and subsequent secretion CXCL10 by tissue resident cells and

endothelial cells. (2) CXCL10 recruits NK and $CD4^+$ Th1 cells into the target tissue. (3) $CD4^+$ cells release IFN-γ in an antigen-specific manner. (4) IFN-γ signaling in tissue resident cells, including DCs and tissue histiocytes induce the production and secretion of CXCL9 and CXCL10. (5) Secreted CXCL9 and CXCL10 recruit $CD8^+$ CTLs into the tissue. (6) CTL-derived IFN-y further stimulate tissue resident cells to produce more CXCL9 and CXCL10, thus, amplifying the Th1-type inflammatory response.

Table 1

CXCR3 and its ligands

Receptor	Highly expressed	Ligands	Activity	Ligand inducers	Promoter elements
CXCR3	Effector $CD4^+$Th1, $CD8^+$CTL, NK and NKT cells, pDCs	**CXCL9**	Activate to induce chemotaxis, cell migration and adhesion	IFN-γ⋙TNF	γIRE-1, NF-κB2
		CXCL10		IFN-γ>IFN-α/β>TNF	IRSE, NF-κB1
		CXCL11		IFN-γ=IFN-β>IFN-α>TNF	STAT3, NF-κB2

Abbreviations: CTL, cytotoxic lymphocyte; DC, dendritic cell; IFN, interferon; NF, nuclear factor; NK, natural killer; NKT, natural killer T celI; Th1, type-1 helper; TNF, tumor necrosis factor.

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Table 2

CXCR3 and its ligands in human disease and murine disease models

Disease/disease model	Receptor	Ligands		
	CXCR3	CXCL9	CXCL10	CXCL11
Autoimmmune				
Psoriasis		91, 92	91, 93	91
Sarcoid	94, 95	95, 96	94, 95	95, 96
Rheumatoid arthritis	21, 97–100	98	99, 101	
Asthma	102, 103	102	102, 104–106	102
Atherosclerosis	107, 108	107	107, 109	107
Multiple sclerosis	110–116	111	110, 111, 117, 118	
IBD	119		73	
Idiopathic pulmonary fibrosis	120, 121		59, 60	122
Type 1 diabetes mellitus	70, 123		69, 123, 124	
SLE	75, 125, 126	75	126, 127	
Cigarette smoke injury/COPD	128–131	131	128, 131	131
Myocarditis	132		96, 133	
Transplantation				
Heart transplant	86, 134–137	41, 138	41, 139	
Lung transplant	38, 140	38, 89	38, 89, 140	89
GVH	141, 142		142	
Small bowel	72		72	
Infections				
Leprosy	143			
Tuberculosis			144, 145	
Influenza	146, 147		146, 147	
Toxoplasma gondii			17, 148	
Malaria	42, 78	42, 78	42, 78, 79, 149	
Dengue	66		66, 150	
Hepatitis B and C	151–153	151, 152	64, 151, 153, 154	151
Herpes simplex	22, 80	22, 80	22, 80, 155, 156	
HIV-1	157	157	157–159	158
Leishmania	160	161	161, 162	
Chlamydia trachomatis	163, 164		164	
Lyme	165	166, 167	166, 167	
West nile virus	67		67	
Cancer				
Renal	168	168	168	168
Colon			169, 170	
Melanoma	171	171	171	
Lymphoma	172–174		175	
Breast	176		176	

Abbreviations: COPD, chronic obstructive pulmonary disease; GVH, graft-versus-host; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus.