HHS Public Access

Author manuscript

Discov Med. Author manuscript; available in PMC 2021 July 08.

Published in final edited form as:

Discov Med. 2017 August ; 24(130): 31–39.

Consider the Chemokines: a Review of the Interplay Between Chemokines and T Cell Subset Function

Marianne Strazza[1], **Adam Mor**[1,2]

[1]Department of Medicine, New York University School of Medicine, New York, NY 10016, USA.

[2]Perlmutter Cancer Center, New York University School of Medicine, New York, NY 10016, USA.

Abstract

Subsets of T cells can be classified by the functions executed or by the anatomic location at which they operate. *In vitro* analysis of T cell subsets and even commercial kits for subset separation often incorporate chemokine receptors into the panel of markers to distinguish among them, but what is the functional significance of these receptors? In this review, we discuss chemokine receptors that are expressed exclusively on different T cell subsets as well as those that are commonly expressed across subsets with the goal of linking receptor expression to cellular localization and intended cellular function. By understanding the chemokine network, we can better predict T cell migration and the immune reactivity of a given tissue environment. This is of particular importance for the chemokine expression patterns of solid tumor microenvironments as it relates to T cell infiltration. A successful immunotherapeutic strategy needs to incorporate not only the activation state of cytotoxic T cells but also the likelihood that these cells come into contact with tumor cells. We highlight what is currently known about chemokine expression by tumors of various origins and how this relates to immune suppression or activation. Chemokine signaling represents a promising area of potential anti-tumor intervention and the current state of agonists or antagonists is discussed. Overall, this review relates chemokine signaling to T cell function and emphasizes the importance of chemokines and chemokine receptors in tumor infiltration by T cells.

Introduction

T cell subsets are a functional classification of the T cell compartment, and the identification of subsets is often made by unique combinations of cell surface proteins. Many of these subset markers are receptors, and these signaling cascades lend defining functions to T cell subsets. Cell surface expression of chemokine receptors within the T cell compartment is often used in the identification of subsets, however, it is important to consider that chemokine receptors are signaling molecules essential to proper T cell trafficking and function rather than inert surface markers.

Corresponding Author: Adam Mor, M.D., Ph.D., (Adam.Mor@nyumc.org).

Disclosure

The authors report no conflicts of interest.

Chemokine receptors orchestrate the trafficking of leukocytes throughout the body under homeostatic and inflammatory conditions. Through the restricted expression of chemokine receptors, T cell subsets can be individually and selectively recruited to various sites throughout the body. Often in the discussion of subset markers, the signaling of these surface proteins is neglected when in fact the signaling cascades go hand in hand with the role of the subset. As the field of cancer immunotherapy expands the consideration of T cells beyond the cytotoxic $CD8^+$ subset, the understanding of the interplay between cell types must also include recruitment or exclusion from the sites of interest. By understanding the relationship between chemokine axes and T cell subsets, anti-tumor and anti-inflammatory therapeutic strategies can be enhanced by incorporating recruitment and infiltration into the equation that currently centers on activation state.

Chemokine Receptor Expression Patterns Across the T Cell Subsets

The chemokine receptor CCR7 is expressed on naïve and central memory T cells. Through interaction with the chemokine ligands CCL19 and CCL21, this receptor plays a role in homing to secondary lymphoid organs including lymph nodes and spleen. The expression level of CCR7 is considered to be a distinguishing factor between central memory ($CCR7^+$) and effector memory ($CCR7^-$) T cells. This expression pattern corresponds with cellular localization in that the central memory population is commonly found in both peripheral circulation and, importantly, the lymph nodes. Conversely, effector memory T cells are surveying for cognate peptides in peripheral circulation and in tissue, a task made possible by the lack of homing signal generated by the CCR7 axis. Functionally, the effector memory population is responsible for carrying out protective memory by migrating into the inflamed peripheral tissues and displaying immediate effector function (Sallusto and Mackay, 2004). The role of central memory T cells within the T cell areas of secondary lymphoid organs is to proliferate and differentiate into effector cells in the presence of specific antigen (Sallusto and Mackay, 2004). It has recently been shown that CCR7 expression on memory $CD8^+$ T cells may contribute to localization within IL-7-dependent niches rather than IL-15-dependent niches, and that exposure to IL-7 establishes the homeostatic turnover rate of these cells (Jung *et al.*, 2016). In fact, $CCR7^-$ $CD8^+$ memory T cells that are exposed to high IL-15 and lower IL-7 concentrations are shorter lived with an enhanced rate of turnover (Jung *et al.*, 2016).

A deeper look at the central memory T cell population allows for the subdivision of $CCR7^+$ $CXCR5^+$ cells that localize to the B cell follicles within secondary lymphoid organs. This population of $CCR7^+$ $CXCR5^+$ $CD4^+$ T cells is known as germinal center residing follicular helper T cells (Tfh), which contribute to the selection and survival of B cells that will differentiate into plasma cells or memory B cells (Kim *et al.*, 2001b). Here it is the combined expression of these two chemokine receptors that localizes these cells first within the secondary lymphoid organs and then within the B cell follicles where the CXCR5 ligand CXCL13 is highly expressed. In the blood, $CCR7^-$ $CXCR5^+$ $CD4^+$ T cells are considered to be circulating Tfh cells that can be further classified into subsets based on cell function and expression of CXCR3 and CCR6. Tfh1 cells are $CXCR5^+$ $CXCR3^+$ $CCR6^-$, Tfh2 cells are $CXCR5^+$ $CXCR3^-$ $CCR6^-$, and Tfh17 cells are $CXCR5^+$ $CXCR3^-$ $CCR6^+$ (Morita *et al.*, 2011). Circulating Tfh cells have been shown to share functions with germinal Tfh cells and

can be considered a circulating memory compartment (Morita *et al.*, 2011). Altered distributions of these circulating Tfh subsets have been shown to contribute to the pathogenesis of numerous autoimmune diseases (Gong *et al.*, 2014).

Memory T cells that are $CCR7^+$ $CXCR5^-$ $CXCR3^+$ are considered to be pre-type 1 helper T cells (Th1) and pre-effector cells while those that are $CCR7^+$ $CXCR5^-$ $CCR4^+$ are pre-type 2 helper T cells (Th2) (Rivino *et al.*, 2004). These cells are positioned within the T cell zones of secondary lymphoid organs, and signaling through CXCR3 and CCR4 contributes to differentiation and polarization. On the other hand, $CCR7^-$ effector memory cells can be divided based on the CXCR3, CCR4, CXCR6, and CCR5 expression. Those T cells that are $CCR7^-$ $CCR5^+$ $CXCR3^+$ function as Th1 cells whereas those that are $CCR7^-$ $CCR4^+$ function as Th2 (Kim *et al.*, 2001a; Rivino *et al.*, 2004).

Within the $CD4^+$ T cell compartment, Th1 cells have been shown to express CCR1, CCR5, and CXCR3. These chemokine axes are important for the recruitment to sites of inflammation. The CXCR3 ligands CXCL9, CXC10, and CXC11 are IFN-γ inducible chemokines that are expressed to promote a Th1 response, so in this way, chemokines do not just influence cellular infiltration and recruitment but also differentiation. Th2 cells are characterized by the expression of CCR3, CCR4, and CCR8, and similarly the chemokine ligands for these receptors are involved in proper cellular recruitment and differentiation during a Th2 response. Despite these seemingly clear lines of receptor expression, there is the interplay between these two that work together to calibrate immune responses. Recent work has shown that CCL11, a chemokine ligand for CCR3, is able to bind CXCR3 with high affinity, though it does not function as a CXCR3 agonist (Xanthou *et al.*, 2003a). In this way, CXCR3 may act as a decoy receptor to sequester CCL11 and contribute to Th1 polarization (Xanthou *et al.*, 2003a). Even further, CXCL11 is an agonist for CXCR3 and can function as an antagonist for CCR3, promoting Th1 polarization through an additional means (Xanthou *et al.*, 2003a; 2003b). Cytotoxic $CD8^+$ T cells characteristically express CXCR3 on the surface. As mentioned, CXCR3 is also highly expressed on Th1 cells. This allows for the coordinated recruitment of Th1 cells and cytotoxic effectors to the same sites of infection or inflammation.

A third distinct lineage of $CD4^+$ T cells is the Th17 cells, so called for the production of IL-17. In addition to the expression of IL-17, these cells are identified by the expression of CCR4 and CCR6. These chemokine receptors are also expressed on the IL-22-producing population of $CD4^+$ cells, Th22 cells; though, Th22 cells have a distinct gene expression profile and function (Eyerich *et al.*, 2009; Plank *et al.*, 2017). In addition to CCR4 and CCR6, Th22 cells also express CCR10. The chemokines CCL27 and CCL28 that bind CCR10 are highly expressed in the skin, and these cells play an essential role in Th22-mediated skin inflammation (Mirshafiey *et al.*, 2015). Overall, the coordination among chemokine axes is to attract or detract select T cell types, and this is essential for the crosstalk and functional interplay among T cell subsets during an immune response (Table 1).

Chemokines, Subsets, and Tumor Microenvironment

Cellular environments throughout the body are microscale niches that are formed by resident cells, infiltrating cells, blood vessels, extracellular matrices, and secreted signaling molecules. These environments are extremely dynamic and always evolving, partially dictated by the cellular infiltrates, particularly T cells and other immune cells. Chemokines play an influential regulatory role in this process as the expression of chemokines by resident cells or the blood vessel endothelium will dictate the identity of infiltrating cells. In the case of T cells, only those cells that express the cognate chemokine receptors are recruited to infiltrate into the area, then the secretion of signaling molecules, particularly cytokines and chemokines, by these infiltrating T cells will mold the environment further. This process is true of inflammatory sites in general, and is of particular interest in the context of the tumor microenvironment.

In the tumor microenvironment, tumor cells, immune cells, and also the stromal cells express chemokines. In response to specific chemokines, different immune cell subsets migrate into the tumor microenvironment to regulate anti-tumor immune responses (Sackstein *et al.*, 2017). In addition, chemokines can directly target tumor cells and endothelial cells, as they have been shown to regulate some tumor proliferation, invasiveness, and metastasis (Nagarsheth *et al.*, 2017). Thus, chemokines directly and indirectly affect tumor immunity, and influence cancer progression, cancer therapy, and patient prognosis.

T cells that traffic into the microenvironment of the tumors can modulate local immune responses in both primary tumors and metastatic sites (Sackstein *et al.*, 2017). $CD8^+$ cytotoxic T cells that are specific for tumor antigens can interact with tumor cells in an antigen-specific manner, to drive anti-tumor immunity by secreting effector cytokines and cytotoxic molecules (such as granzyme B and perforin). In addition to $CD8^+$ T cells, interferon-expressing Th1 cells and natural killer (NK) cells have potent local anti-tumor activity. Effector $CD8^+$ cells, Th1 cells, and NK cells express CXCR3, which is the receptor for CXCL9 and CXCL10. Accordingly, increased levels of CXCL9 and CXCL10 are related to increased numbers of tumor-infiltrating $CD8^+$ T cells, and correlate with decreased levels of cancer metastasis and improved survival in patients with ovarian and colon cancers (Bronger *et al.*, 2016; Chow and Luster, 2014; Ding *et al.*, 2016; Mukaida *et al.*, 2014). Recent studies have demonstrated that tumor-infiltrating $CD8^+$ T cells and Th1 chemokines were associated with positive responses to therapeutic blockade of PD-1 or PD-L1 (Zou *et al.*, 2016). Interestingly, $CD8^+$ T cells in the tumor microenvironment were shown also to regulate the metabolism of the chemotherapeutic agent cisplatin in ovarian cancer (Akkari and Joyce, 2016). Thus, Th1 chemokines can recruit effector immune cells into the tumor microenvironment, and these cells can subsequently support anti-tumor immunity and desirable therapeutic responses.

As mentioned, Th17 cells express high levels of CCR6 and CXCR4. These receptors are associated with migration and retention within inflammatory sites and potentially also within tumors. High levels of CCL20 and CXCL12 (SDF-1), the respective ligands for these receptors, are found in tumor microenvironments, and may facilitate the trafficking of Th17

cells to the tumors (Li *et al.*, 2012). Th17 cells do not express CD62L (L-selectin) or CCR7, which promotes T cell recruitment to lymph nodes, suggesting that their potential to migrate to lymphoid tissues is limited. In both humans and mice, tumor-infiltrating Th17 cells are polyfunctional, have stem-like properties, and more importantly, mediate potent anti-tumor immunity. Th17 cells do not secrete cytotoxic molecules, but instead mediate anti-tumor activity by recruiting additional $CD8^+$ cytotoxic T cells, NK cells, and even dendritic cells into the tumor microenvironment.

A successful anti-tumor immune response extends beyond the activation of antigen-specific cytotoxic $CD8^+$ T cells (Sackstein *et al.*, 2017). Evidence of melanoma antigen-specific $CD8^+$ T cells from a patient with progressing melanoma raised a major question of why tumor growth was not controlled by the presence of a specific effector T cell population (Joyce and Fearon, 2015; van der Bruggen *et al.*, 1991). These results and others (Joyce and Fearon, 2015; Rosenberg *et al.*, 2005) raise two possible explanations: there are high numbers of antigen-specific T cells in peripheral circulation but tumor infiltration is limited or the tumor microenvironment is immunosuppressive and greatly limiting cytotoxic T and/or Th1 cell function (Sackstein *et al.*, 2017). It is probable that these two scenarios are not mutually exclusive, and that both contribute to the tumor's immune evasion and growth. The challenge of recruitment and infiltration is highlighted by the limited success of vaccines immunizing against cancers and adoptive T cell transfers in limiting solid tumor growth. Interestingly, T cell infiltration into tumors, overall, is significantly reduced compared to entry into diseased tissues (Bellone and Calcinotto, 2013; Sackstein *et al.*, 2017). Previous studies have demonstrated that tumor cells can interfere with T cell recruitment through abnormal blood vessel formation, altered expression of adhesion molecules, and hijacking of the chemokine networks (Sackstein *et al.*, 2017). As tumor cells and surrounding stroma express chemokines that attract immune dampening cell populations, the overall tumor microenvironment becomes more suppressive of proper effector T cell localization and function. Even as $CD8^+$ T cells enter the tumor site these cells are actively excluded from the immediate vicinity of cancer cells (Feig *et al.*, 2013; Galon *et al.*, 2006; Joyce and Fearon, 2015; Naito *et al.*, 1998; Sato *et al.*, 2005; Zhang *et al.*, 2003). This suggests that effector cell function is suppressed even after infiltration, perhaps in part due to other tumor-infiltrating lymphocyte populations.

Th22 cells are found in the microenvironment of several human cancers, including colon, pancreatic, and hepatocellular carcinoma. Th22 cells express CCR6, migrate towards CCL20 in the colon cancer microenvironment, and have been shown to promote and support tumorigenesis. Th22-derived IL-22 acts on cancer cells to promote the activation of STAT3 and increase the expression of H3K79 and H3K27 methyltransferases polycomb repressive complex 2, resulting in increased tumorigenic potential and proliferation of colon cancer cells (Kryczek *et al.*, 2014). A pro-tumor role of IL-22 has been supported by studies in two mouse models of colon cancer. In a bacteria-induced colon cancer model, IL-22 expressing colonic lymphoid cells gather in the tumor microenvironment, and their depletion blocks the development of invasive colon cancer (Jiang *et al.*, 2013; Kirchberger *et al.*, 2013). In a colon tumor model that is induced by azoxymethane and dextran sulfate sodium, down-regulation of IL-22 binding protein also promotes tumorigenesis (Huber *et al.*, 2012; Tong *et*

al., 2011). Thus, the recruitment of Th22 cells into the tumor microenvironment via the CCR6-CCL20 axis may promote tumorigenesis.

An additional mode in which chemokines may promote tumorigenesis is by mediating the recruitment of regulatory T cells (Treg) into the tumor microenvironment. Treg express CCR4 and are recruited into the tumor microenvironment in response to CCL22, produced mainly by the macrophages and the tumor cells themselves. These cells suppress other T cell anti-tumor immunity, leading to tumor growth and poor patient outcomes. In addition to the CCR4-CCL22 signaling pathway, Treg express CCR10 and migrate in response to CCL28 found in hypoxic regions of the tumors (Ren *et al.*, 2016). The bone marrow is a common site of tumor metastasis, suggesting that this anatomic location may provide an immunosuppressive environment to support tumor survival and growth. In line with this idea, high frequencies of Treg are found in the bone marrow (Zhao *et al.*, 2012). Bone marrow T cells exhibit a memory phenotype and express CXCR4. Treg can be mobilized from the bone marrow into the periphery by granulocyte colony-stimulating factor (GCSF) that promotes the degradation of CXCL12. High numbers of Treg in the bone marrow provide an immune protection that facilitates metastasis to this site. This may explain why cancers often metastasize to the bone marrow. In further support of this mechanism, the numbers of Treg are further increased in the bone marrow of patients with prostate cancer who show bone metastasis. These Treg populations are recruited into the bone marrow via the CXCR4-CXCL12 signaling pathway and are expanded by dendritic cells via the receptor activator of NF-κB (RANK)-RANKL pathway (Zhao *et al.*, 2012). Worth mentioning is the potential for tumor cells to also express CXCR4, allowing for the co-migration of tumor cells and Treg contribution to an overall pro-tumor survival environment to be established at once. Treg also express inflammatory cytokines including CXCL8 and IL-17. Interestingly, $CXCL8^+$ and $IL\text{-}7^+$ T cells not only mediate T cell suppression but also promote inflammation in the cancer microenvironment. Thus, chemokine-mediated recruitment of Treg into the tumor microenvironment and their presence at premetastatic sites support tumor initiation, progression, and subsequent metastasis.

Overall, the chemokines and the adhesion molecules that are expressed within the tumor microenvironment act as gatekeepers to peripheral T cell populations (Sackstein *et al.*, 2017). Through the upregulation of chemokines that recruit Th22 and Treg populations and the down-regulation of chemokines that recruit effector T cell populations, the tumor can successfully evade effective immune clearance. For these reasons, it is important to consider chemokine expression in the tumor microenvironment in the design of future effective immunotherapeutics (Nagarsheth *et al.*, 2017; Vela *et al.*, 2015).

Agonists and Antagonists

Chemokine receptors are poorly antigenic and it is technically difficult to purify receptors and to use them as targets for antibodies by *in vivo* or *in vitro* approaches (Vela *et al.*, 2015). For this reason, small molecules were favored, especially in view of the previous success of targeting this class of receptors. In contrast to the chemokine receptors, chemokines themselves are amenable to antibodies as a therapeutic strategy (Vela *et al.*, 2015). To date, very few antibodies targeting chemokines have reached the market. The first is an anti-

CXCL8 antibody for the treatment of psoriasis (Lowes *et al.*, 2014; Ye, 1998). The second is anti-CCR4 (mogamulizumab), for adult T cell leukemia (Makita and Tobinai, 2017). Antibodies targeting CCL2, CCL5, CXCL10, CCR2, CCR4, CCR5, and CXCR4 are currently in clinical trials. Certain intriguing observations have been made from these trials, the most striking of which is the phase II trial with ABN912, an anti-CCL2 antibody for rheumatoid arthritis patients. During this trial an unexpected dose-related increase in circulating CCL2 was observed, resulting in further increase of the highest dose tested (Haringman *et al.*, 2006), indicating that targeting ligands is more complicated than originally thought.

The majority of the research to identify candidates as therapeutics has focused on the development of small molecule inhibitors of chemokine receptors (Vela *et al.*, 2015). The first antagonist for CCR1, BX471 (described in more detail below), was a selective, potent, and orally available drug. However, the compound failed in a phase II study for patients with multiple sclerosis due to lack of efficacy *in vivo* (Gladue *et al.*, 2010). Since then, many antagonists have been developed but the majority have failed in clinical trials. CCR9 is a chemokine receptor that mediates recruitment of T cells to sites of inflammation by interaction with CCL25. CCCX282-B (Vercirnon) was an orally administered small molecule inhibitor of CCR9 that was designed for patients with inflammatory bowel disease. However, a randomized controlled phase II study failed to show clinical benefit despite the absence of substantial adverse events (Feagan *et al.*, 2015; Zhang *et al.*, 2015).

To date only two small molecules have reached the market, maraviroc (Pfizer) a CCR5 inhibitor for HIV infection, and plerixafor (Anormed) a CXCR4 inhibitor for stem cell mobilization during chemotherapy. Some of the reasons for failure in clinical trials have been incorrect target selection, insufficient dosing to ensure sufficient receptor coverage, and poor trial design, such that endpoints, which gave successful results in phase II, are different from those measured in phase III. In addition, the majority of target validation has been performed with murine disease models but the role of particular receptor-ligand pairs in the chemokine system is different between mice and man. A redundancy of biological functions has often been cited as being the cause for failure, and it highlights the point that there is still a lot to learn about the basic biology and selectivity of the chemokine system.

CCR1 (also designated CD191) is a member of the beta chemokine receptor family. The ligands of this receptor include CCL3, CCL5 (RANTES), CCL7, and CCL23. Knockout studies of the mouse homolog suggested a role for this receptor in host protection against inflammation (Braunersreuther *et al.*, 2007). BX471 was a strong and selective CCR1 antagonist. *In vivo* murine studies demonstrated its ability to block CCR1 signaling and leukocyte migration. BX471 inhibited RANTES-mediated adhesion of both monocytes and T cells to activated endothelium. Though it has a borderline significant effect on the number of $CD8^+$ $CCR5^+$ cells in the peripheral blood, it effectively reduces disease in the rat experimental allergic encephalomyelitis model (the model for multiple sclerosis) (Liang *et al.*, 2000).

CCR5 (also known as CD195) is important for T cell trafficking to specific tissue and organ targets in response to expression of the ligands CCL3, CCL4, or CCL5 (RANTES). The

HIV virus uses CCR5 as a co-receptor for entry into and infection of host cells, and, strikingly, individuals who carry a mutation known as CCR5-Δ32 in the CCR5 gene, are seemingly protected from HIV infection. Maraviroc is an antiretroviral drug and a CCR5 antagonist, a negative allosteric modulator. In two randomized, placebo-controlled clinical trials that compared HIV patients receiving optimized therapy plus a placebo to patients receiving optimized therapy plus maraviroc, the participants receiving maraviroc had a mean increase in $CD4^+$ counts and lower viral loads (Hunt *et al.*, 2013). In a different study, maraviroc also appeared to reduce graft-versus-host disease in patients treated with allogeneic bone marrow transplantation (Reshef *et al.*, 2012).

CXCR4 (also known as CD184) is a chemokine receptor for CXCL12 (SDF-1) which is a potent chemotactic factor of T cells. CXCL12 is known to be important in hematopoietic stem cell homing to the bone marrow and in hematopoietic stem cell quiescence. It has been also shown that CXCR4 signaling regulates the expression of CD20 on B cells. SDF-1 and CXCR4 were believed to be a relatively monogamous ligand-receptor pair, though recent evidence demonstrates ubiquitin and MIF are also natural ligands of CXCR4 (Li *et al.*, 2012). While expression of CXCR4 is low in many healthy tissues, it has been demonstrated to be expressed in over 23 types of cancer, including breast cancer, ovarian cancer, melanoma, and prostate cancer. Expression of this receptor in cancer cells has been linked to metastasis to tissues containing a high concentration of CXCL12, such as lungs, liver, brain, and bone marrow (Chu *et al.*, 2017; Chung *et al.*, 2017). However, in breast cancer where CXCL12 is also expressed by the cancer cells themselves along with CXCR4, CXCL12 expression is positively correlated with disease-free (metastasis-free) survival (Samarendra *et al.*, 2017). CXCL12 expressing cancers might not sense the CXCL12 gradient released from the metastatic target tissues since the receptor, CXCR4, is saturated with the ligand produced in an autocrine manner. Another explanation of this observation is provided by a study that shows the ability of CXCL12 (and CCL2)-producing tumors to entrain neutrophils that inhibit seeding of tumor cells in the lung (Granot *et al.*, 2011).

Drugs that block the CXCR4 receptor appear to be capable of mobilizing hematopoietic stem cells into the bloodstream, a very important point in hematopoietic stem cell transplantation. Plerixafor (AMD3100), a direct block of CXCR4, was recently approved for routine clinical use. In addition, the drug is approved for patients with lymphoma and multiple myeloma. Though in patients with leukemia, mobilization of tumor cells has occurred after treatment with plerixafor (Fruehauf, 2013; Konopleva *et al.*, 2015). Plerixafor was shown to reduce metastasis in mice in several studies, and has also been shown to reduce recurrence of glioblastoma in a mouse model when administered after radiotherapy (Tabouret *et al.*, 2015). Blockade of CXCR4 signaling by plerixafor has also unexpectedly been found to be effective at counteracting opioid-induced hyperalgesia produced by chronic treatment with morphine, though only animal studies have been conducted as yet (Xie *et al.*, 2016).

Conclusions

This review highlights the expression patterns of chemokine receptors across T cell subsets, and connects expression to the sites of function and recruitment. While chemokine receptors

have become definitional of subsets within the T cell compartment, such as CXCR5 and CCR7, others are expressed across multiple subsets that must be recruited to the same sites of activity.

Given that chemokines and their receptors have crucial roles in inflammatory human diseases, efforts have been made to target chemokine networks in patients with autoimmune diseases and chronic inflammation. Drugs that target CCR5 and CXCR4 have been approved for use in HIV infection and for the mobilization of stem cells for transplantation. However, the targeting of chemokines and chemokine receptors has so far failed to yield any viable anti-inflammatory drugs.

As discussed above, the chemokines CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, and CXCL12 are relatively well studied in human cancer, yet only now, the field is developing an understanding of the mechanism of tumor infiltration for Treg and Th22 cells which may limit the efficacy of $CD8^+$ and Th1 cells. In the next generation of immunotherapeutic design, it will be important to capitalize on these studies of chemokines in the microenvironment in order to control selective T cell recruitment into the tumor site.

Acknowledgments

The project was supported by NIH grant (1R01AI125640-02), Rheumatology Research Foundation, and the Colton family scholarship program.

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Table 1.

Chemokines Expression and T Cell Subsets.

Chemokine Receptor	Chemokine Ligand	T Cell Subset	Ligand Expression Pattern	Axis Function
CCR7	CCL19 CCL21	Naïve Central memory	Secondary lymphoid organs Blood-brain barrier	Homing of T cells to various secondary lymphoid organs, trafficking within spleen; recruitment to the CNS
CXCR3	CXCL4 CXCL9 (MIG) CXCL10 (IP-10) CXCL11 (I-TAC)	Th1 CD8+ cytotoxic	Sites of injury and inflammation	Recruitment to inflammatory sites and wound healing
CCR5	CCL3, CCL3L1 CCL4 (MIP-1) CCL5 (RANTES)	Th1	Sites of injury and inflammation	Recruitment to inflammatory sites and wound healing
CCR4	CCL2 (MCP-1) CCL4 (MIP-1) CCL5 (RANTES) CCL17 (TARC, CCL22 (Macrophage-derived chemokine)	Th2 Th17 Th22 Treg	Sites of injury and inflammation	Recruitment to inflammatory sites; plays a role in pathogenesis of inflammatory diseases
CCR3	CCL5 (RANTES) CCL7 (MCP-3) CCL11 CCL13 (MCP-4) CCL26 (eotax-in3)	Th2	Sites of inflammation or infection	Recruitment to inflammatory or infection sites
CCR6	CCL20 (MIP-3α)	Th17 Th22	Mucosal lymphoid tissue Lymph nodes Liver Appendix	Recruitment in response to infection or inflammation at these sites
CCR10	CCL27 CCL28	Th22 Treg	Skin	T cell-mediated skin inflammation
CXCR5	CXCL13 (BLC/BCA-1)	Tfh	B cell follicles of lymph nodes Spleen	Enables T cells to migrate to lymph node B cell zones
CCR8	CCL1 CCL8	Th2	Thymus	Positioning of activated T cells within the antigenic challenge sites and specialized areas of lymphoid tissues
CCR1	CCL3 (MIP-1 α) CCL5 (RANTES) CCL7 (MCP-3) CCL23 (MPIF-1)	Th1	Sites of inflammation or infection	Recruitment to inflammatory or infection sites