DOI: 10.1002/JLB.2MR1217-494R

JLB JOURNAL OF LEUKOCYTE BIOLOGY

REVIEW

Beyond migration—Chemokines in lymphocyte priming, differentiation, and modulating effector functions

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Abstract

Chemokines and their receptors coordinate the positioning of leukocytes, and lymphocytes in particular, in space and time. Discrete lymphocyte subsets, depending on their activation and differentiation status, express various sets of chemokine receptors to be recruited to distinct tissues. Thus, the network of chemokines and their receptors ensures the correct localization of specialized lymphocyte subsets within the appropriate microenvironment enabling them to search for cognate antigens, to become activated, and to fulfill their effector functions. The chemokine system therefore is vital for the initiation as well as the regulation of immune responses to protect the body from pathogens while maintaining tolerance towards self. Besides the well investigated function of orchestrating directed cell migration, chemokines additionally act on lymphocytes in multiple ways to shape immune responses. In this review, we highlight and discuss the role of chemokines and chemokine receptors in controlling cell-to-cell contacts required for lymphocyte arrest on endothelial cells and immunological synapse formation, in lymphocyte priming and differentiation, survival, as well as in modulating effector functions.

KEYWORDS

adhesion, B cell, cytokine, integrin, signal transduction, T cell

1 | INTRODUCTION

Chemokines are chemotactic cytokines that belong to a group of small, structurally related peptides. Chemokines constitute the largest family of cytokines comprising about 45 different members in humans and mice.[1,2] The function of chemokines is mediated by binding to chemokine receptors of the γ subfamily of class A rhodopsin-like G-protein coupled receptors. Today 18 classical chemokine receptors that signal by coupling to $G\alpha_i$ to promote cell migration are known. In addition, 4 atypical chemokine receptors that bind and scavenge chemokines to facilitate chemokine gradient formation in a G protein-independent manner, are described.[3,4] Different subsets of immune cells express diverse repertoires of chemokine receptors, also depending on their differentiation or maturation status, enabling them to respond to appropriate ligands to mediate their individual functions. Thus, by temporally and spatially positioning immune cells, chemokines are essential for the development of the immune system, immune surveillance, immune priming, effector responses, as well as regulation of the immune system.[2] Chemokines and their receptors are best-described for their function in guiding directional cell migration.[5] Nevertheless, chemokines also mediate additional cellular responses that go beyond simply guiding directional migration, including cell-to-cell contacts, adhesion and arrest of immune cells, immune cell priming, survival, as well as effector responses, although these functions are often intimately associated with the positioning of the cells in vivo. These additional functions of chemokines in lymphocyte biology have not been investigated as thoroughly yet. In this review, we aim to outline the current knowledge on chemokine functions in lymphocyte biology beyond guiding directional migration.

Abbreviations: ADAP, adhesion and degranulation adapter protein; CalDAG-GEF1, calcium and DAG regulated GEF1; Cdc42, cell division cycle 42; DC, dendritic cell; DOCK2, dedicator of cytokinesis 2; GEF, guanidine nucleotide exchange factor; HEV, high endothelial venules; IS, immunological synapse; LN, lymph node; LPAM-1, lymphocyte peyer's patch adhesion molecule-1; MAdCAM-1, mucosal addressin cell adhesion molecule-1; mLN, mesenteric lymph node; PKC, protein kinase C; PLC, phospholipase C; pLN, peripheral lymph node; PPs, Peyer's patches; Rac1, Ras-related C3 botulinum toxin substrate 1; Rap1, Ras-proximate 1; RAPL, regulator of cell adhesion and proliferation enriched in lymphoid tissue; RIAM, Rap1-GTP interacting adapter molecule; SKAP55, Src kinase associated protein of 55 kDa; SLP76, SH2 domain-containing leukocyte phosphoprotein of 76 kDa

Received: 14 December 2017 | Revised: 8 March 2018 | Accepted: 12 March 2018

TABLE 1 Chemokines and their receptors described to mediate inside-signaling to integrins on lymphocytes

Receptor	Chemokine	Cell type	Integrins	References
CCR1	CCL3, CCL5	T cells, B cells, pre-B cells	$\alpha_L\beta_2, \alpha_4\beta_1, \alpha_4\beta_7$	14,15,40,163
CCR4	CCL17, CCL22	Memory CD4+ T cells	$\alpha_L\beta_2$	31
CCR5	CCL4	Anti-CD3 activated T cells	$\alpha_L\beta_2, \alpha_4\beta_1$	14
CCR6	CCL20	Memory CD4+ T cells, T cells, B cells	$\alpha_L\beta_2, \alpha_4\beta_7$	16,18,40,164
CCR7	CCL19, CCL21	Circulating lymphocytes, T cells, PBLs	$\alpha_L\beta_2, \alpha_4\beta_1, \alpha_4\beta_7$	16,18,28,40,75,165
CCR8	CCL18	Th2 cells	$\alpha_L\beta_2$	20
CCR9	CCL25	Thymocytes, T cells, B cells	$\alpha_4\beta_1, \alpha_4\beta_7$	19,40
CXCR1	CXCL8	Pre-B cells	$\alpha_4\beta_1$	166
CXCR3	CXCL9, CXCL10	T cells, B cells	$\alpha_4\beta_1, \alpha_4\beta_7$	14,40,167
CXCR4	CXCL12	Naïve CD4+ T cells, memory CD4+ T cells, T cells, PBLs	$\alpha_L\beta_2, \alpha_4\beta_1, \alpha_4\beta_7$	16,22,40,43,75,168
CXCR5	CXCL13	B cells	$\alpha_L\beta_2$	21
CX3CR1	CX3CL1	T cells, NK cells		169

2 | MODULATION OF LYMPHOCYTE ADHESION BY CHEMOKINES

Chemokine functions are not limited to transmit signals leading to directional migration of lymphocytes, but they additionally initiate cell-to-cell contacts and adhesion by inducing inside-out signaling to integrins.[6,7] Integrin-mediated adhesion of lymphocytes is on the one hand important for integrin-dependent cell migration and extravasation into tissues, but on the other hand also controls the arrest of patrolling cells. Examples are lymphocyte adhesion to endothelial cells, lymphocyte-dendritic cell (DC)/stroma interactions to facilitate lymphocyte priming, and effector functions like CTL-target cell interaction for cytotoxic killing.[7–10]

Integrins are type 1 transmembrane proteins that form heterodimers consisting of one α and one β chain, which are noncovalently associated. In mammals, 18 different α and 8 β chains, forming about 24 distinct $\alpha\beta$ pairs are described.[8] Integrins consist of a large extracellular domain and a small, although functionally essential, intracellular domain.[11] The intracellular domain of integrins is vital for $\alpha\beta$ heterodimer formation, binding of signaling molecules, and for regulation of integrin endocytosis and recycling. On the surface of lymphocytes, integrins are normally inactive in a cell's resting state, however, they undergo dynamic changes in their adhesive properties after stimulation of either lymphocyte Ag receptors, or chemokine receptors.[8] One exception from this are effector lymphocytes, which were shown to express constitutively active integrins and are thus able to adhere to, for example, inflamed endothelial cells without chemokine signaling.[12] To allow a very dynamic regulation of ligand binding properties, the total affinity (avidity) of integrins to their ligands can be modulated in two ways, by regulation of affinity of the single integrin (conformation) and by clustering of integrins (valency).[13] Moreover, two directions of signaling, inside-out and outside-in, further increase the regulatory properties of integrins.[8,9] Ligand binding to integrins initiates outside-in signaling that controls, for example, the morphology and differentiation of cells. Whereas inside-out signaling describes the ability of other signaling receptors, mainly Ag receptors and chemokine receptors on lymphocytes, to induce changes in affinity and valency of integrins.[8,9]

2.1 | Lymphocyte integrins and their ligands

Lymphocytes express primarily the integrins $\alpha_4\beta_1$ (CD49d/CD29, VLA-4), $\alpha_L\beta_2$ (CD11a/CD18, LFA-1), and $\alpha_4\beta_7$ (lymphocyte peyer's patch adhesion molecule (LPAM)-1),[14–21] and many chemokines were shown to initiate inside-out signaling to one or several integrins, including CCL19, CCL21, and CXCL12 (Table 1). The three major lymphocyte integrins bind to different ligands: $\alpha_L\beta_2$ binds ICAM-1/2/3, $\alpha_4\beta_1$ binds VCAM-1, whereas $\alpha_4\beta_7$ binds both, VCAM-1 and mucosal peyer's patch adhesion molecule (MAdCAM)-1. Depending on the site of expression of their ligands, integrins are involved in diverse biological functions and the cell–cell contacts they control are important in diverse processes, such as rolling and firm arrest on endothelium within distinct tissues, as well as formation of an immunological synapse (IS).[8,13,22–24] The integrin ligands ICAM-1 and VCAM-1, for example, are expressed on high endothelial venules (HEVs) of peripheral lymph nodes (pLNs) or on inflamed, activated endothelial cells.[13] Here, chemokine-mediated signaling to $\alpha_L\beta_2$ and $\alpha_4\beta_1$ is important for the arrest of lymphocytes on HEVs to enter LN, or for effector lymphocytes to enter inflamed tissues, respectively.[8] In contrast, MAdCAM-1 is expressed on endothelia of mucosal tissue and the GALT, for example, HEVs of peyer's patches (PPs) and mesenteric lymph nodes (mLNs), to control arrest of lymphocytes at these sites.[25,26] Furthermore, besides the differences in integrin ligands, distinct tissues display different chemokines immobilized on their surface. For instance, pLNs present immobilized CCL21 and CXCL12, whereas mLNs and PPs in addition have CXCL13 immobilized on their surface.[25] Moreover, different subsets of lymphocytes express various sets of chemokine receptors. For example, naïve T cells express CCR7 and CXCR4, whereby naïve B cells express high levels of CXCR5 in addition to CCR7 and CXCR4.[27] To adhere to HEVs of pLNs and mLNs T cells rely on CCR7 and partially on CXCR4, whereby arrest of B cells is driven by CCR7 and CXCR4 on HEVs of pLNs or CXCR5

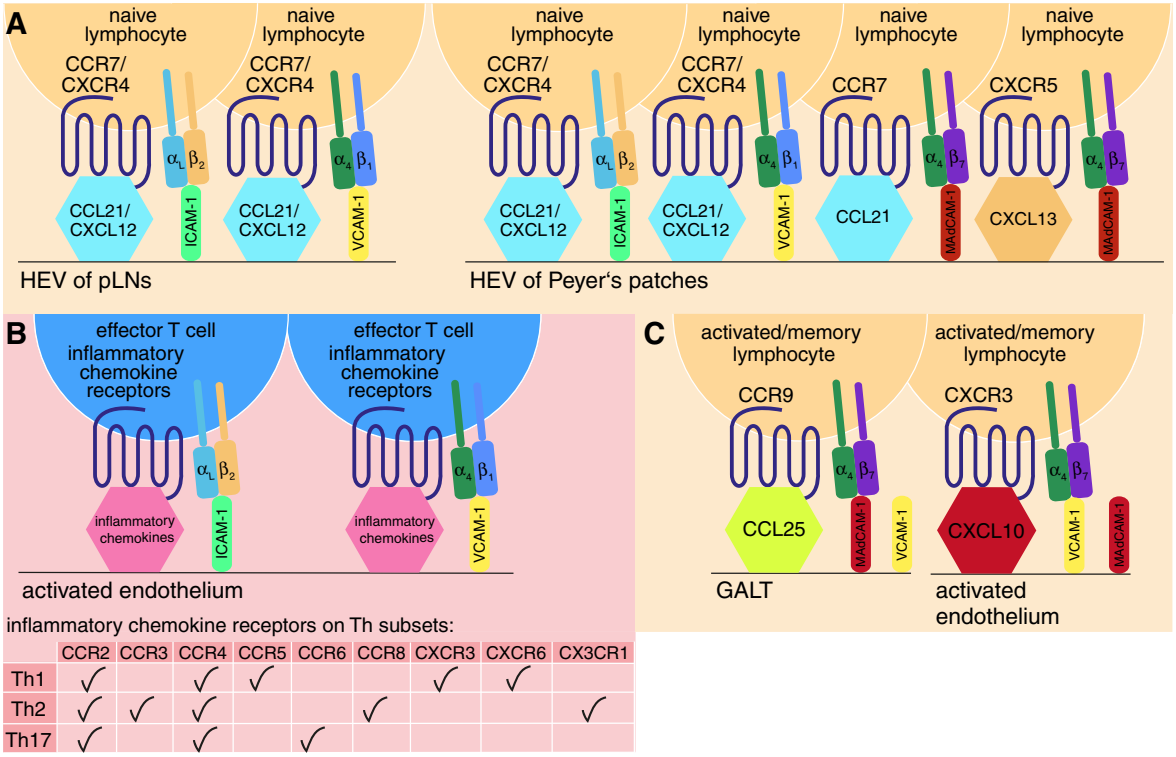

FIGURE 1 **Distinct patterns of integrins and chemokine receptors determine lymphocyte trafficking.** (A) Naïve lymphocytes expressing CCR7, CXCR4, $\alpha_L\beta_2$, and $\alpha_4\beta_1$ arrest on ICAM-1 or VCAM-1 of HEVs in pLNs or PPs in a CCL21- and CXCL12-dependent manner. Naïve lymphocytes can also utilize CCL21-CCR7 induced, or CXCL13-CXCR5 induced inside-out signaling to adhere to the $\alpha_4\beta_7$ ligand MAdCAM-1 on HEVs of PPs. (B) Effector T cells expressing inflammatory chemokine receptors arrest on integrin ligands of the activated endothelium. Expression patterns of inflammatory chemokine receptors on distinct Th subsets are depicted as a chart. (C) Activated/memory lymphocytes can adhere to either MAdCAM-1 of GALT or VCAM-1 of the activated endothelium mediated by $\alpha_4\beta_7$, depending on whether inside-out signaling is activated by the CCL25-CCR9 axis or by CXCL10 triggered CXCR3

together with CCR7 and CXCR4 on HEVs of PPs.[18,28,29] Moreover, the LFA-1 mediated arrest of naïve T cells and B cells on ICAM-1 can be induced on HEVs of pLNs by the chemokines CCL21 and CXCL12, but not by inflammatory chemokines, as naïve lymphocytes lack the expression of inflammatory chemokine receptors.[16] Consequently, naïve T and B cells do not enter inflamed tissues, but home to LNs (Fig. 1A). In contrast, Th1, Th2, and Th17 effector T cells that express $\alpha_L\beta_2$ or $\alpha_4\beta_1$ together with receptors for inflammatory chemokines, adhere to ICAM-1 or VCAM-1 within inflamed tissues. While the different Th effector T cell subsets have some chemokine receptors in common, for example, CCR2 and CCR4, several chemokine receptors are characteristically expressed by distinct effector Th subsets, coordinating the guidance of Th effector T cells to specific sites to mediate their specific functions in the inflamed tissues (Fig. 1B).[2,16,30,31] Th1 cells express CCR5, CXCR3, and CXCR6, Th2 cells express CCR3 and CCR8, whereas Th17 express CCR6.[2,32–39] Thus, the expression of different sets of chemokine receptors and integrins on lymphocytes, together with diverse patterns of integrin ligands and chemokines on endothelial cells, permits distinct lymphocyte subtypes to initiate locally confined integrin-mediated arrest, which in addition is regulated by environmental cues.

Interestingly, on a given cell type activation of the same integrin by different chemokine receptors can result in distinct integrin ligand binding, as exemplified for the lymphocyte integrin $\alpha_4\beta_7$ (Fig. 1C). Here, the CCL25-CCR9 axis leads lymphocytes to adhere to MAdCAM-1, whereas the CXCL10-CXCR3 axis facilitates their arrest on VCAM-1.[40] The different capabilities are attributed to distinct inside-out signaling by the two chemokine receptors. Thereby, CCR9 signals via PKC-α and p38 to talin, whereas CXCR3 signals through Src and Syk to recruit both talin and kindlin-3 to $\alpha_4\beta_7$.[40] Consequently, the same integrin, activated by inside-out signaling pathways of different chemokine receptors, controls lymphocyte trafficking by promoting firm adhesion and arrest at distinct tissues. Thus, the integrin $\alpha_4\beta_7$ on lymphocytes can bind either to VCAM-1 on activated endothelium, pLN and bone marrow, or to MAdCAM-1 found in mucosal tissues, GALT and mLN, depending on the chemokine receptor that initiated and specified the inside-out signaling pathway.

2.2 | Chemokine-mediated integrin activation in different environments

The mode of activation of integrins on lymphocytes differs depending on the environment a cell resides in. Under shear-flow conditions, for example, within blood vessels, integrins of rolling lymphocytes are rapidly (<1 s) activated by chemokine receptor triggering.[6,16,41–46] This fast integrin activation follows a 3-step model involving a bi-directional activation of ligand-bound integrins. The first step is initiated by inside-out signaling of chemokine receptors resulting in talin binding to the cytoplasmic tail of the integrin and subsequent integrin

extension. The next step involves ligand binding and results in integrin headpiece opening. In the last step, full integrin activation is achieved by the association of the actin cytoskeleton to the integrin tail through talin and kindlin-3.[6] Notably, this rapid integrin activation occurs under shear-flow and hence relies on immobilized chemokines, such as CCL21.[41,47,48] Under shear-free conditions, for example, within LNs, also soluble chemokines, including CCL19 that cannot trigger integrin signaling under shear-flow conditions, are able to trigger high-affinity integrin conformations,[47] but integrin activation is much slower and takes 10–30 min.[45]

Rapid integrin activation is best illustrated for LN homing of lymphocytes. Here, T cell rolling mediated by selectins is enhanced on the luminal surface of HEVs, where CCL21 is immobilized on glycosaminoglycans,[49] resulting in a CCR7 signaling-driven initiation of firm arrest[28] controlled by binding of high-affinity $\alpha_L\beta_2$ to its ligand ICAM-1, a prerequisite for subsequent diapedesis.[50,51]

2.3 | Chemokine receptor inside-out signaling pathways

As elucidated above, integrin inside-out signaling pathways are distinct among various lymphocyte subsets and depend on the cellular context and on the integrin. In other words, signaling events that control integrin inside-out signaling are not universal but differ depending on the cell type, the integrin, the chemokine, and the chemokine receptor.[52,53] Although not all signaling pathways elicited by chemokine receptors mediating inside-out signaling to integrins have been itemized, some molecular details are well characterized, especially for CCR7 and CXCR4. Key signaling molecules in chemokine-mediated signaling to $\alpha_L\beta_2$ include Rap1, its guanidine nucleotide exchange factors (GEFs) RapGEF1 and CalDAG-GEF1, as well as talin, kindlin-3, PIP5Kγ87, and phospholipase C (PLC)[9,54–57] as described in more detail in the following paragraphs.

The arrest of non-activated lymphocytes on endothelial cells mediated by chemokine receptor inside-out signaling depends on Gα_i signaling[16,58–60] and its downstream effector PLC.[13,55] Downstream of PLC, CalDAG-GEF1[13,54,55,61] and the small GTPase Rap1 become activated in a Gα_i-dependent manner upon CCR7 and CXCR4 triggering to control both affinity regulation and clustering of the integrins $\alpha_L\beta_2$ and $\alpha_4\beta_1$.[57,62–65] Thereby, regulator of cell adhesion and proliferation enriched in lymphoid tissue (RAPL), through binding to Rap1-GTP, associates with the cytoplasmic tail of the integrin's α chain.[13,66,67] Furthermore, the Ste20-like serine/threonine kinase Mst1, a downstream effector of RAPL is needed for lymphocyte arrest under physiological flow conditions.[68,69]

Recently, another Rap1 GEF, namely RapGEF1, was found to be important for CXCR4 triggered inside-out signaling to $\alpha_L\beta_2$.[70] In this pathway, dynamin2 by involving RapGEF1 and FAK/Pyk2 is vital for CXCL12 induced clustering, but not affinity regulation, of $\alpha_L\beta_2$ on naïve CD4$^+$ T cells.[70] Moreover, the Rac/Rho-GEFs Vav1, SOS1, and DOCK2 were shown to contribute to CXCR4-driven Rap1 activation for inside-out signaling.[71] However, residual chemokine-driven Rap1 activation was observed in DOCK2 deficient T and B cells, and DOCK2 was dispensable for CCR7 and CXCR4-mediated inside-out signaling to $\alpha_L\beta_2$ and $\alpha_4\beta_1$ in T cells, but not for CCR7, CXCR4, and CXCR5-mediated inside-out signaling to $\alpha_L\beta_2$, $\alpha_4\beta_1$, and $\alpha_4\beta_7$ in B cells.[72]

Furthermore, the small GTPases RhoA and Rac1 and their downstream effector phosphatidylinositol-4-phosphate 5 kinase are involved in chemokine-mediated integrin affinity regulation and adhesion of T cells under shear flow,[53,73,74] whereas Cdc42 fulfills an inhibitory function in chemokine-driven integrin activation.[73]

An additional layer of regulation comes from common and distinct chemokine receptor pathways exploited for inside-out signaling to specific integrins. For example, CXCR4-driven T cell adhesion relies on CalDAG-GEF1 and Rap1 to signal to $\alpha_L\beta_2$,[55] while $\alpha_4\beta_1$-mediated T cell arrest involves PKC[55] and the non-receptor tyrosine kinase ZAP70.[75] Notably, ZAP70 acts downstream of both CXCR4 and CCR7 and phosphorylates Vav1, thereby liberating talin required for its association with β_1 integrins resulting in the high-affinity conformation of $\alpha_4\beta_1$.[75–77] Whether ZAP70 is also involved in CCR7 and CXCR4-mediated inside-out signaling to $\alpha_L\beta_2$ integrins remains to be determined.

2.4 | Detailed pathways of integrin inside-out signaling by CCR7 in lymphocytes

CCR7 is expressed on several subsets of lymphocytes: on thymocytes during defined stages of development, on regulatory T cells, central memory T cells, as well as on naïve T cells and B cells.[78] CCR7-induced inside-out signaling modulates both, affinity and valency of $\alpha_L\beta_2$ as well as $\alpha_4\beta_1$ and $\alpha_4\beta_7$ in multiple ways (Fig. 2). To recapitulate, activation of $\alpha_L\beta_2$ is solely achieved by immobilized CCL21, but not soluble CCL19, to promote lymphocyte arrest in the presence of shear forces and happens in a part of a second.[41,45–47] In the absence of shear forces, both CCR7 ligands are able to enhance the affinity of $\alpha_L\beta_2$.[8,16,47,48,79] PI3K was one of the first signaling molecules identified in the CCR7 pathway mediating inside-out signaling to $\alpha_L\beta_2$ in a G protein-dependent manner. In fact, inhibition of PI3K blocked CCR7-mediated clustering of $\alpha_L\beta_2$, while affinity regulation remained intact, irrespective whether cells were exposed to shear forces or not.[48] Notably, PI3K was critical for CCR7-driven arrest under limiting availability of the $\alpha_L\beta_2$ ligand ICAM-1, whereas cell adhesion was normal at high ligand density.[48] Alternatively, CCR7 engagement modulates $\alpha_L\beta_2$ valency and affinity regulation through RhoA.[74] In addition, valency regulation of $\alpha_L\beta_2$ can be mediated by PKCζ[13,74] (Fig. 2). Interestingly, two distinct active Rap1 (Rap1-GTP) containing signaling complexes were recently identified to control CCR7-mediated affinity and valency regulation of $\alpha_L\beta_2$.[80] Whereas both signaling complexes share the kinase Mst1 and the adapter proteins adhesion and degranulation adapter protein (ADAP) and SKAP55, one complex further includes RAPL, the other complex comprises Rap1-GTP interacting adapter molecule (RIAM), talin, and kindlin-3 (Fig. 2). Interestingly, both signaling complexes are independently recruited to the integrin upon CCR7 triggering and lymphocytes lacking ADAP and SKAP55 show a delayed LN homing and reduced intranodal motility.[80] This study is supported by previous findings showing that RAPL and Mst1 contribute to CCR7-mediated $\alpha_L\beta_2$ clustering.[68] Thereby, RAPL not only regulates the association of Rap1 with the

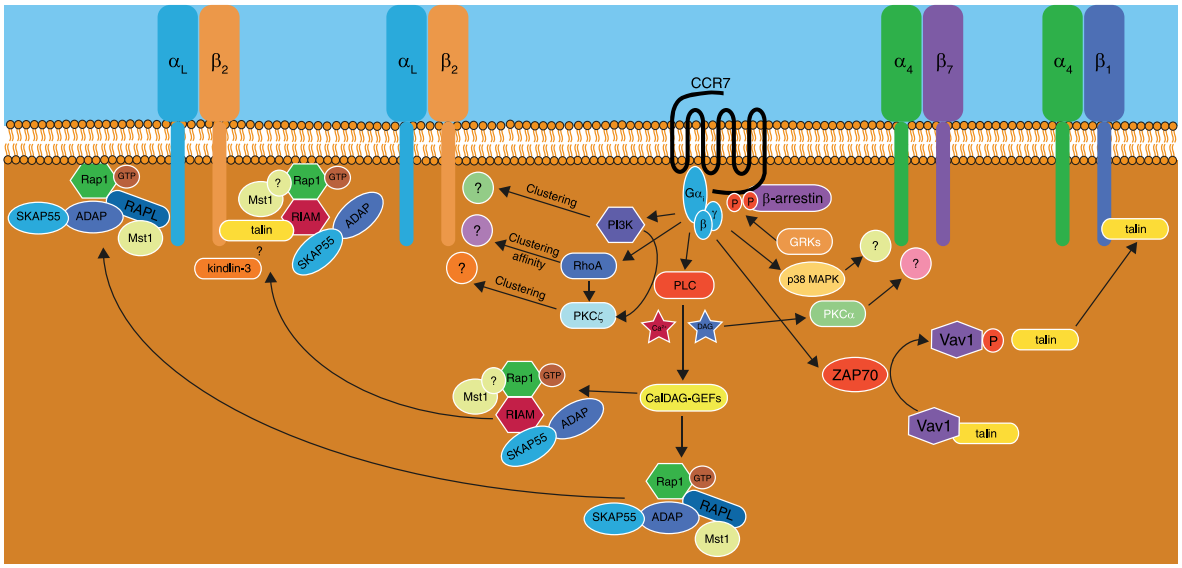

FIGURE 2 **Signaling pathways of CCR7 inside-out signaling to the three main lymphocyte integrins.** For inside-out signaling of CCR7 to $\alpha_L\beta_2$ signaling via PI3K and PKCζ induces clustering, but not affinity regulation, whereas RhoA is involved in both, affinity regulation and clustering of $\alpha_L\beta_2$. Moreover, a pathway is described involving PLC and CalDAG-GEFs leading to activation of Rap1 that forms two distinct complexes with its downstream-effectors, mediating inside-out signaling of CCR7 to $\alpha_L\beta_2$. CCR7 inside-out signaling to $\alpha_4\beta_1$ involves a pathway depending on ZAP70 that phosphorylates Vav1, leading to dissociation of the Vav1-talin complex, allowing talin to bind to the β_1 intracellular domain. Inside-out signaling of CCR7 to $\alpha_4\beta_7$ involves PKCα and p38 MAPK

α-chain of $\alpha_L\beta_2$,[13,66,81] it also regulates the subcellular localization and the kinase activity of Mst1.[13] In line with this, Mst1-deficient lymphocytes barely adhere to ICAM-1 under shear flow and are impaired in LN homing.[13,69,82] Based on these results, a two-step model has been proposed[80] in which ligand binding to CCR7 results in the activation of Rap1. Active Rap1-GTP is able to bind to ADAP/SKAP via RIAM, which links Rap1 with the actin cytoskeleton and promotes the recruitment of the RAP1/RIAM/ADAP/SKAP55-complex to the intracellular domain of the β_2 integrin chain. In the second step, the membrane-associated complex comprising RAP1/RIAM/ADAP/SKAP55 facilitates the binding of talin to the β_2 integrin chain, linking the integrin to the actin cytoskeleton that allows its activation. The second, Rap1/RAPL/ADAP/SKAP55-consisting complex, through RAPL, might preferentially interacts with the integrin α chain to control CCR7-mediated inside-out signaling to $\alpha_L\beta_2$.

Considerably less is known about how CCR7 controls inside-out signaling to α_4 integrins. However, PKCα and p38 MAPK are phosphorylated after CCL21 stimulation of T and B cells, increasing $\alpha_4\beta_7$-dependent arrest on VCAM-1.[40] CCR7 signaling to $\alpha_4\beta_1$ depends on Vav1 and talin as described above for CXCR4. Basically, binding of CCL21 to CCR7 induces the dissociation of the Vav1-talin heterodimer, thereupon liberated talin directly associates with the β_1 chain to initiating $\alpha_4\beta_1$ inside-out signaling.[75]

3 | CHEMOKINE RECEPTORS AS CO-STIMULATORY MOLECULES FOR EFFICIENT T CELL PRIMING

Upon entering the LN, T cells crawl along a network of fibroblastic reticular cells in a random walk-like manner depending on chemokine receptors and $\alpha_L\beta_2$ integrin to scan DCs for cognate Ags.[10,51,83–86] On the search for cognate Ags naïve T cells scan about 100 DCs per hour.[87] When a T cell recognizes a peptide presented in the context of MHC and co-stimulatory molecules on a DC, T cells interrupt their migration path to form an IS with the DC, resulting in T cell activation, proliferation, and differentiation.[88,89] The outcome of T cell activation depends on the context of Ag recognition and is largely controlled by various co-stimulatory molecules.

Distinct co-stimulatory activities have been attributed to the chemokines CCL5, CCL19, CCL21, and CXCL12.[90–97] T cell co-stimulation via TCR and CXCR4 was shown to enhance the expression of the activation markers CD69, CD25, and CD154 to increase T cell proliferation, as well as to augment the production of the cytokines IL-2, IFN-γ, IL-4, and IL-10.[90–92] CXCR4-driven IL-10 and IL-2 secretion was further noted to enhance activation of the transcription factor AP-1.[92] Similarly, co-stimulation of T cells with CCR7 ligands, where CCL21 shows stronger effects compared to CCL19, resulted in increased cell proliferation, higher expression of CD69 and CD25, and enhanced secretion of IL-2, TNF-α, and IFN-γ.[93,94] It needs to be mentioned that addition of high concentrations of CCR7 ligands (2.5 μM) to T cell cultures was found to arrest the cell cycle and to hamper cell proliferation and IL-2 production.[98] Molecular mechanisms that underlie the co-stimulatory activity are only vaguely understood.

Several suggestions were made to explain the co-stimulatory role of chemokines in T cells. The most advanced is the "stop and go" hypothesis.[99] This hypothesis describes that during the formation of T cell–DC conjugates the strength of two opposed signals, a migratory one driven by chemokine receptors, and a "stop" signal transduced by the TCR, is decisive for the duration of the interaction.[99,100] Thus, the stability of T cell-APC conjugates is regulated on the one hand by the affinity of the MHC-peptide-TCR interaction and on the other

hand by the effectiveness of chemokine receptor signaling.[101] Some chemokines owing co-stimulatory functions, including CCL5, CCL19, and CXCL12, can be produced by APCs themselves.[91,101,102] Accordingly, interfering with chemokine secretion by APCs dampened the co-stimulatory function of chemokine receptors as manifested by reduced IFN-γ production by T cells.[91,101] Moreover, localization of CCR5 and CXCR4 at the IS and exposure to their ligands presented by APCs might desensitize the chemokine receptor signal and stabilize the contact site.[91] In line with this, interfering with G protein-dependent CXCR4 and JAK1/2 signaling correlated with reduced actin polymerization at the contact site, altered structure of the IS, and mislocalization of the microtubule-organizing center.[95]

CXCR4 directly interacts with the TCR, allowing CXCR4 to utilize the ITAMs of TCR to signal through ZAP70.[92] CXCR4 and TCR co-stimulation also stabilizes SLP76 cluster formation facilitating its phosphorylation by ZAP70.[96] CCR7 and TCR co-stimulation, by a pathway involving DOCK2 and Rac increases Erk1/2 phosphorylation and IL-2 secretion.[94] Notably, the threshold for T cell activation is reduced if cells experienced CCL21 during the first hours of TCR stimulation and might be a mechanism to promote T cell activation within appropriate micro-anatomical compartments.[94] Apart from that, CCL21 on APCs is proposed to activate CCR7 on the T cell to form a transient tether rendering the cell hyper-responsive to Ags.[97] This tether formation is also attributed to CXCR3-CXCL10, CXCR4-CXCL12, and CCR5-CCL5 and additionally involves $\alpha_L\beta_2$-intergin/ICAM-1 at T cell-APC interface.[97]

3.1 | Integrins in chemokine-mediated T cell co-stimulation

Besides acting as co-stimulatory molecules themselves, chemokine receptors are also able to fulfill a co-stimulatory function indirectly by increasing the avidity of integrins to their ligands, thereby supporting the cell–cell contact between the T cell and the APC.[91,103,104] However, the signal for increased avidity of integrins might not be induced by the chemokine receptors alone, but in concert with the TCR during IS formation.[91,104]

A critical role in the formation of an IS between a naïve T cell and a DC has been attributed to $\alpha_L\beta_2$ and ICAM-1. Micro-clustering and affinity regulation of $\alpha_L\beta_2$ are vital for effective signaling at the IS. The head of activated, unbend, high-affinity $\alpha_L\beta_2$ is 25 nm away from the membrane compared to 5 nm of the "bent" inactive conformation of the integrin,[105] hence, the conformation of $\alpha_L\beta_2$ might not only strengthen the cell-to-cell-contact at the synapse, but also controls the intercellular space to ease TCR-MHC/peptide interactions.[7,106] In this scenario, CCR7-mediated $\alpha_L\beta_2$ activation at the IS would contribute to efficient T cell priming.[7]

4 | REGULATION OF T CELL HOMEOSTASIS AND SURVIVAL BY CHEMOKINES

Besides supporting activation, chemokines also promote survival of T cells.[107] Stimulation of CD4$^+$ T cells with CXCL12 results in enhanced cell survival in a PI3K-and MAPK-dependent manner to increase the expression of genes associated with cell survival while simultaneously pro-apoptotic factors are posttranscriptionally inactivated.[107] Similarly, CCR7 signaling protects CD8$^+$ T cells from apoptosis.[108] Moreover, CCL19 has a key function in naïve T cell homeostasis by its anti-apoptotic function[109] whereas CCL21 has been shown to regulate naïve T cell proliferation.[110] The precise mechanisms have not been investigated in detail.

5 | CHEMOKINES ORCHESTRATE T CELL DIFFERENTIATION

Chemokines can orchestrate the differentiation of effector T cells and thereby shape immune responses basically in 2 ways: by acting directly on T cells or indirectly by acting on DCs to influence their maturation and cytokine secretion pattern[111–116] (Fig. 3). The effect of chemokines on T cell-mediated immunity and on the differentiation of Th subsets has previously been reviewed for the CCL2-CCR2 and CCL3-CCR5 axis[111] and for CCL2, CCL3, CCL19, and CCL21.[112] Here, we therefore provide a short summary and an update on recent advances.

T helper cell differentiation starts when naïve CD4$^+$ T cells interact with DCs in lymphoid organs and is, especially during the early stages, driven by cytokines.[117] The cytokines IL-12 and IFN-γ are well known to shift differentiation towards Th1 cells required for cellular immunity against intracellular pathogens and to contribute to inflammatory diseases, whereas IL-4 is a major driver for Th2 cell differentiation playing important roles in humoral immunity and allergic reactions.[117,118] Th17 cells contribute to effective host-defense against bacteria and fungi, as well as to the pathology of inflammatory diseases and the development of autoimmune diseases and their differentiation is more complex and mediated by multiple cytokines including IL-6, IL-1β, TGF-β, and IL-23.[117–120]

CCL3 was the first chemokine shown to modulate Th cell differentiation. Karpus et al. have shown that stimulation of the TCR in presence of CCL3 resulted in increased IFN-γ production.[115] Subsequently, CCL4 and CCL5 were found to own Th1 polarizing activity.[121] Moreover, several other chemokines, including CCL21, CXCL12, and CX3CL1 were found to promote Th1 polarization, mainly by triggering IFN-γ production.[92,93,122] While there has been conflicting results on the role of Th2 cell differentiation, substantial evidence emerged that CCL2 and its receptor CCR2 are important for Th1 differentiation as discussed elsewhere.[111,112] Whether that is a direct effect of CCL2–CCR2 signaling in DCs or T cells as opposed to influencing immune cell composition in the priming LN or cell positioning within the LN is currently not clear.

The IFN-γ-inducible chemokines CXCL9 and CXCL10 by triggering CXCR3 induce Th1 polarization through STAT1/4/5, whereas CXCL11, by binding to the same receptor, drives the differentiation of IL-10 producing regulatory Tr1 (IL-10 producing regulatory T cells) and IL-4 producing Th2 cells through STAT3/6 and p70 kinase/mTOR.[123–125] Notably, CXCL11 not only promotes the polarization of

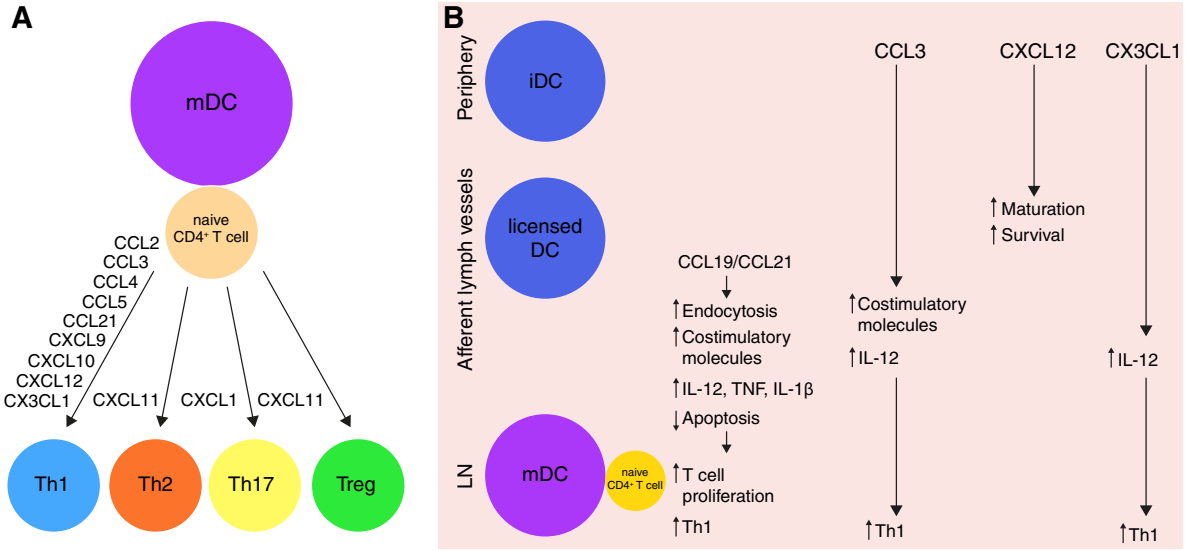

FIGURE 3 **Chemokines modulate the differentiation of Th cells.** (A) Direct effects of chemokines on Th cells. CCL2, CCL3, CCL4, CCL5, CCL21, CXCL9, CXCL10, CXCL12, and CX3CL1 promote Th1 differentiation when present during $CD4^+$ T cell-priming. CXCL1 promotes differentiation of Th17 cells, while CXCL11 supports Th2 polarization. In addition, CXCL11 drives polarization of regulatory T cell. (B) Indirect effects of chemokines on Th polarization by acting on DCs. The CCR7 ligands CCL19 and CCL21 increase endocytosis, expression of co-stimulatory molecules, IL-12, TNF and IL-1β production and decrease apoptosis of DCs to indirectly promote T cell proliferation and polarization of Th1 responses. CCL3 increases the expression of co-stimulatory molecules and IL-12 production supporting Th1 responses. CX3CL1 acts on DCs to promote Th1 differentiation by increasing IL-12 secretion

naïve T cells into regulatory T cells, this chemokine is in addition able to repolarize experimental autoimmune encephalomyelitis-associated effector cells into IL-10 producing regulatory T cells to dampen the autoimmune response.[124] Noteworthy, these effects are more pronounced in C57BL/6 mice which lack functional CXCL11, compared to SJL/J mice expressing functional CXCL11[124] implying that CXCL11 might only play a role in Th differentiation in certain settings.

CCR7 ligands indirectly promote Th17 polarization by inducing IL-23 induction in DCs through a PI3K and NF-κB signaling pathway.[126] Consequently, CCR7 knockout and *plt/plt* mice show reduced IL-17 production due to lower IL-23 production of DCs.[127] In contrast, CXCL1, the ligand of CXCR2, directly acted on $CD4^+$ T cells to augment Th17 differentiation and to enhance IL-17 production by an unknown pathway.[128]

6 | CHEMOKINES IN DENDRITIC CELL SURVIVAL AND MATURATION – INDIRECT ROLE FOR T CELLS

DCs are highly versatile APCs owing multiple functions in immunity and tolerance[129] that produce numerous chemokines[130] and express distinct patterns of chemokine receptors[131] depending on their maturation stage. Notably, by acting on DCs, chemokines indirectly impact T cell functions. The chemokines CCL19 and CCL21 are best known for DC guidance to LNs,[78] however, both CCR7 ligands can induce dendritic extensions[132] and enhance the endocytic capacities of DCs.[133] CCR7 ligands also act as survival signals through a PI3K/GSK3β/NF-κB pathway.[134,135] Simultaneously, CCR7-mediated Akt activation results in the phosphorylation and inhibition of the pro-apoptotic transcription factor FOXO1.[135] Moreover, CCL19 and CCL21 were found to be required for full maturation of TLR-activated DCs and CCR7 ligand experienced DCs secrete more IL-12, IL-1β, and TNF required for efficient T cell proliferation.[136]

Also the CXCR4 ligand CXCL12 was shown to promote DC maturation and survival[137] through Akt and subsequent phosphorylation and inhibition of the pro-apoptotic transcription factors FOXO1/3.[138] Furthermore, DCs exposed to CCL3 up-regulate the expression of the co-stimulatory molecules B7-1 and B7-2,[139] and CCL3 augments the secretion of IL-12 by DCs to mount an efficient antiviral Th1 response against mouse hepatitis virus infection.[140]

The chemokine CX3CL1 is unique in its property to be membrane-anchored and to act as adhesion molecule. Expression of CX3CL1 by tumor cells thereby allows DCs, by binding CX3CL1, to directly interact with tumor cells.[141] These CX3CL1-experienced DCs mature and produce IL-12 to enhance Th1 polarization.[141]

7 | CHEMOKINES REGULATE THE FUNCTION OF NATURAL KILLER CELLS

Lymphocytes not only comprise T and B cells, but also NK cells, cytotoxic lymphocytes of the innate immune system. NK cells can be quickly activated without priming and exert their function by directly killing their target cells or indirectly by secreting cytokines that shape the adaptive arm of the immune system.[142] Both functions of NK cells are influenced by chemokines.[143] The cytotoxic activity of NK cells was attributed to chemokine-driven re-distribution of adhesion molecules on their surface to facilitate interaction with the target cell.[144] In addition, CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CXCL10,

and CX3CL1 were shown to provoke the release of cytotoxic granules.[145–149] The chemokines CCL19, CCL20, and CCL21 were shown to augment IL-2-induced proliferation of NK cells,[150] whereas CXCL2 and CX3CL1 increased IFN-γ-secretion from activated NK cells resulting in Th1 polarization.[139,151]

Although NK cells per se do not require prior activation to fulfill effector functions, DCs are able to prime NK cells to enhance their efficiency.[152] In this process, CX3CL1 expressed by DCs can promote NK cell priming,[153] but the precise mechanisms remain to be determined.

8 | APPLICATION OF CHEMOKINES TO MODULATE IMMUNE RESPONSES

Due to their multifaceted functions that go much beyond guiding cell migration, chemokines, or chemokine-binders, could be used to deliberately shape the immune response as therapeutic option. Such strategies are successfully exploited by certain pathogens. One example is the parasitic protozoan *Toxoplasma gondii* that produces cyclophilin-18 mimicking a chemokine acting as agonist for CCR5.[113,154] Binding of cyclophilin-18 to CCR5 on DCs induces IL-12 production, promoting a Th1 response that is key for *T. gondii* to establish a persistent infection of the host and avoiding to overwhelm the host with too many parasites.[113,154] In contrast, ticks produce evasins, highly selective chemokine binding proteins, to neutralize pro-inflammatory chemokines to dampen the host's immune response.[155] One of these, evasin-4, has been modified for preclinical applications in inflammatory disease models.[156]

Chemokines are also useful to shape the immune response in cancer immunotherapies.[157] For instance, injection or ectopic expression of CCR7 ligands in cancer cells was used to target effector cells to the tumor for its eradication.[158,159] Alternatively, chemokines can also be used to modulate the properties of ex vivo-generated DCs that are loaded with tumor-associated Ags to induce tumor-specific immunity.[160,161] DCs transfected with CCL21 were shown to induce stronger antitumor immunity by increasing T cell proliferation, and by inducing a stronger cytotoxic T cell response acquainted with Th1 differentiation.[162]

9 | CONCLUDING REMARKS

Advances in the field clearly reveal that chemokines fulfill pleiotropic functions that go much beyond simply guiding cell migration. Chemokines additionally play an important role in lymphocyte adhesion and activation, in orchestrating lymphocyte differentiation, and in modulating their effector functions. Future studies are required to unravel the complex network of chemokine action. More detailed information is particularly needed on distinct signal transduction pathways orchestrating the multifaceted events elicited by distinct chemokines and their receptors.

AUTHORSHIP

J.M.L. and D.F.L. wrote the manuscript.

ACKNOWLEDGMENTS

This work is supported by the Swiss National Science Foundation [Grant 31003A_169936], the Thurgauische Stiftung für Wissenschaft und Forschung, and the State Secretariat for Education, Research and Innovation to D.F.L. J.M.L. is a recipient of a stipend from KoRS-CB.

DISCLOSURE

The authors declare no conflict of interest.

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How to cite this article: Laufer JM, Legler DF. Beyond migration—Chemokines in lymphocyte priming, differentiation and modulating effector functions. *J Leukoc Biol*. 2018;104:301–312. https://doi.org/10.1002/JLB.2MR1217-494R