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CXCR3 in T cell function

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Abstract

CXCR3 is a chemokine receptor that is highly expressed on effector T cells and plays an important role in T cell trafficking and function. CXCR3 is rapidly induced on naïve cells following activation and preferentially remains highly expressed on Th1-type CD4+ T cells and effector CD8+ T cells. CXCR3 is activated by three interferon-inducible ligands CXCL9 (MIG), CXCL10 (IP-10) and CXCL11 (I-TAC). Early studies demonstrated a role for CXCR3 in the trafficking of Th1 and CD8 T cells to peripheral sites of Th1-type inflammation and the establishment on Th1 amplification loop mediated by IFNγ and the IFNγ-inducible CXCR3 ligands. More recent studies have also suggested that CXCR3 plays a role in the migration of T cells in the microenvironment of the peripheral tissue and lymphoid compartment, facilitating the interaction of T cells with antigen presenting cells leading to the generation of effector and memory cells.

Introduction

During the course of an immune response distinct functional subsets of effector and regulatory T cells are generated in the lymphoid compartment following the differentiation of naïve T cells under the influence of specific cytokines. CD4+ effector subsets include type-1 helper (Th1), Th2 and Th17, which are characterized by the production of different inflammatory cytokines to drive immunity and T regulatory cells (Tregs), which counterbalance these responses. Similar to Th1 cells that produce large amounts of interferon-gamma (IFNγ), CD8+ T cells can differentiate to become cytotoxic lymphocytes (CTLs), which secrete IFNγ along with other effector molecules. Once differentiated, these T cell subsets upregulate chemokine receptors, which guide them out of the lymphoid compartment and into sites of inflammation or infection to deliver an adaptive immune response. Effector T cell subsets differ profoundly in their migratory properties [1]. The induction of Th1 and CTL cells is strongly linked to the upregulation of the chemokine receptor CXCR3. CXCR3 binds three chemokines CXCL9 (also known as MIG, monokine induced by gamma-interferon), CXCL10 (IP-10, interferon-induced protein of 10kDa), CXCL11 (I-TAC, interferon inducible T cell alpha chemoattractant) to induce migration of activated T cells *in vitro* and *in vivo* [2–6]. CXCR3 and its ligands are undoubtedly an inflammatory chemokine system, capable of coordinating T cell responses in the inflamed periphery. In addition, this system may also play a role in the generation of both inflammatory and suppressive T cell responses.

While this review will focus exclusively on the role of CXCR3 on effector CD4+ and CD8+ T cells, it is also worth noting that CXCR3 is also highly expressed on innate lymphocytes, such as NK cells and NKT cells where CXCR3 is thought to participate in the localization of these first line defenders at sites of infection and inflammation [7,8]. Further, CXCR3 is expressed on plasmacytoid dendritic cells (DCs) and subsets of B cells where it may play a role in the migration of these cells in the inflamed lymph node (LN) [9,10].

CXCR3 – the inflammatory T cell chemokine receptor

Early studies found that T cells recovered from inflamed peripheral tissue in human autoimmune disease were highly enriched in CXCR3 surface expression relative to T cells found in the blood [7,11,12]. In addition, CXCR3 ligands were also found to be highly expressed in these same diseased tissues where CXCR3 positive T cells had accumulated (Table 1). These observations indicated a specific role for CXCR3 and its ligands in the recruitment of T cells into these otherwise restricted sites. While absent on naïve T cells, effector and memory T cells highly express CXCR3 [13]. This upregulation of CXCR3 occurs rapidly following DC-induced T cell activation, prior to T cell proliferation in an antigen-specific manner [14,15]. The expression of CXCR3, along with CCR5 and CXCR6, discriminates between different effector T cell populations. Specifically, naturally occurring IFNγ-producing Th1 cells are almost exclusively CXCR3 positive [14,16]. In addition, *in vitro* Th1-polarized T cells highly upregulate CXCR3 [17]. The tight correlation between CXCR3 expression and Th1 differentiation lead 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 (Table 1) [2,3,15,18].

Induction of CXCR3 on T cells

Naïve T cells differentiate into Th1 cells under the direction of the cytokine IL12 and the transcription factor Tbet (Tbx21, T-box expressed in T cells). Th1 cell-mediated inflammation is characterized by the recruitment of IFNγ producing CD4 T cells that normally mediate protection against intracellular pathogens, but are also dysregulated in autoimmunity. T-bet is the master transcription factor of Th1 and CTL commitment. T-bet directly activates transcription of a set of genes important for Th1 and CTL cell function, including those encoding *IFNγ* [19–21]. The resistance of *T-bet* deficient mice to inflammatory diseases is characterized by a lack of T cell infiltration at the pathological site [22,23]. T-bet imprints a migratory program upon developing effector T cells to ensure appropriate homing to inflammatory sites. Defects in migration of *T-bet* deficient (−/−) T cells are primarily due to loss of CXCR3 expression, as T-bet directly transactivates CXCR3, and retroviral-mediated CXCR3 expression in *T-bet* −/− CD8 T cells reconstitutes their ability to infiltrate inflamed tissues [20,24,25]. Indeed, the deficiency of *Cxcr3* or one of its ligands has been shown to limit the infiltrations of Th1 and CTL cells in a multitude of Th1-driven disease models (Table 1).

CXCR3 permits entry into inflammatory sites

CXCR3 expression on effector T cells grants them entry into sites otherwise restricted. This seems particularly true during infections in the brain. CXCR3 is required on CD8+ cells for infiltration into the brain during *P. berghei* ANKA infection for the development of cerebral malaria symptoms [26,27]. *Cxcr3*−/− mice are protected from cerebral malaria due to reduced CD8+ CTL sequestration in the brain. This protection is mediated by both CXCL9 and CXCL10, as mice deficient in either one of these ligands showed partial disease protection [26]. In other models of brain inflammation, CXCL10 appeared to have a primary role in the recruitment of effector T cells into the brain. In West Nile virus infection, CXCL10 is expressed by neurons, and directs the migration of CD8+ T cells into the brain

[28]. T cell infiltration of mucosal tissues is also highly dependent on CXCR3 expression. This is true during Herpes Simplex Virus-2 (HSV-2) infection of the vaginal mucosa [29–31] and during colitis. In the IL10 null Inflammatory Bowel Disease (IBD) model, CXCL10 and CXCR3 are highly expressed at sites of colitis due to local production of the ligands leading to the recruitment of CXCR3 positive T cells. In this model, CXCL10 neutralization could attenuate the severity of colitis [32]. In the adoptive transfer model of colitis CD4+CD25- T cells require expression of CXCR3 to cause disease in *Rag1*−/−mice. Interestingly, the transfer of Tregs for disease protection in this model does not require CXCR3, indicating that these cells access the site of suppression via a different mechanism [33]. Accumulation of effector T cells at sites of autoimmune inflammation is strongly correlated with CXCR3 expression. In addition to autoimmune rheumatoid arthritis synovium where CXCR3 expressing cells were first characterized in a human disease [7] and subsequently shown to regulate T cell recruitment in murine models [34,35], deficiency in CXCR3 also reduces autoimmune insulitis diabetes and infiltration of T cells into the kidney in systemic lupus erythematosus (SLE) [36–38].

CXCR3 chemokine ligands

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 whole tissues. While this method confirms timing and tissue expression, it offers little information about the types of cells that elicit effector T cell recruitment, and the molecules that induce this expression. However, in the cerebral malaria model mentioned above, immunohistochemistry of *P. berghei* infected mice revealed that CXCL9 was predominantly expressed by endothelial cells and CXCL10 was predominantly expressed by neurons perhaps explaining the non overlapping roles of these two CXCR3 ligands in the pathogenesis of cerebral malaria [26]. Likewise, in a murine model of granulomatous liver disease induced by *Propionibacterium acnes*, hepatic LN DCs produced CXCL10, while hepatic granuloma cells in the liver parenchyma produced CXCL9, perhaps explaining why neutralization of CXCL9 and CXCL10 gave different results [39].

As their original names suggest, IFNγ (TypęIIinterferon) mediates the induction of all three CXCR3 ligands [40–42]. However, the CXCR3 ligands are also differentially regulated by other stimuli, such as the TypęIinterferonsIFNα/β̦and NF-κB. *CXCL10* induction is more sensitive to innate stimuli, such as the Type I interferons and NF-κB induction, leading to the preferential induction of CXCL10 by Toll like receptors that activate IRF3 and the release of Type I interferon, while *CXCL9* is more dependent and more strongly induced by IFNγ. *CXCL10* is also preferentially induced by hypoxia-reperfusion injury via NF-κB activation [43], and has been shown to play an early role in the hypoxia-induced inflammation associated with solid organ transplantation, such as the heart and lung [43,44].

Possible role for CXCR3 on other T helper subsets

While the expression of CXCR3 is tightly linked to Th1 CD4+ and CD8+ effector cells, it has also been observed on populations of IL4-secreting Th2 cells [5,14,15] and IL17-secreting Th17 cells [38,45] in inflamed tissues. *Cxcr3*- and *Cxcl9*-deficiency protect MRL/lpr mice from autoimmune lupus-like inflammation [37]. Recently it was shown that deficiency of *Cxcr3* in this model is associated with a block in the infiltration of not only Th1 cells, but also IL17 secreting cells into the kidney [38]. It is likely that the high levels of IFNγ or IFNα/β present in the kidney result in production of CXCL9, CXCL10 and CXCL11. While this study did not investigate the presence of double positive IFNγ and IL17 expressing cells, one third of IL17 secreting cells also expressed CXCR3, suggesting these cells may express transcription factors for both Th1 and Th17 effector cells. Further

studies of this kind will evaluate a role for CXCR3 in the recruitment of CD4+ helper subsets other than Th1, or effector populations that do not fit into the paradigm of CD4+ cell polarization, such as cells dually expressing IFNγ and IL17 [45].

CXCR3-dependent amplification of immune responses

Multiple studies have demonstrated that recruitment of effector T cells and inflammation drives further recruitment and 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 [26,38]. However, in addition to promoting the effector cell inflammation via CXCR3-independent means, an inflammatory CXCR3-chemokine dependent amplification loop also exits (Figure 1). For example, during malarial infection, the entry of CXCR3+CD8+ cells into the brain leads to increases in the levels of CXCL9 and CXCL10 [26]. Although not assessed in this work, presumably this is due to the local secretion of IFNγ by T cells in inflamed tissues. The increased secretion of CXCR3 ligands promotes additional recruitment of CXCR3+ effector cells. In turn, these effectors secrete IFNγ locally, which further amplifies infiltration of effector cells. This inflammatory loop allows CXCR3 and its ligands to coordinate T cell responses in the inflamed periphery, and suggests why expression of CXCR3 is tightly linked to autoimmunity. This CXCR3-dependant coordination of inflammation has also been elegantly demonstrated in the vaginal mucosa during HSV-2 infection [29]. In this model, CXCR3 permits the entry of CTL CD8+ cells into the infected tissues. This recruitment is dependent on the invasion of mucosa by CD4+ Th1 helper cells, which enter prior to CTLs. Critically, IFNγ specifically from the infiltrating CD4+ T cells is required in this process to increase CXCL9 and CXCL10 production by cells in the vaginal epithelium (Figure 1). IFNγ from CD4+ cells is likely due to the presentation of antigen by DCs in the infected tissue [46]. Presumably, IFNγ activates the transcription factor *Stat* in tissue resident cells to induce the production of CXCL9, CXCL10 and CXCL11 in inflammatory tissues [47]. The upregulation of CXCR3 ligands then mediates the mobilization of effector CTLs to the peripheral site of infection, as *Cxcr3*−/− CTLs failed to migrate into virally infected vaginal tissues [29]. This work is supported by previous results showing *Cxcl9*−/− and *Cxcl10*−/− are more susceptible to HSV-2 due to delayed recruitment of CTL CD8+ cells into the vaginal tissue [31]. NK cells recruitment into the mucosa was also reduced in *Cxcr3* ligand−/− mice. How these cells contribute to the amplification of inflammation in this setting was not tested in this model. However, in a murine model of CMV infection, NK cells were an important source of early IFNγ, which induces the expression of CXCR3 ligands in the liver resulting on the recruitment of CXCR3+ T cells [48]. IFNγ from NK cells has also been shown drive CD4+ Th1 cell differentiation in the lymph node, which may also apply Th1 responses in inflamed tissues [49]. Interestingly, effector CD4+ T cell entry into the vaginal tissue also required IFNγ secretion and responsiveness to IFNγ by the CD4+ themselves. The role NK cells play in this mechanism, or dependence on CXCR3 for the entry of Th1 CD4+ cells into the inflamed vaginal tissue is likely, but was not assessed [29]. It remains to be investigated if CXCR3 is required for CTL entry into all virus-infected tissues (e.g., brain). The CXCR3-inflammatory loop potentially may not only increase recruitment of CTLs into peripheral tissues, but also may enhance the generation of CTLs [50] and promote increased effector responses through STAT1 signaling [51].

Although 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 if the T cells involved in

this amplification loop directly contact cells that upregulate CXCL9 and CXCL10, or if soluble chemokine gradients dispersed throughout the inflamed tissue recruit more effector cells.

Breaking the Inflammatory Loop – a role for CXCR3+ T regulatory cells

Although strong Th1 and CTL responses are beneficial during infection, these responses must be counterbalanced to prevent unwanted tissue destruction and immunopathology. Indeed, as detailed above, the identification of CXCR3+ Th1 cells was originally characterized in the affected tissues of patients with autoimmune arthritis and many autoimmune diseases are thought to result from deregulated Th1 responses. The induction of (Tregs) expressing the transcription factor FOXP3 is important for maintaining immune tolerance and preventing autoimmunity [52,53]. The presence Tregs during diabetes induction inhibited expression of CXCR3 on effector CD4+ T cells, reducing pancreatic islet infiltration [54].

Tregs exert their suppressive activity on CD4+ Th1 or CTLs at the site of peripheral antigen presentation [46,55]. Transfecting CD4+CD25+Foxp3+ cells with *Cxcr3* increases their accumulation in target organs, indicating these cells can be recruited to sites of inflammation in a manner similar to the effector cells they suppress [56]. Recently, a subset of Th1-specific Tregs has been identified that express CXCR3 [57]. Presumably, although not yet formally demonstrated, it is likely the same cytokine (IFNγ)-chemokine (Cxcl9/10) inflammatory loop that amplifies effector responses, may also “invite” Tregs into peripheral tissues as Th1-specific Tregs are activated in a similar cytokine milieu as CD4 helper T cells. Although IL12 signaling does not appear necessary, IFNγ signaling through *Ifnγr1* and *Stat1* is required for the induction of CXCR3+ Tregs [57]. In this study, the source of IFNγ was not directly examined. It will be interesting to learn if Tregs are induced in these conditions, when effector cells are deficient in IFNγ, or if accessory cells, such as NK cells, are responsible for Treg induction. IFNγ derived from NKT cells have been shown to promote the migration of CXCR3+ Tregs into the inflamed liver [58]. IFNγ signaling induces the Th1 transcription factor *T-bet*, which in turn promotes the expression of CXCR3 expression, which may allow Th1-specific Tregs to gain to sites of inflammation, such as the lung, draining lymph node and spleen following aerosol infection with *Mycobacterium tuberculosis* [57].

T-bet-expressing Foxp3+ Tregs specifically suppress Th1 inflammation, and not Th2- or Th17-driven inflammation, which have separately been shown to be suppressed by IRF4-expressing and Stat3-expressing Tregs, respectively [59,60]. These observations may explain the subtle phenotypes seen in *Cxcr3* knockout mice in models that rely on multiple effector populations, such as Experimental Autoimmune Encephalomyelitis (EAE), the mouse model for Multiple Sclerosis, which is dependent on both Th1 and Th17 cells. In this model, *Cxcr3*−/− mice display no difference in incidence and severity of disease, but show reduced disease contraction accompanied by a reduction in the recruitment of Tregs into the spinal cord [61]. In addition, *Cxcr3*−/− Tregs that did enter the spinal cord, failed to cluster in CD3+Foxp3- T cell areas, as was seen for wildtype Tregs. These results indicate that CXCR3 expression is required for Treg entry into peripheral tissues, and also their function and interaction with effector T cells in these sites.

However, not all Th1 inflammation appears to induce CXCR3-expressing Tregs. Acute MHC-mismatch allograft rejection is characterized by infiltrating CXCR3+ effector T cells. Combined blocking of CXCR3 and CCR5 in this model, induces the recruitment of Treg cells, indicating unique chemokine requirements for these cells [62]. Similarly, in the *ApoE*

−/− mouse model of atherogenesis, deficiency in *Cxcl10* reduced the number of CD4+ T effector cells, but enhanced the accumulation of Tregs [63].

It is clear that CXCR3+ Tregs are induced and recruited by pro-inflammatory cytokines in order to circumvent the consequences of chronic inflammation. However, the presence of Tregs in sites of persistent inflammation argues that these suppressor cells may not be fully functional [64–66]. Interestingly, Tregs found in synovial fluid from patients with rheumatoid arthritis (RA) showed increased suppressive activity [65]. It is likely that these Tregs are either out numbered or their suppressive ability diminished by other cells, such that these Tregs are unable to counteract the over-exuberant effector T cells that drive persistent inflammation [65,66].

While much work has been done on CD4+ Tregs, much less is known about CD8+ regulatory T cells. Recently, CXCR3 was shown to be a marker of CD8+ IL10 producing cells with suppressive activity in both mice and humans [67]. Further work is required to determine how these cells respond during *in vivo* immune responses, as their cell markers overlap with the CD8+ central memory population, and thus it is not clear if these cells will remain suppressive or if they will enter the effector pool.

CXCR3 in the induction and recall of immune responses

It is well established that CXCR3 expression by effector and regulatory T cells allows these cells entry into inflamed peripheral tissues. By contrast, the requirements for CXCR3 and its ligands during primary and secondary responses in the LN remain incompletely studied. Indeed, the use of *in vitro* activated effector cell transfer models in order to specifically investigate events in peripheral tissue has avoided scrutiny of the potential importance of CXCR3 during CD4+ and CD8+ T cell activation. The immediate up regulation of CXCR3 on CD4+ and CD8+ following DC activation, makes this an interesting proposal, as activated T cells remain sequestered in draining LN for up to 4 days prior to being recruited to peripheral tissues. Interestingly, T cell upregulation of CXCR3 coincides with the expression of *Cxcl10* and *Cxcl9* in the lymphoid organs at times relevant to T cell polarization and restimulation [31,39]. Although not directly focused on, multiple studies have hinted an important role to be likely.

Potential role for CXCR3 during T cell priming

The original paper describing the *Cxcl10*−/− mouse showed decreased T cell activation, proliferation and IFNγ secretion following Th1-skewed *in vivo* immunization and mouse hepatitis virus (MHV) infection [68]. However, these outcomes were not correlated with differences in T cell-DC interactions in the LN. *In vitro* CXCL10 increases tethering of T cells to antigen presenting cells and synergy has been shown between CXCR3 and CD3ε signaling, due to spatial association of these receptors and subsequent tyrosine phosphorylation of the same signaling molecules [69–71]. DEC-205+ DCs appear to be a primary source of CXCL10 in the draining LN. These DCs rapidly up regulate *Cxcl10* following *Propionibacterium acnes* infection [39]. CXCL10-expressing DCs actively interact with T cell clusters, indicating a role for CXCL10 in the DC-CD4+ interactions in draining LNs. This hypothesis is further supported, as blocking CXCL10 resulted in a decrease in clusters between proliferating CD4+ T cells and DEC-205+ DCs [39]. Although the effect of this blocking antibody treatment was assessed in the periphery, the impact of treatment on LN T cell activation and cytokine secretion, and Th1 polarization was not addressed. In contrast, it was recently demonstrated in a model of allograft rejection that CXCL9 produced by allograft DCs promotes priming towards CTL CD8+ and Th1 CD4+ IFNγ-producing T cells [72]. Surprisingly, CXCL10 appeared to have the opposite effect on T cell priming, where a deficiency of *Cxcl10* in the allograft resulted in increased IFNγ-

producing CD8+ T cells [72]. *Cxcr3*−/− T cells exhibited impaired CD8+ cytotoxicity, and reduced expression of T-bet, IFNγ, perforin and granzyme B following HSV-2 infection [30]. While these phenotypes were seen in the LN, this study correlated these findings with reduced plasmacytoid DC recruitment and activation, and did not investigate the relevance of CXCR3 loss exclusively on T cells. Future studies are needed to determine a role for CXCR3 and it's ligands during initial T cell activation.

Potential role for CXCR3 during induction of T cell memory

In addition to a potential role during primary responses, CXCR3 expression by T cells in LNs may be important for the induction of T cell memory. CXCR3+ cells make up between 60–90% of CD8+ memory T cells [73,74] and 40% of CD4+ memory T cells [75,76]. CXCR3 expression has been proposed as a reliable marker for T memory responses, as viral recall responses for both CD8+ and CD4+ T cells are largely restricted to CXCR3+ cells [74,76]. The expression of CXCR3 indicates the ability for recall responses, although the requirement for CXCR3 interactions in this process has not formally been tested using *Cxcr3*−/− T cells. The CXCR3 ligands expressed at times of antigen recall, either expressed by LN stroma or antigen presenting cells have also yet to be investigated.

Once effector T cells have left the LN for peripheral tissues, T effector memory cells (T_{EM}) can return to reactive LNs to either halt or promote future immune responses. CXCL9 is displayed on LN high endothelial venules (HEV) rapidly and transiently following induction of a reactive LN. This window allows CD8+ T effector memory (T_{EM}) cells to gain access to the LN to interact with antigen presenting DCs [73]. CXCR3+ CD8+ memory cells engage and kill DCs as an efficient mechanism to regulate and reduce future T cell responses. In contrast, CD4+ T_{EM} cells gain access to reactive LNs via CXCR3-independent means to interact with DCs and increase future T cell priming through CD40 upregulation [49]. Once T_{EM} cells enter the LN, it is unknown if CD8+ or CD4+ interactions with DCs are also dependent on CXCR3 and its ligands, although it has been shown that CD40L stimulated DCs increase expression of CXCL10 [77]. Future studies into the role of CXCR3-dependent interactions in the development of primary, secondary and contraction of adaptive immune responses will therefore yield interesting results with applications for vaccinology.

Concluding comments and future directions

In the past few years much has been learned of the involvement of the CXCR3 chemokine system during inflammation. These studies have highlighted the role for CXCR3-dependent interactions in the coordination of inflammatory events in the periphery, both to increase recruitment of CD4+ and CD8+ effector T lymphocytes to drive inflammation, but also perhaps for the induction and recruitment of Th1-specific T regulatory cells to dampen over exuberant responses. How CXCR3 balances the choice between these critical responses remains to be determined. In addition, the factors influencing the described CXCR3-dependent amplification loop between IFNγ-expressing T cells and the cells expressing the IFNγ inducible ligands needs to be further characterized. Finally, although not studied in great detail yet, it is now becoming increasingly clear that the CXCR3 chemokine system plays important roles in the migratory behavior and cellular interactions of T cells in the lymphoid compartment and within peripheral tissue that likely have consequences for the generation of effector, regulatory and memory T cells. Future studies aimed at studying the role of the CXCR3 and its ligands in these processes in detail will undoubtedly shed new light on this important chemokine system in the control of T cell function.

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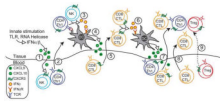

Figure 1. Model for Interferon-CXCR3 chemokine ligand-dependent inflammatory amplification in the periphery

This model describes the sequential events from left (1) to right (7) involving Type I and Type II interferon and the CXCR3 ligands, CXCL9 and CXCL10, in the initiation, amplification and resolution of Th1-type inflammation in the periphery. Open arrowheads indicate cytokine/chemokine secretion and closed arrowheads indicate cellular movements.

1. Initial innate challenge, such as bacterial or viral infection, activates TLRs and RNA helicases leading to the release of IFNα/β and subsequent secretion of chemokines, predominantly CXCL10.
2. CXCL10 recruits CD4+ Th1 cells and possibly NK cells into the target tissue.
3. DCs in the tissue present antigen to CD4+ Th1 cells, which in turn secrete IFNγ.
4. Tissue resident DCs and other cells take up IFNγ leading to secretion of CXCL9 and CXCL10.
5. CXCL9 and CXCL10 recruit CD8+ CTLs into the tissue
6. Migrated CD8+ CTLs secrete IFNγ, further stimulating tissue resident cells to produce more CXCL9 and CXCL10.
7. Increased chemokine release amplifies inflammation, leading to further recruitment of CXCR3-expressing Th1 T cells and CTLs.
8. Increased inflammation can also attract in CTLs in a CXCR3-independent manner.
9. CXCR3-expressing CD4+ Treg cells may also enter the tissue, to counterbalance the CTL and Th1 cell response and lead to resolution of Th1 inflammation.

Table 1

CXCR3 and its ligands in human disease and murine disease models

Human Disease	[ref]	Mouse Models	CXCR3	CXCL9	CXCL10	[ref]
Autoimmmune						
Psoriasis	[78–80]					
Sarcoid	[81–83]					
Rheumatoid Arthritis	[7,10,84–86]	Adjuvant-induced arthritis	√		√	[34,35]
Asthma	[87–89]	Allergic Pulmonary Inflammation	√	√	√	[90,91]
Atherosclerosis	[92]	ApoE−/−, LDLR−/−	√		√	[63,93]
Multiple Sclerosis	[94–96]	EAE	√		√	[61,97–101]
IBD	[102]	IL-10$^{-/-}$, RB^{hi} transfer	√		√	[103]
Idiopathic Pulmonary Fibrosis	[104]	Bleomycin-induced injury	√		√	[105–107]
Type I Diabetes Mellitus	[108,109]	Insulitis	√	√	√	[36,110]
SLE	[111–113]	MRL/lpr	√	√	√	[37]
Cigarette smoke injury/COPD	[114,115]	Cigarette smoke injury	√			[116,117]
		Myocarditis	√		√	[25,118]
Transplantation						
Heart Transplant	[119,120]	Orthotopic Heart Transplant	√	√	√	[44,121–125]
Lung Transplant	[126]	Orthotopic Tracheal Transplant	√	√	√	[43,127]
GVH	[128]	GVH	√		√	[129]
		Small Bowel			√	[130]
Infections						
Leprosy	[131]					
Tuberculosis	[132,133]					
		Influenza	√			[134,135]
		Toxoplasma gondii	√		√	[18,136]
Malaria (P. falciparium)	[137]	Malaria (P. berghei)	√	√	√	[26,27]
Dengue	[138]	Dengue	√		√	[139]
Hepatitis B and C	[140–142]	Mouse Hepatitis Virus			√	[68,143]
Herpes Simplex	[144]	Herpes Simplex	√	√	√	[29–31,145]
HIV-1	[146–148]					
Leishmania	[149]	Leishmania	√		√	[150,151]
		Chlamydia Trachomatis	√			[152,153]
Lyme	[154,155]	Lyme	√			[156]
		Klebsiealla			√	[157]
West Nile Virus						[28]
Cancer						
Renal	[158]	Renal	√	√		[86]
Colon	[159]	Colon			√	[160]
Melanoma	[161]	Melanoma		√	√	[161]

Human Disease	[ref]	Mouse Models	CXCR3	CXCL9	CXCL10	[ref]
Lymphoma	[162–164]	Lymphoma			√	[165]
Breast	[166]	Breast	√		√	[166,167]