Chemokines: attractive mediators of the immune response

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Abstract

An effective inflammatory immune response first requires the recruitment of cells to the site of inflammation and then their appropriate activation and regulation. Chemokines are critical in this response since they are both chemotactic and immunoregulatory molecules. In this regard, the interaction between CCL5 and CCR5 may be critical in regulating T cell functions, by mediating their recruitment and polarization, activation, and differentiation. Various tyrosine phosphorylation signaling cascades can be engaged following chemokine receptor aggregation on T cells, including the Jak–Stat pathway, FAK activation, the MAP kinase pathway, PI3-kinase activation, and transactivation of the T cell receptor. This review will address specific aspects related to chemokine–T cell interactions and the molecular signaling mechanisms that influence T cell function in an inflammatory immune response.

Keywords: Chemokine; T cell; Receptor; Signal transduction

1. Introduction

Chemokines have a fundamental role in providing directional cues for the trafficking of leukocytes to sites of inflammation. Accumulating evidence suggests that their function is not restricted to chemotaxis, since chemokines have been implicated in dendritic cell maturation, macrophage activation, neutrophil degranulation, B cell antibody class switching, and T cell activation. The data infer that chemokines influence both the innate and acquired phase of an immune response to host insult. The following is a review of the role of chemokines in T cell mediated inflammatory responses and the molecular underpinnings of these activities. Those events integral to the processes depicted in Fig. 1, that are chemokine regulated, will be considered. Specific emphasis will be placed on the chemokine CCL5regulated upon activation normal T cell expressed and secreted (RANTES) and its cognate receptor, CC chemokine receptor (CCR)-5 (CCR5), in the context of discrete signaling pathways.

2. A role for chemokines in the recruitment and polarization of T cells

The various stages involved in the recruitment of leukocytes out of the vasculature, a process known as diapedesis, have been reviewed elsewhere [1] (see Fig. 1). Briefly, in order for a cell to respond to a chemotactic gradient, intracellular and extracellular components must spatially reorganize, resulting in the acquisition of a front end (leading edge or lamellapodium) and a back end (trailing edge or uropod). This process is known as polarization. It is the initial polarization of a T cell in response to chemokines that facilitates the formation of the immunological synapse or supramolecular activation complex. The immunological synapse is a highly organized structure that forms at the interface between the antigen presenting cell (APC) and the T cell, and is all-important for T cell activation [2]. Membrane lipid rafts aggregate at the immunological synapse, a prerequisite for signaling through the T cell receptor (TCR) [3]. Lipid rafts, also known as detergent insoluble, glycolipid-enriched complexes (DIGs) or glycosphingolipid enriched membranes (GEMs), are microdomains within the lipid membrane that are enriched in sphingolipids and cholesterol. Lipid rafts are also enriched for various signaling molecules and are thought to serve as platforms for efficient signaling or compartmentalization of signaling pathways. CCR function depends on lipid rafts. Indeed, CCR5 once activated by CCL4 will localize to lipid rafts [4]. Treatment with
cholesterol extracting agent disrupts both ligand binding to and signaling from CCR5, indicating that CCR5 activation depends on the integrity of lipid rafts [4]. T cells are rapidly polarized upon chemokine exposure [5] and this polarization is abrogated by disruption of lipid rafts [6]. Perhaps, in the context of CCR5, activation-induced signaling coordinates lipid raft aggregation, thereby facilitating immunological synapse formation. The polarized T cell is already spatially organized in terms of its response to antigen, as the leading edge is more sensitive to CD3 stimulation than the trailing edge, denoting that TCRs are localized to the front edge of the cell [7]. Treatment of T lymphocytes with chemokines or other chemoattractant agents leads to the recruitment of CCRs such as CCR2 and CCR5 to this leading edge [8]. Apparently, receptors involved in sensing chemotactic gradients are preferentially localized to the leading edge in a polarized cell. CCR5 also colocalizes with CD4 at the cell surface [9]. Viewed altogether, these data suggest that the localization of CCRs to the leading edge may allow for interaction with TCRs, thereby modulating TCR mediated signaling cascades. The implications are that CCRs, especially CCR5, have multiple roles in an immune response: first in the recruitment of cells to a site of inflammation and subsequently in setting the stage for the appropriate immune response by facilitating immunological synapse formation.

3. Chemokines are (co)stimulatory for T cells

There is growing evidence that chemokines can (co)stimulate T cells. Using both purified human T cells and T cell clones, Taub et al. [10] demonstrated that CC chemokines, including CCL5, were able to costimulate T cell proliferation and IL-2 production in the context of anti-CD3 activation. Interestingly, all CCR5 ligands are able costimulate T cells, implying that it is this receptor that is crucial for costimulation. Genetic evidence indicates that CCL5 is important in T cell stimulation and a DTH response [11]. CCL5 deficient mice exhibit impaired T cell proliferation and cytokine (IL-2 and interferon-γ) production following anti-CD3 or antigen stimulation. Indeed, the data suggest that IL-2 and chemokines such as CCL5 act in concert, since the costimulatory activity of CCL5 is dependent on the presence of IL-2 [10]. IL-2 will induce the expression of CCR5 on human T cells of the memory phenotype, mediating a positive feedback for CCR5.
expression [12]. CXCL12 (SDF-1α) will also costimulate human CD4 positive T cells, implying that T cell stimulatory activity is exhibited by different chemokines [13]. As for CCR5, membrane-associated lipid rafts are important for CXCL12-CXCR4 binding and signaling [14]. Of note, CC chemokine costimulatory activity is exhibited in the nanomolar range. Using a Th0 T cell clone, Bacon et al. [15] showed that micromolar doses of CCL5 can induce T cell proliferation and cytokine production in an antigen-independent manner. Estimation of in vivo soluble chemokine concentrations in the nanomolar range has cast some doubt on the validity of this in vitro phenomenon. Chemokines probably do not act as soluble entities, but as solid phase bound aggregates. Chemokines can bind proteoglycans through interactions with the glycosaminoglycan (GAG) component of the proteins [16]. The association of chemokines with GAGs of the extracellular matrix and on the cell surface has important implications in terms of presentation and increasing local chemokine levels. Using GAG deficient Chinese hamster ovary cells transfected with CCR1 and CCR5, Ali et al. [17] demonstrated that surface GAG deficient Chinese hamster ovary cells transfected with CCR1 and CCR5, Ali et al. [17] demonstrated that surface GAGs increase the concentration of chemokines presented to the CCRs at the molecular level. CCL5 has been shown to bind GAGs with distinct specificity [16] suggesting that GAGs may be crucial in mediating inflammatory responses. Furthermore, release of a GAG, chondroitin sulfate A, from platelets in vivo blocked CCL5 binding and CCR5 signaling [18]. Therefore, micromolar concentrations of soluble chemokines shown to activate T cells may mimic surface bound aggregates of chemokines. The antigen-independent activation of T cells by CCL5 has important implications in terms of autoimmunity, as high levels of CCL5, present at sites of autoimmune activation, may lead to the enhanced proliferation and cytokine production by bystander T cells. Using Jurkat T cells, Dairaghi et al. [19] showed that T cell proliferation and cytokine production by bystander T cells. Chemokines probably do not act as soluble entities, but as solid phase bound aggregates. Chemokines can bind proteoglycans through interactions with the glycosaminoglycan (GAG) component of the proteins [16]. The association of chemokines with GAGs of the extracellular matrix and on the cell surface has important implications in terms of presentation and increasing local chemokine levels. Using GAG deficient Chinese hamster ovary cells transfected with CCR1 and CCR5, Ali et al. [17] demonstrated that surface GAG deficient Chinese hamster ovary cells transfected with CCR1 and CCR5, Ali et al. [17] demonstrated that surface GAGs increase the concentration of chemokines presented to the CCRs at the molecular level. CCL5 has been shown to bind GAGs with distinct specificity [16] suggesting that GAGs may be crucial in mediating inflammatory responses. Furthermore, release of a GAG, chondroitin sulfate A, from platelets in vivo blocked CCL5 binding and CCR5 signaling [18]. Therefore, micromolar concentrations of soluble chemokines shown to activate T cells may mimic surface bound aggregates of chemokines. The antigen-independent activation of T cells by CCL5 has important implications in terms of autoimmunity, as high levels of CCL5, present at sites of autoimmune activation, may lead to the enhanced proliferation and cytokine production by bystander T cells. Using Jurkat T cells, Dairaghi et al. [19] showed that T cell responses to CCL5 are dependent on the surface expression of CD3. This suggests that chemokine receptors can co-opt components of the TCR signaling machinery to potentiate activation. When viewed together, these data support the notion that proinflammatory chemokines are involved in the activation of T cells localized to an inflammatory site.

4. Chemokines influence T cell fate

Emerging evidence suggests that chemokines can affect T cell differentiation. A cellular or T helper (Th1) response is associated with interferon-γ production and macrophage activation, whereas a humoral or Th2 response is characterized by IL-4 and IL-5 production, B cell help and an antibody response. Chemokine receptors are markers for T helper subsets: CCR5 and CXCR3 are markers for Th1 cells [20-21], while CCR2 and CXR4 are expressed by Th2 cells [22-23]. Furthermore, ligands for CCR5 (CCL3, CCL4, and CCL5) have been shown to be chemoattractant for Th1 and not Th2 cells [24]. Indeed, in rheumatoid arthritis (RA), a Th1 disease, most of the T cells infiltrating affected rheumatic joints express CCR5 [25]. Taken together, these data indicate that chemokines can differentiate between Th1 and Th2 T cells. Chemokines can also determine the polarization of T helper cell responses. For example, CCL5 is produced by and can activate a Th0 T cell clone [15,26]. CCL3, CCL4 and CCL5 are produced by Th1 T cell clones and are associated with a Th1 response [26,27]. Recent evidence points to a role for chemokines in the resolution of an immune response. CXCL12 can induce apoptosis in Jurkat T cells [31]. The induction of apoptosis was a late phenomenon, 3 days after CXCL12 exposure, and was dependent on Fas and Fas ligand expression. In the absence of information relating to cell activation events prior to cell death, it is intriguing to speculate that CXCL12-induced apoptosis may be a regulatory process that follows T cell activation, similar to activation induced cell death (AICD). Indeed the chemokine, XCL1 (lymphotactin), can costimulate the apoptosis of human CD4 positive T cells through AICD [32]. Mellado et al. [33] have recently reported that CCL5, produced by melanoma tumor cells, can induce apoptosis of tumor infiltrating T cells, by binding to and activating CCR5. This apoptosis was not dependent on Fas/Fas ligand, but the release of cytochrome c into the cytosol. In other studies, we have evidence that CCL5 will induce apoptosis in T cells, at doses where GAG and CCR5 interactions are demonstrable (unpublished observation). The implications are that chemokine-dependent cell death is invoked as a late stage regulatory mechanism at an inflammatory site by initiating apoptosis after T cell activation.

5. Molecular mechanisms of chemokine function: signal transduction

As mentioned, chemokines function in the recruitment, polarization, activation and differentiation of T cells. The challenge has been to define the molecular mechanisms that determine these diverse functions. Certainly, an understanding of the signaling pathways and subsequent gene
regulatory events that follow activation of cognate receptors is important. As seven transmembrane G-protein coupled receptor (GPCR)s, chemokine receptor activation results in the exchange of GTP for GDP by the Gs subunit and the dissociation of the heterotrimeric G-proteins into Gs and G\(\alpha\) subunits \[34\]. It is now clear that signaling through GPCRs is more complex, invoking tyrosine phosphorylation signaling cascades (see Fig. 2).

6. Chemokine receptor dimerization: a prerequisite for signaling?

For cytokine receptor activation, receptor dimerization or oligomerization is a critical prerequisite for receptor tyrosine kinase activation and subsequent signal transduction. For many years it was believed that GPCRs did not oligomerize upon ligand activation. Recent evidence suggests that,
similar to cytokine receptors, GPCRs can form dimers and oligomers [35], implying that GPCR dimerization/oligomerization may be an important prerequisite for signaling. Coimmunoprecipitation studies confirmed GPCR homodimerization for the β2 adrenergic [36], δ-opioid [37], dopamine and serotonin [38], angiotensin AT1, and CCR2b [39], CCR5 [40] and CXCR4 [41] receptors. Studies have indicated that chemokine receptor dimerization is functionally relevant. Using bivalent and monovalent antibodies, the importance of CCR5 oligomerization for receptor internalization was demonstrated [42]. Cotransfection of a mutant CCR2b, in which tyrosine 139 in the conserved intracellular DRY motif was mutated to phenylalanine, with wild type receptor into cells, resulted in functionally inactive ligand-bound receptor dimers [43]. Presumably, the mutant receptor behaved as a dominant-negative, limiting tyrrosine kinase activity of the receptor dimers. Notably, dimerization of CCR2b by an activating antibody invokes signaling events similar to ligand (CCL2) binding [39]. The Fab monovalent fragment of the antibody does not invoke signaling, but crosslinking the Fab fragment restores signaling through CCR2b. Taken together, these data indicate that chemokine receptor dimerization effects intracellular kinase activation and signal transduction. GPCRs can also form heterodimers. Heterodimers of κ-β- and µ-δ-opioid receptors exhibit not only increased sensitivity to ligand, but are also receptors with distinct functional properties [44,45]. Similar results have been reported for the somatostatin and dopamine receptors [46]. Chemokine receptors can also heterodimerize. Mellado et al. [47] have shown that CCR2b and CCR5, when coexpressed in human embryonic kidney (HEK)-293 cells, form heterodimers. It is appealing to speculate that chemokine receptor heterodimers may also exhibit novel binding and functional properties distinct from receptor monomers or homodimers. Indeed, heterodimerization of CCR2b and CCR5 increased the sensitivity of the chemokine receptors to ligand induced calcium fluxes and invoked distinct G-protein coupling and signaling, resulting in preferential cell adhesive properties rather than chemotaxis. Viewed together, these data provide evidence that dimerization of chemokine receptors is functionally relevant and necessary for initiating certain signaling events, specifically related to tyrosine phosphorylation.

7. The Jak–Stat connection

Many cytokines and growth factors mediate their effects via activation of a common signal transduction pathway, the Jak–Stat pathway. Binding of the ligand to its specific transmembrane receptor results in receptor aggregation, leading to the catalytic activation of receptor-associated cytoplasmic protein tyrosine kinases, termed Janus kinases (Jaks) and phosphorylation-activation of latent monomeric signal transducers and activators of transcription, Stat proteins. Receptor-associated phosphorylated Stats then dimerize via SH2–phosphotyrosyl interactions, and translocate to the nucleus, where they bind specific promoter sequences, thereby regulating gene expression. (reviewed by Gudina et al. [48]). It is now clear that ligand-induced chemokine receptor activation can also invoke Jak–Stat signaling, perhaps by a mechanism that requires receptor homodimerization and heterodimerization [39–41,47,49,50]. Nuclear extracts from Molt-4 and Jurkat T cells treated with CCL3 or CCL5 contained tyrosine phosphorylated Stat1:Stat1 and Stat1:Stat3 dimers that exhibited DNA-binding activity [51]. This activation was dependent on CCR5 gene expression. CCL5 treatment of PM1 T cells results in the rapid tyrosine phosphorylation-activation of CCR5, Jak2 and Jak3 [50]. Phosphorylated Jak2 associates with phosphorylated CCR5. CCL5-inducible Jak phosphorylation is insensitive to pertussis toxin inhibition, indicating that CCL5–CCR5-mediated tyrosine phosphorylation events are not coupled directly to Gαi, protein-mediated events. In other studies, Rodriguez-Frade et al. [40] showed that in CCR5-transfected HEK-293 cells, CCL5 induces the phosphorylation-activation of Jak1 and Stat5 and their association with the receptor. Which Jaks and Stats are recruited to CCR5 following CCL5 activation appears to be cell type specific. Moreover, different chemokine-receptor pairs inductively activate different Jaks and Stats, adding further complexity to the system: CXCL12–CXCR4 interactions result in Jak1, Jak2, Stat1, Stat2, Stat3 and Stat5 phosphorylation-activation [41], and CCL2 (MCP-1) induces the activation and association of Jak2 and Stat3 with CCR2, upstream of G-protein signaling [43].

Targets of the Jak–Stat pathway have been implicated in regulating cellular growth and differentiation. Constitutive activation of the Jak–Stat pathway has been shown to result in growth factor independent proliferation of leukemic cell lines [52]. Indeed, a constitutively active form of Stat3 is able to transform cells, indicating a critical role for Stat3 in regulating cell growth and differentiation [53]. Stat5 is required for cell cycle progression facilitated by IL-2, since T cells derived from mice lacking Stat5a, Stat5b, or both, exhibit impaired growth responses to IL-2 mediated costimulation [54–56]. Indeed, activation of the TCR will result in Stat5 phosphorylation-activation and a subsequent proliferative response by the T cell [57]. In the context of chemokine–CCR5 interactions in T cells, these data infer that chemokine involvement in Stat activation will influence T cell activation mediated, in part, by cross-talk with the activated TCR. We have shown that CCL5 induces the expression of a putative Stat inducible gene, c-fos, in T cells [51]. The induction of c-fos gene expression correlated with the expression of CCR5. These data provide further support that CCL5–CCR5 interact to activate a putative growth response gene through a Stat dependent pathway. Notably, Stat activation is also important for cytokine-induced differentiation of T cells. In Stat4 deficient mice, Th1 development is impaired, since IL-12 signaling through Stat4 is abrogated [58,59]. In Stat6 deficient mice, Th2...
responses are defective, due to the absence of IL-4 inducible Stat6 activation [60,61]. In the absence of supportive data, it is intriguing to speculate that chemokine-mediated, IL-12 independent, induction of Th1 differentiation may be attributable to chemokine activation of Stat4 [29]. Alternatively, other chemokine-activated Stats may be involved in determining T helper phenotype fate.

Distinct from their effector functions associated with the differentiation of T cells, activated Stats have also been implicated in mediating apoptosis. Both epidermal growth factor and interferon-γ will stimulate their cognate receptors to activate Stat1, which mediates growth arrest and apoptosis [62,63]. In Jurkat T cells, Stat3 activation has been linked with MHC class I-induced apoptosis [64]. These data raise the possibility that chemokine-mediated T cell apoptosis may depend on Stat activation. Given that different Stats have been implicated in regulating different facets of T cell growth—proliferation, differentiation, growth arrest and apoptosis—the contribution of chemokine activation of specific Stats may be critical for determining T cell fate.

8. Focal adhesion kinases (FAKs) and chemokine signaling

As mentioned earlier, exposure to chemokines leads to the rapid polarization of T cells and recruitment of chemokine receptors to the leading edge. The initial polarization of a T cell involves concentration of membrane F actin and the redistribution of specific receptors, such as the TCR, to the leading edge of the migrating cell. Among the intracellular molecules recruited to the leading edge is FAK. The FAK family of tyrosine kinases consists of two members: FAK and Pyk2 (also known as related adhesion focal tyrosine kinase) [65,66]. FAKs have been reported to be positively regulated by Src family tyrosine kinases and to bind to cytoskeletal elements such as paxillin and talin [67–69]. FAK is important in cell migration, as fibroblasts from FAK−−/− mouse embryos manifest defective migration [70]. Notably, migration is only restored in cells expressing FAK variants that contain the intact kinase, SH2 and SH3 binding domains, implying that multiple protein interactions are important for FAK activity. FAK activity has also been implicated in cell activation studies. Activation of FAK has been shown to be reduced in cells expressing FAK variants that contain a deletion of the SH2 domain, indicating that multiple protein interactions are required for FAK activity.

9. MAP kinases and chemokine signaling

The MAP kinases are a family of serine/threonine kinases that are activated in response to growth factors, cytokines and cellular stress (reviewed by Pearson et al. [83]). The three main members of the MAP kinase family are the Erks, JNKs and p38. Chemokine–receptor interactions have been shown to activate MAP kinase signalling cascades. Both Erk and p38 are activated by CCL5–CCR5 interactions in T cells [50,81,84]. CCL4 will activate Erk2 in human thymocytes, possibly mediated by CCR5 [85]. Recently, Bajetto et al. [86] demonstrated that CXCL12 induces astrocyte proliferation via Erk1/2 activation. Given the important role for Erks in regulating cell proliferation, their involvement in CCL5-induced T cell proliferation deserves consideration. The consequence of chemokine activation of p38 MAPK in T cells has not been determined. Certainly, p38 activation is necessary for the transcriptional activation of IL-2 in Jurkat T cells and interferon-γ in Th1 cells [87,88]. Given that Th1 cells express CCR5, p38 activation by CCL5 may determine the transcriptional activation of specific cytokine genes. The p38 activation may also be important for chemokine T cell costimulation. Activation of p38 is critical for the effector functions of T cell costimulatory molecules such as CD28 and 4-1BB [89–92]. Accordingly, chemokine activation of p38 may also be critical for their costimulatory activities in T cells. The inference is that chemokine activation of distinct MAP kinase signaling cascades may be important in
10. Phosphoinositide 3-kinase (PI3K) and other signaling events

PI3Ks are a family of kinases that phosphorylate the 3'-OH position of the inositol ring of phosphoinositides [93]. There are three classes of PI3Ks: class I PI3Ks are dimers consisting of a catalytic and a regulatory subunit, class II PI3Ks are large molecules which contain a C terminal C2 domain, and class III PI3Ks are homologues of the yeast protein Vps34. PI3Ks function to phosphorylate lipids to form phosphatidylinositol-3-phosphates. PI3K activated lipid metabolites serve as scaffolds for the recruitment of plextrin homology (PH) domain containing proteins to the plasma membrane. Important targets for the products of PI3K include tyrosine kinases, guanine nucleotide binding proteins and serine/threonine kinases, providing the biochemical links for the crucial role of PI3Ks in T lymphocyte activation and effector functions [94]. Given the importance of PI3Ks in T cell activation and that chemokines can stimulate T cells, it is not surprising that chemokine stimulation of T cells will invoke the biochemical activation of PI3Ks [95]. The roles of PI3Ks in chemokine responses have been reviewed extensively elsewhere [96,97], and will only be discussed briefly here. CCL5 can activate class I PI3K in freshly isolated human T cells [98]. Pharmacological inhibition of PI3K by wortmannin, revealed that CCL5 inducible chemotaxis and cell polarization is dependent on PI3K. CXCL12 activation of PI3K has also been shown to mediate similar effects in human peripheral blood leukocytes [99]. PI3Ks mediate chemotaxis and cell polarization by activating the small GTPases Rho and Rac, which coordinate the dynamic organization of the actin cytoskeleton and the assembly of associated integrin structures. Actin reorganization is important in regulating adhesion and motility of cells. In the Jurkat T cell line, CCL5 can activate phospholipase D through activating RhoA, yet the functional consequence of phospholipase D activation is unclear [102]. Rho GTase may mediate cellular polarization through a known downstream target, the Wiskott–Aldrich syndrome protein (WASP). Indeed, in monocytes from Wiskott–Aldrich syndrome patients, CCL2 induced reduced chemotaxis and cell polarization [103]. Recently, Haddad et al. [104] demonstrated that CXCL12 induced T cell chemotaxis through Cdc42 activation and interaction with WASP. Mice with mutations in Vav or WASP exhibit deficiencies in T cell proliferation, cytoskeletal rearrangement and receptor capping [105,106]. These data indicate that cytoskeletal reorganization is important not only for T cell polarization but also for activation. In summary, these data infer that chemokine-directed cell polarization and facilitation of SMAC formation may be regulated through PI3Ks and their effectors.

11. CCR cross-talk with the TCR signaling complex

Clearly, activated chemokine receptors are able to invoke many different signaling cascades. Moreover, receptor oligomerization increases the complexity of signaling, allowing for a network of signaling cascades. Another level of complexity may be associated with interactions with nonchemokine receptors present on the cell surface, by a process known as "transactivation." GPCR-mediated transactivation of the epidermal growth factor [107] and the platelet-derived growth factor receptors [108] have been reported. Given that CCL5–CCR5 activation of Jurkat T cells correlates with the expression of CD3 [19], that CCR5 expression is associated with constitutive CD4 [9] expression and CCR5 localizes to lipid rafts upon ligand binding [4,6], activated CCR5 may function to recruit signaling intermediates of the TCR to potenti ate (co)stimulation of T cells. CCL5 at micromolar doses can induce two distinct calcium fluxes in T cells: one dependent on G-proteins and the other on tyrosine kinases [15]. Notably, CCL5 induced a similar protein phosphorylation profile to that observed following direct TCR activation, indicating that CCL5 may activate proximal TCR signaling events. In a subsequent study, Bacon et al. [79] provided evidence that CCL5 treatment of T cells induces the phosphorylation and association of FAK, ZAP-70 and paxillin, as well as partial phosphorylation of the TCR–ζ chain. Additionally, CCL4 can mediate a pattern of protein phosphorylation similar to direct CD3 stimulation in human thymocytes [85]. Extrapolating from these data, the implications are that CCL5 activation of CCR5 allows for signaling cross-talk with the TCR signaling machinery to effect T cell activation.

12. Summary

The preceding attest to the fact that chemokines are now recognized as more than just mediators of cellular trafficking. However, the molecular mechanisms underlying specific chemokine functions remain largely unknown. Moreover, the circuitry associated with cross-talk between signal transduction from chemokine receptors and other receptors, e.g. the TCR, is also unspecified. Clearly, chemokines can regulate gene expression in target cells, but the functional consequences of altered gene expression profiles also remain ill-defined. Recent data indicate that chemokines do not function as soluble entities, but are localized to GAGs in the extracellular space and on the surface of cells. The in vivo functional significance of chemokine binding to a solid substratum is still unclear. The last decade has borne witness to accumulating evidence of chemokine participation in the immune system, confirming that they have a sentinel
role in immunosurveillance. The outstanding challenge is to characterize the sequence of events that are precipitated following chemokine receptor activation in this context of immune regulation.

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References


