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Chemokine-guided cell positioning in the lymph node orchestrates the generation of adaptive immune responses

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The generation of adaptive immune responses occurs in the lymph node (LN) and requires that lymphocytes locate and interact with cognate antigen-bearing dendritic cells. This process requires the coordinated movement of both innate and adaptive immune cells, and is orchestrated by the chemokine family of chemotactic cytokines. Upon initiation of inflammation, the LN undergoes dramatic changes that include the marked induction of specific chemokines in distinct regions of the reactive LN. These chemokine rich domains establish LN niches that facilitate the differentiation of CD4+ T cells into effector cell subsets and the rapid activation of memory CD8+ T cells. This review will focus on recent advances highlighting the importance of LN chemokines for shaping adaptive immune responses by controlling immune cell migration, positioning, and interactions in the reactive LN.

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Introduction

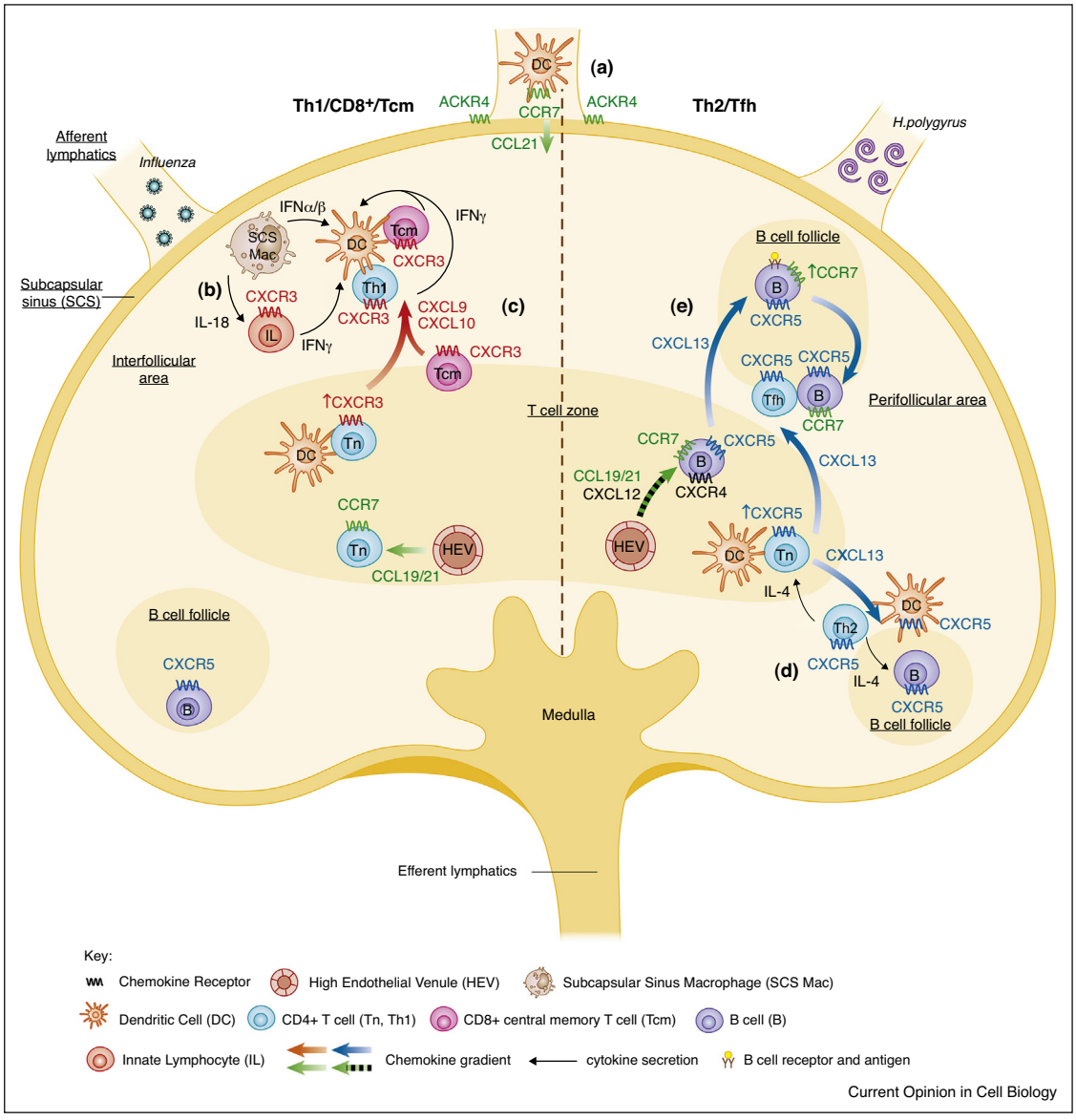
The generation of adaptive immune responses requires interactions between naïve lymphocytes and antigen-presenting cells (APCs). Naïve lymphocytes expressing the chemokine receptor CCR7 continuously migrate into lymph nodes (LNs) from the blood via specialized high endothelial venules (HEV), while antigen-bearing dendritic cells (DC), also expressing CCR7, carry antigen from the periphery into the LN via afferent lymphatics [1]. CC chemokine ligand 19 (CCL19) and CCL21 guide both cell types into the deep paracortex of the LN, where colocalization of these cells facilitates T cell scanning and early initiation of immune responses [2]. Upon the initiation of inflammation and the onset of the immune response, LNs undergo marked changes to their structure coinciding with dramatic changes in LN chemokine expression. This review will focus on recent studies that have identified the guidance cues that position both innate and adaptive immune cells in this highly dynamic environment that allow for the cellular interactions necessary for antigen-specific highly differentiated immune responses (Figure 1).

Innate immune response

The initiation of adaptive immunity to antigens in the tissue depends on DC expression of CCR7 for successful navigation into afferent lymphatics and into draining LNs. Soluble CCL19 in the tissue helps guide DC polarization and chemotaxis towards lymphatic vessels [3], although CCL19 is not absolutely required for DC migration into the LN, since CCL21 alone was sufficient to mediate this migration [4]. Experiments tracking DC behavior in mouse ear explants showed that DCs migrate using immobilized CCL21, a process called haptotaxis, to navigate the interstitial space and enter lymphatic vessels. CCL21 was immobilized in the tissue bound to heparan sulfate containing proteoglcyans, in a gradient directing DCs towards lymphatic vessels [5]. DCs continue their migration into afferent lymphatic vessels until arriving at the subcapsular sinus (SCS) of LN. Until recently, the mechanism by which DCs entered LNs was unclear. Ulvmar and colleagues showed that the atypical chemokine receptor ACKR4 (CCLR1) was expressed only on lymphatic endothelial cells comprising the ceiling and not the floor of the SCS [6•]. ACKR4 scavenging of CCL21 specifically by ceiling lymphatic endothelial cells is thus able to create a local gradient for CCL21-directed migration into the LN cortex.

Specialized macrophages reside just underneath the LN capsule in the SCS, acting as a filter for the LN and preventing the systemic spread of lymph-borne pathogens, while medullary macrophages play a crucial role in handling particulate antigens to promote B cell responses [7]. Experiments using a modified vaccinia virus infection demonstrated that several innate lymphoid effector cell populations (e.g., NK, NKT, γδ and innate-like CD8+ T cells) are prepositioned and accumulate near SCS macrophages, making them able to quickly respond to IL-18 released by infected macrophages by producing IFNγ [8••]. In addition, NK cell recruitment to inflamed

Figure 1



Chemokine-mediated cellular positioning in the reactive lymph node creates specialized niches to facilitate T cell differentiation and activation. **(a)** Antigen from the site of infection arrives via the afferent lymphatics in soluble form or carried by dendritic cells (DC). Atypical chemokine receptor 4 (ACKR4) expressed on ceiling lymphatic endothelial cells scavenges CCL21 and creates a localized gradient for DC entry into the draining lymph node (LN) via the floor of the subcapsular sinus (SCS). **(b)** Specialized macrophages are positioned within the subcapsular sinus (SCS Mac) and take up antigen, secreting inflammatory cytokines, such as IL-18 and type I interferons upon activation. Innate lymphocytes expressing CXCR3 are positioned near the SCS, responding to IL-18 and producing IFNγ upon activation. Type 1 and II IFNs induce the production of CXCL9 and CXCL10 by local stromal cells and DCs, attracting and priming CXCR3-expressing CD4+ T helper-type 1 (Th1) cells. CD8+ central memory T cells (Tcm) are prepositioned in the outermost region of the T cell zone or are preferentially recruited to these regions by their constitutive expression of CXCR3. **(c)** Naïve T cells (Tn) enter the LN via high endothelial cells (HEV) in the deep T cell zone. In response to a Th1-type inducing stimulus, such as influenza virus, Tn are initially primed by antigen-bearing DCs, become activated, and upregulate CXCR3 expression. CXCL9 and CXCL10 gradients direct priming CD4+ T cells and Tcm out of the T cell zone and towards peripheral regions of the LN. T cells localize to the interfollicular and medullary regions and interact with infected and activated antigen presenting cells (APCs), resulting in optimal Th1 differentiation and IFNγ production. **(d)** Newly activated naïve T cells respond to a Th2-type inducing stimulus, such as a parasite, by upregulating CXCR5 and migrating out of the T cell zone via a CXCL13 gradient into the perifollicular areas near B cell follicles. There they interact with DCs, which have also upregulated CXCR5 in response to a Th2-indcuing stimulus to generate a Th2 response. **(e)** Naïve B cells also enter the LN via HEV in chemokine-mediated process that is dependent on CXCR4 and CCR7 in a partially redundant manner. B cells are then recruited into the B cell follicle in response to CXCL13. Following B cell activation, B cells upregulate CCR7, which guide their movement the to the border of the follicle where they are in position to interact with T follicular helper cells (Tfh). Tfh cells express high levels of CXCR5 and are specialized to provide B cell help for class switching.
Figure was modified from Ref. [43].