PERSPECTIVE

CXCR6-based immunotherapy in autoimmune, cancer and inflammatory infliction

Tingting Li,*, Jie Pan, Hongqi Chen, Yongliang Fang, Yang Sun

*Department of Gastroenterology, the Second Medical Center, National Clinical Research Center for Geriatric Diseases, State Key Laboratory of Kidney Diseases, Chinese PLA General Hospital, Beijing 100853, China
^State Key Laboratory of Pharmaceutical Biotechnology, Department of Biotechnology and Pharmaceutical Sciences, School of Life Sciences, Nanjing University, Nanjing 210023, China
†Department of General Surgery, Shanghai Jiao Tong University Affiliated Sixth People’s Hospital, Shanghai 200233, China
Department of Urology, Boston Children’s Hospital, Departments of Microbiology and Surgery, Harvard Medical School, Boston, MA 02115, USA
Department of Clinical Laboratory, Jiangsu Key Laboratory of New Drug Research and Clinical Pharmacy, Xuzhou Medical University, Xuzhou 221004, China

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Abstract  T cells, including both CD4⁺ and CD8⁺ T cells, play a pivotal role in mediating various inflammation and immune disorders. A long-standing challenge in T cell-based immunotherapy is to precisely inactivate or delete the pathogenic T cells in inflammation and autoimmune diseases, or to selectively expand the immunocompetent T cell in tumor or other immune compromised situations, without inducing global immunosuppression or zealous immune activation respectively. To achieve this, a specific marker is needed to differentiate the pathogenic or immunocompetent T cell among the rests. Indeed, recent progress of immunology strongly suggests that CXC chemokine receptor 6 (CXCR6, CD186) is such a kind of marker. Here, we review the emerging role of CXCR6 as a novel target for immunotherapy and discuss the underlying mechanism. We propose that CXCR6-based immunotherapy will play a significant role in autoimmune, nonalcoholic steatohepatitis (NASH), tumor, coronavirus disease 2019 (COVID-19) and even ageing-related inflammatory infliction.

*Corresponding authors.
E-mail addresses: yangsun@nju.edu.cn (Yang Sun), lilylismiling@126.com (Tingting Li).
†These authors made equal contributions to this work.
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1. Introduction

CXCR6 (CD186), previously known as “Bonzo” and “STRL33”, is a chemokine receptor and was cloned decades ago with its solo ligand known as CXC chemokine ligand 16 (CXCL16). CXCR6 gene is localized on chromosome 3p21.31 with 4 splice variants. It is a G protein-coupled receptor with 7 transmembrane domains that belongs to the CXC chemokine receptor family which consists of 6 members including CXC chemokine receptor 1 (CXCR1), CXC chemokine receptor 2 (CXCR2), CXC chemokine receptor 3 (CXCR3), CXC chemokine receptor 4 (CXCR4), CXC chemokine receptor 5 (CXCR5) and CXC chemokine receptor 6 (CXCR7). Some studies suggested that CXCR6 expression was a marker of T cell differentiation and may also be a biomarker of some diseases. This protein is expressed on some subpopulations of T cells, natural killer T (NK T) cells. CXCL16 gene is located on chromosome 17p13 with two transcripts which are peculiarly expressed in different organs. CXCL16 is a membrane protein with a CXC chemokine domain, a highly glycosylated mucin-like stalk, a transmembrane domain and a cytoplasmic tail with a potential tyrosine phosphorylation site that has the predicted Src homology domain 2 (SH2) binding domain. Transmembrane CXCL16 (mCXCL16) will be cleaved by disintegrin and metalloproteinase 10 (ADAM10) to release the 35 kDa chemokine domain and become a soluble form of CXCL16 (sCXCL16) when stimulated with PMA or proinflammatory cytokines. The sCXCL16 is a chemokine that is responsible for the migration and recruitment of cells expressing the CXCR6 receptor while mCXCL16 is a transmembrane protein which may have the adhesion protein property that binds to CXCR6 expressing cells and promotes cell-cell interaction (Fig. 1). CXCL16 is mainly expressed on dendritic cell (DC), monocytes, and tissue cells such as hepatocytes, keratinocytes, fibroblasts and endothelial cells. CXCR6–CXCL16 chemotactic axis regulates immune cell homing, activating, expanding and cytotoxicity. Binding of CXCL16 to CXCR6 activates the calcium mobilization, Akt/mTOR and ERK/MAPK pathways and its downstream effectors such as NF-κB which may be the reason of increased cytokine secretion such as tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ) (Fig. 1).

CXCR6 has been reported to be highly expressed by T cells existed in the synovial fluid of rheumatoid arthritis patients or by T cells infiltrated in the colon of Crohn’s disease patient. In sharp contrast, CXCR6+ T cells are absent in the peripheral blood, the most accessible biomaterial for immunological research, of both healthy controls and autoimmune patients. Compared with many other chemokine receptors, CXCR6 has been deemed primarily as a marker of tissue resident memory T cell with its function largely unknown. Recently, CXCR6 is receiving increased attention. Initially, CXCR6 was reported to be an exquisite marker preferentially expressed by encephalitogenic CD4+ T cells or granulocyte-macrophage colony stimulating factor (GM-CSF) producing CD4+ T cells in experimental autoimmune encephalomyelitis (EAE) model, mouse model mimicking human multiple sclerosis, and depleting CXCR6-bearing T cells were able to treat mouse EAE disease. Then, liver-infiltrated CXCR6+CD8+ T cells were reported to be the driven force for nonalcoholic steatohepatitis (NASH) in both mouse model and human patients. Most recently, we and others reported that CXCR6 expression is essential for CD8+ T cells to exert anti-tumor function. In addition, CXCR6+CD8+ T cells were significantly accumulated in the peripheral blood of normal but aged person; CXCR6+CD8+ T cells were highly enriched in the lung upon severe coronavirus disease 2019 (COVID-19).

Here, we will review our knowledge of CXCR6, its ligand CXCL16, and CXCR6-bearing T cells in the circumstance of inflammation and immune disorders (Fig. 2 and Table 1). We will also discuss the potential role of CXCR6/CXCL16 axis in mediating the immune homeostasis and immunopathology. Finally, we will propose the CXCR6-based immunotherapy with high selectivity as its advantage when compared with other immunosuppressive agents or immune checkpoint inhibitors.

2. CXCR6 identifying pathogenic T cell or immune-competent T cell in various disease settings

2.1. CXCR6+ T cells in autoimmune

CXCR6+CD4+ T cells and CXCR6+CD8+ T cells, with higher cytokine-producing capability, higher cytotoxicity and proliferation potential, were highly enriched in the inflammatory tissue, such as synovial fluid from patients with inflammatory arthritis, skin from psoriasis patient, and colon from Crohn’s disease. All of these suggest that CXCR6 might play a critical role in pathogenic T cell migration into inflammatory tissue in autoimmune disease. In sharp contrast, CXCR6 deficient mice (Cxcr6-KO) only present marginal or even negligible amelioration when they were induced to develop autoimmune models, such as EAE and inflammatory bowel disease (IBD). In collagen-induced arthritis model, Cxcr6-KO mice showed reduced severity and incidence. CXCR6- and CXCR6+CD4+ T cells subsets in the inflamed colon both contained effector and effector-memory cells. Moreover, the CXCR6+ subset was indeed terminally differentiated effector cells and less proliferative compared to the CXCR6− counterpart upon in vitro restimulation. Besides, the CXCR6+ subset retained the ability to proliferate and differentiate into pathogenic CXCR6+ effector cells in colitis mouse model. Therefore, it is not a surprise to find CXCR6 plays a dispensable role in EAE and other autoimmune disease. However, CXCR6 was recently found to be a marker specifically expressed by the most pathogenic CD4 cells, which proliferate rapidly and produce several pathogenic cytokines. Thus, using anti-CXCR6 antibody to specifically deplete these pathogenic CD4+ T cells showed beneficial effect on treating EAE model.

In addition to directly using Cxcr6-KO mice, antibody against CXCL16, ligand of CXCR6, has also been applied to indirectly investigate the role of CXCR6 in autoimmune disease models. CXCL16 is the second transmembrane-type chemokine with a chemokine domain fused to a mucin like stalk, a structure very similar to fractalkine. Although Cxcr6-KO and wild type mice...
developed comparable EAE symptom, anti-CXCL16 mAb treated mice were almost completely resistant to induction of acute EAE. Interestingly, CXCL16 was shown to possess two different biological activities, originally as scavenger receptor that bound phosphatidylserine and oxidized lipoprotein and later as chemokine/ligand binding to CXCR6. At normal situation, CXCL16 is constitutively expressed by myeloid cells as a membrane protein. Upon inflammation, the chemokine part of CXCL16 will be released from cell membrane and then function as a scavenger receptor. Since anti-CXCL16 mAb is only capable to prevent EAE when treated at Days 0 and 2 after EAE induction, and no longer functional when treated at Day 4 after EAE induction, the inconsistent effects between CXCR6 deficiency and anti-CXCL16 antibody on EAE model might be due to that anti-CXCL16 antibody function through depleting or compromising myeloid cells during antigen immunization of EAE model induction and functions as a scavenger receptor referred to as the scavenger receptor that binds phosphatidylserine and oxidized lipoprotein expressed on the surface of apoptotic cells and injured tissues to remove dead cells and relieve inflammation, which is unrelated with CXCL16–CXCR6 interaction. In addition, CXCL16 can promote the activation and degranulation of platelets and mediate angiogenesis in the serum transferring model of arthritis, which is critical for T cell infiltration. Therefore, CXCR6 and CXCL16 may be different therapeutic targets with various mechanisms in the reduction of inflammation.

Recently, the role of CXCR6 was revisited and confirmed as the exquisite marker identifying the pathogenic CD4+ T cells in autoimmune disease models. The series of study was initiated by revealing serine protease inhibitor B1 (SerpinB1, Sb1), an endogenous protease inhibitor, to be a signature gene of IL-17-producing γδ T cells and Th17 cells. Subsequent studies showed that Sb1-KO mice were resistant to EAE with a paucity of CXCR6+ CD4+ T cells, which (i) secrete inflammatory cytokine IFN-γ and GM-CSF, (ii) contain cytotoxic granules, and (iii) demonstrate an extremely rapid proliferation. Depletion of this population by anti-CXCR6 mAb in wild type mice dramatically reverted the EAE, confirming that CXCR6 marked pathogenic CD4+ T cells in EAE. By using OT-II cell transferring system, CXCR6 was further discovered to be able to identify the pathogenic CD4+ T cell in all CD4+ T cell-driven immune response sharing delayed-type-hyposensitivity as prototype. Differed from mouse EAE model, the major T cells existed in the brain lesions of human multiple sclerosis (MS) patients are CXCR6+ CD8+ T cells, rather than CD4+ T cells. Correspondingly, CXCL16 is highly induced in the rim of active lesions in the brain of MS patient. Thus, although CXCR6-deficiency does not affect mouse MS model, it could not be excluded that, in human
MS patients, CXCR6/CXCL16 axis still plays a critical role to recruit and/or maintain the survival of pathogenic CXCR6\(^+\)CD8\(^+\) T cells in the lesions in MS patients.

2.2. CXCR6\(^+\) T cells in tumor

Pathogenic T cells, a subset of highly differentiated hyper-activated T cells, are the driving force for inflammation and tissue damage in autoimmune diseases. In the contrasting scenario of tumor pathology, T cells infiltrate into the tumor to eliminate the tumor cells. CXCR6\(^+\) T cells are highly pathogenic ones that mediate tissue damage in autoimmune setting, which leads to the hypothesis that this population might play a role in anti-tumor immunity. Indeed, most recently, we and others 16,17 independently reported that CXCR6 is preferentially expressed on CD8\(^+\) T cells infiltrated in the tumor. Both studies confirmed that CXCR6 expression is essential for CD8\(^+\) T cells to properly mount anti-tumor response, differing from the dispensable role of CXCR6 in autoimmune animal models. This inconsistency might be the consequence of different format of CXCL16 existed in different microenvironment. In autoimmune setting, shedding of membrane CXCL16 releases the chemokine part of CXCL16, which however is the weakest chemokine compared to other chemokine/chemokine receptor\(^2\) because of the DRF motif in the structure of CXCR6. Koenen et al. 35 demonstrated that CXCR6 carried a DRF motif instead of the typical DRY motif as a key element in receptor activation and G protein coupling. Mutation of DRF into DRY in CXCR6 did not influence the function of ligand binding, receptor internalization, receptor recycling, and protein kinase B signaling but significantly increased the CXCL16-induced calcium signaling and migration, which indicated increased chemotaxis. Furthermore, when mutation of typical DRY motif into DRF in CX3CR1, the migratory response towards its ligand CX3CL1 was diminished35. Therefore, the DRF motif in CXCR6 generally impairs its chemotaxis in chemokine receptors. In contrast, the relatively immune-silent microenvironment in tumor setting keeps CXCL16 molecule intact as a membrane protein on tumor infiltrating DC, which in turn contributes to CXCR6\(^+\) T cell positioning and survival, rather than recruitment 35.

Indeed, the role of CXCL16 in tumor is still controversial. One study suggested that CXCL16 expressed by tumor infiltrating dendritic cells is required for maintaining the survival of CXCR6\(^+\)CD8\(^+\) T cells in tumor 16; while our study claimed that, although CXCR6 was induced to be expressed on CD8\(^+\) T cells...
within the tumor, CXCL16 expression in tumor is stable and not required for CD8⁺ T cell functioning in tumor. Given the complex about CXCL16 expression that myeloid-derived DCs express both membrane and soluble CXCL16, while the plasmacytoid DC does not express membrane CXCL16 and only produce soluble CXCL16, no definitive conclusion could be drawn about the role of CXCL16 in tumor at this stage.

Since CXCR6 expressed on T cells was crucial, the mechanisms of CXCR6 in anti-tumor immunity were discovered in several studies. In a recent article, Di Pilato et al. identified that CXCR6 expressed on T cells were responsible for the conversion of stem-like into effector-like cytotoxic T lymphocytes (CTLs) and positioned effector-like CTLs in a niche of the tumor stroma that was densely occupied by chemokine C–C receptor 7 (CCR7) DCs expressing CXCL16. This suggested that CXCR6–CXCL16 promoted persistent interactions between CTLs and DCs within the perivascular tumor stroma. The activated DC cells secreted IL-15 that was an important cytokine for the survival and expansion of effector-like CTLs in the tumor microenvironment. Additionally, CXCR6 expressed CD4⁺ T cells and NK T cells in the context of senescence surveillance during hepatocellular carcinoma development promoted the activation of immune response with increasing cytotoxic cytokines such as Granzyme B which mediated the recognition and removal of senescent hepatocytes. Moreover, the CXCR6–CXCL16 axis induced the migration of CD8⁺ resident memory T cells in lung mucosa after vaccination. The increased CXCR6⁺ CD8⁺ T cells were antigen-specific and could be rapidly activated after vaccination, resulting in the control of tumor growth. Another study also found the similar chemotaxis of CXCR6–CXCL16 axis in attracting more activated and cytotoxic effector CD8⁺ T into tumor microenvironment. Overall, although emerging studies suggest that CXCR6 is required for T cells to exert anti-tumor immunity, additional efforts are still needed to elucidate the mechanism for CXCR6 to boost anti-tumor immunity in some cancers.

### 2.3. Auto-aggressive activation of CXCR6⁺ T cells in tissue inflammation

Nonalcoholic steatohepatitis (NASH), manifestation of systemic metabolic disease, is a liver damage caused by the buildup of fat in the liver. Overall, inflammation has been clearly identified as the driving force for liver injury and fibrosis during NASH. A previous publication showed that CXCR6-dependent hepatic NK T cell accumulation promotes inflammation and liver fibrosis in mouse NASH model. Strikingly, most recent studies showed that CXCR6⁺ CD8⁺ T cells were abundant in the liver of NASH mice and in patients with NASH and pivotally mediated the NASH pathology, which was the first time to show that, CD8⁺ T cells, an important adaptive immune compartment, played a pivotal role in NASH pathology, a metabolic liver injury without involvement of MHC-1 molecule to date. Mechanism studies revealed that, CXCR6⁺ CD8⁺ T cells were activated through “auto-aggressive” manner, which no long need T cell receptor (TCR)/major histocompatibility complex 1 (MHC-1) recognition, the first step for CD8⁺ T cell activation.

Possibly, NASH is not the only situation that CXCR6⁺ CD8⁺ T cells will be inflammation-primed with lower threshold for activation without strict requirement for TCR/MHC-1 recognition. Similar to NASH, ageing is another kind of chronic inflammation priming, which leads to prominent accumulation of CXCR6⁺ CD8⁺ T cells in the peripheral blood in aged persons. Upon COVID-19 infection, those CXCR6⁺ CD8⁺ T cells were recruited into the lung, auto-aggressively activated and mediated the lung damage, finally resulting in severe COVID-19 symptom and worse survival in aged person, or people with other chronic inflammatory condition. Since ageing will lead to accumulation of CXCR6⁺ CD8⁺ T cells in peripheral blood with lower activation threshold and will also increase blood–brain barrier

| Disease | Involvement of CXCR6⁺ T cells and effects of CXCR6 deficiency |
|---------|---------------------------------------------------------------|
| Multiple sclerosis | CXCR6 identifies pathogenic CD4⁺ T cells in mouse EAE; CXCR6 deficiency showed no protection; however, anti-CXCR6 mAb reverted EAE; CXCR6 CD8⁺ T cells are abundant in the lesion of brain of MS patients. |
| Crohn’s disease | CXCR6⁺ T cells are abundant in the colon of Crohn’s disease patient; however, CXCR6 deficiency showed no protection in IBD mouse model. |
| Inflammatory arthritis | CXCR6⁺ CD4⁺ T cells highly enriched in the synovial fluid of psoriatic arthritis patients; CXCR6 deficiency showed mild protection in collagen-induced arthritis in mouse. |
| Psoriasis | CXCR6⁺ CD8⁺ T cells significantly increased in both peripheral blood and skin in psoriasis patient; animal model data not available. |
| Type 1 diabetes | CXCR6⁺ T cells were highly enriched in islets of NOD mice, while CXCR6-deficiency did not impair T cells infiltrating into NOD islets. |
| NASH | Ccr6-KO mice were slightly protected from mouse NASH model; CXCR6⁺ CD8⁺ T cells were abundant in the liver of both mouse NASH model and human NASH patients. |
| COVID-19 | CXCR6⁺ CD8⁺ T cells significantly accumulated in aged person (older than 65) and infiltrated into lung in severe COVID-19 infection. |
| Lung infection | CXCR6⁺ mucosa-associated invariant T cells highly enriched in lung of LVS infected mice; however, CXCR6 deficiency did not affect mucosa-associated invariant T cell infiltrating into the lung. |
| Tumor | CXCR6⁺ CD8⁺ T cells were highly enriched in tumor and positively correlates with tumor patient survival; CXCR6 expression was required for CD8⁺ T cell anti-tumor response. |

CXCR6, CXC chemokine receptor 6; EAE, encephalomyelitis; IBD, inflammatory bowel disease; NASH, nonalcoholic steatohepatitis.
permeability, it is possible that CXCR6+CD8+ T cells will be involved in neurodegenerative disease in aged person. However, a study also shown that CXCR6 expression was lower in lung resident memory T cells of COVID-19 severe patients, which indicated the protective effect of CXCR6+ T cells.

2.4. Induction and regulation of CXCR6 expression on T cells

Although CXCR6+ T cells are emerging as key players in various inflammation and immune disorders, the fundamental knowledge about CXCR6 has not been advanced for around two decades. To date, it is known that cytokine IL-2 and IL-15 might be the most powerful ones to induce CXCR6 expression on T cells. Frequently, upon cytokines IL-2 and IL-15 treatment, both chemokine C–C receptor 5 (CCR5) and CXCR6 are co-induced to be highly expressed on T cell surface in vitro. However, CCR5 and CXCR6 will be differentially regulated by different cell signaling. For example, CCR5 expression will be largely diminished by protein kinase C pathway, mimicked by PMA stimulation in vitro, but is resistant to ionomycin treatment. In striking contrast to CCR5, CXCR6 expression would not be down-modulated by PMA or mitogen stimulation of T cells, but instead will be largely decreased by ionomycin stimulation in vitro. Direct anti-CD3 and anti-CD28 stimulation will also induce a rapid internalization of CXCR6 and disappearance of CXCR6 on T cell surface, which is mediated by Ca2+-dependent calcineurin pathway activation and could be blocked by the presence of FK506. In addition to TCR recognition, CXCL16 ligation will induce a rapid CXCR6 internalization within 1 h in vitro. In chronic inflammation in the gut, CXCR6+CD4+ T cells, considered as early effector memory cells with the ability to further differentiation, were exposed to large amounts of antigens derived from the commensal microbiota in the gut. Therefore, it is thus reasonable that the majority of colonic CXCR6+CD4+ T cells in this model indeed differentiated into the late effector memory CXCR6+ cells. All of these suggest that CXCR6 is dynamically existed on T cell surface and the adhesion, migration, activation and survival of CXCR6+ T cell are finely regulated through spatiotemporal-dependent manner together with membrane CXCL16 or its shedding in the inflammatory tissue.

3. Conclusions

CXCR6 is a chemokine receptor initially found to be expressed by a subset of activated T cells, γδ T cells, NK cells and NK T cells, although there are other markers that could be able to distinguish the pathogenic or immunocompetent T cells, such as PD-1, LAG-3, TIM-3, etc. CXCR6 might be only one of them. CXCR6 positive T cells have been involved in many immune disorders, such as inflammatory arthritis, psoriasis, multiple sclerosis and Crohn’s disease (summarized in Table 1). However, genetic deficiency of CXCR6 only marginally ameliorates or exerts no effects on immunopathology in murine models. Thus, altering expression of CXCR6 or inhibiting the chemotaxis function of CXCR6 may not be effective in treating inflammation and immune disorders. Instead, depleting CXCR6+ T cells by monoclonal antibody will be feasible in treating inflammation and immune disorders. Additionally, CXCR6+ T cells are only a minor population within the peripheral immune organ and peripheral blood, anti-CXCR6 mouse antibody is unlikely to induce systemic immune suppression and severe side effects. In tumor scenario, CXCR6 expression is essential for CD8+ T cells to mount proper anti-tumor immune response and respond to immune checkpoint inhibitor treatment. Thus, preserving CXCR6 expression or preferentially expanding CXCR6+CD8+ T cells would be promising in tumor immuno-therapy. In fact, a most recently study demonstrated that arming tumor-specific T cells or anti-EpCAM-CAR T cells with CXCR6 enabled cell migration, adhesion and enhanced recognition of CXCL16 producing pancreatic cancer cells and improved therapeutic efficacy of adoptive CAR T cell therapy. Overall, due to its high selectivity and narrowed expression spectrum, CXCR6 based immuno-therapy is promising in treating various autoimmune disease, NASH, allograft rejection, tumor, severe COVID-19 and even other ageing related inflammatory infliction. The effector functions of CXCR6+ T cells may be beneficial in anti-viral response or anti-tumor immunity. However, the same activated effect CXCR6+ T cells may lead to inappropriate recruitment and tissue injury in inflammatory diseases (Fig. 3). Targeting CXCR6 and CXCL16 therefore maybe interesting therapeutic strategy and provoke a dual approach to immune modulation in different diseases.
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Author contributions

Yang Sun and Tingting Li conceived the project and designed this review. Tingting Li and Jie Pan summarized the literature and composed the manuscript. Hongqi Chen and Yongliang Fang proofread the formats and references. Yang Sun and Tingting Li revised the manuscript. All authors gave approved to submit the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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