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Review article

Lymph node macrophages: Scavengers, immune sentinels and trophic effectors

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ABSTRACT

Lymph nodes (LN) are secondary lymphoid organs dispersed throughout the body that filter lymph and assist the immune system in mounting immune responses. These functions are supported by a complex stromal microarchitecture composed of mesenchymal and vascular elements. Different subsets of macrophages (MΦ) reside in the LN and are endowed with immune and trophic functions. Here we review these different subsets with particular emphasis on the recently described T cell zone MΦ. We also address the potential crosstalk between LN stromal cells and MΦ, proposing that the former constitute niches for the latter by supplying factors required for their specification, survival and turnover. In turn, MΦ could inform their stromal partners about the immune status of the LN and orchestrate the remodelling of its microanatomy during immune responses.

Lymph nodes (LN) are secondary lymphoid organs located alongside the lymphatic vasculature that sample lymph borne antigens and act as key sites for the initiation of adaptive immune responses. They contain a stromal cell network whose sophisticated microarchitecture allows the discrete positioning of immune effectors, and thus constitute an efficient venue for immune surveillance [1]. LN are classically divided in four anatomical regions characterized by distinct hematopoietic cells and unique mesenchymal and vascular cells that provide them with structural support, survival factors, regulatory molecules and guidance cues. Afferent lymph enters into the subcapsular sinus (SCS) located just beneath the collagen-rich capsule. This sinus surrounds the superficial cortex which contains the B cell follicles, which are supported by the follicular dendritic cells (FDC). The paracortex corresponds to the T cell area populated and delineated by fibroblastic reticular cells (FRC). Finally, the medulla that contains large blood vessels and interconnected lymphatic sinuses serves as an exit zone for lymphocytes. Macrophages (MΦ) are present in all these regions (Fig. 1), where they exert unique immunological and trophic functions. We review here the different subsets of LN MΦ with a particular emphasis on the recently described population that resides inside the T cell area.

1. Macrophages residing in the lymph node sinuses

LN MΦ can be categorized according to their location: the sinus resident MΦ are in direct contact with the lymph while the parenchymal MΦ are found in the B follicles, T cell zone and medullary cords. Strategically positioned, the subcapsular sinus MΦ (SSM) and the medullary sinus MΦ (MSM) are equipped with multiple pattern recognition receptors that allow them to act as “fly-paper”, capable of capturing and retaining pathogens in a given LN, thereby preventing systemic infections [2]. MSM and SSM can be distinguished according to their location but also based on their phenotype that underlines their distinct ability to capture and clear lymph born particulates. MSM are highly phagocytic cells that efficiently clear different nanoparticles, bacteria or apoptotic cells. In contrast to SSM, they express F4/80 as well as the scavenger receptor MARCO, the Mannose Receptor (CD206) and SIGN-R1 (CD209b) that bind different pathogen-associated molecular patterns. MSM and SSM are also characterized by the expression of CD169, a type I lectin that binds sialic acid and supports adhesion to other leukocytes (Table 1). While SSM are able to capture particles, internalization and degradation seem to occur at a lower rate compared to MSM [3]. This could partly explain their differential susceptibility to viral infection. Whereas LCMV (lymphocytic choriomeningitis virus) efficiently infects both types of MΦ [4], VSV (vesicular stomatitis virus) replication is restricted to SSM [5]. This permissive state promotes a potent inflammatory response essential to coordinate the recruitment of immune effectors and prevent pathogen spreading [5,6]. Along the same line, vaccinia virus induces inflammasome activation in SSM leading to a robust influx of inflammatory cells and the mobilization of T cells from the circulation [7]. Different studies have also highlighted the ability of SSM to present antigen to naive lymphocytes. Dynamic intravital microscopy revealed that SSM induce iNKT activation by retaining, internalizing and presenting lipid antigens [8]. SSM also have the capacity to transfer immune complexes and surface bound viral particles from the

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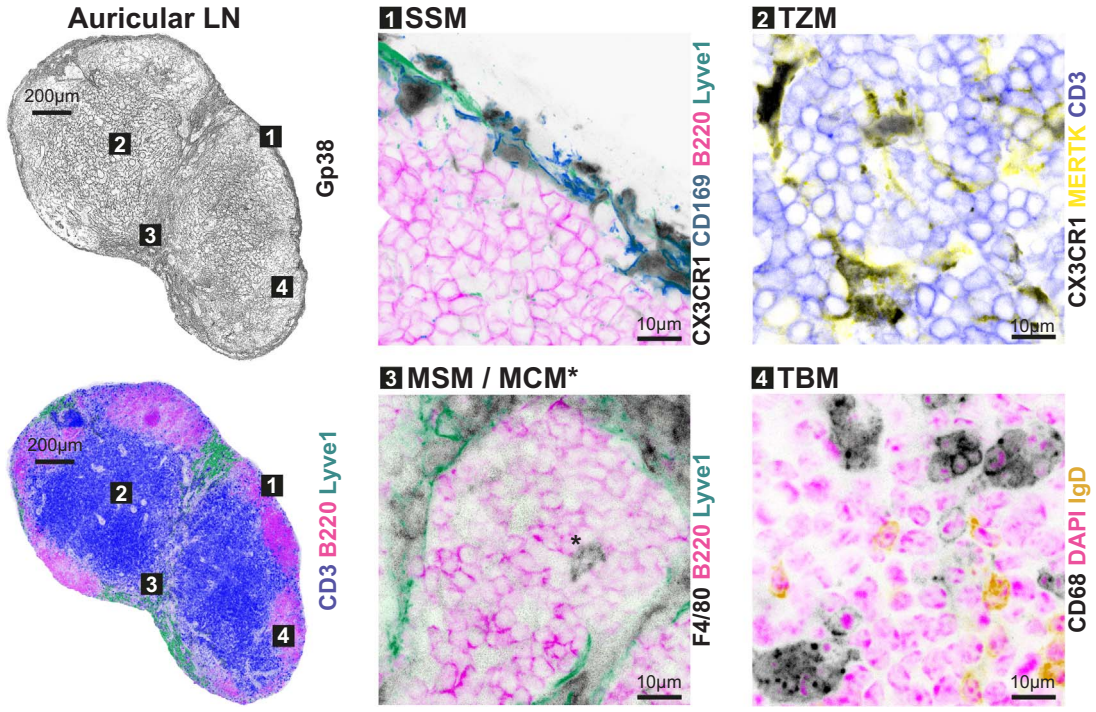

Fig. 1. Confocal microscopy images showing the structure of a LN and the different subsets of resident MΦ. Auricular LN sections were stained to demarcate the Gp38$^+$ stromal network (FRC and LEC, upper left panel) and with antibodies against B220, CD3 and Lyve1 to visualize respectively the B cell follicles, the T cell zone and the medulla (lower left panel). The MΦ subsets were identified by staining LN sections with different antibodies as indicated in the 4 panels on the right. CD169$^+$ CX3CR1$^+$ SSM (1) are located in the subcapsular sinus above the B follicles. MERTK$^+$ CX3CR1$^+$ TZM (2) are scattered in the T cell zone. F4/80$^+$ MSM and MCM (3) reside in the medullary sinuses and in the medullary cords, respectively. Highly phagocytosing CD68$^+$ TBM (4) are found in the germinal centres of reactive LN.

Table 1
Selected markers of LN macrophages.

Subset	Location	Markers
SSM	Subcapsular sinus	CD169$^+$ CX3CR1$^+$ F4/80$^-$
TZM	T cell zone	CD169$^-$ CX3CR1$^+$ MERTK$^+$ F4/80$^-$
TBM	Germinal centre	CX3CR1$^+$ MERTK$^+$ CD68$^+$
MSM	Medullary sinus	CD169$^+$ CX3CR1$^-$ F4/80$^+$ SIGN-R1$^+$ MARCO$^+$ MR (CD206)$^+$
MCM	Medullary cord	CD169$^-$ CX3CR1$^-$ F4/80$^+$

subcapsular sinus to the follicular B cells [6,9,10]. However, the contribution of this mode of antigen presentation to the antibody response or to the control of pathogens is not entirely clear and may depend on the insult. Early B cell activation, for instance, is impaired in response to VSV following SSM depletion [6] and the transient disappearance of the SSM layer after inflammation weakens B cell responses to a secondary infection [11]. Yet, in SSM depleted mice, neutralizing antibody production to VSV is eventually increased [5] and Moseman et al. showed that the protection against a fatal VSV infection is independent from adaptive immune response [12]. Similarly, SSM are important for limiting the spread of influenza virus, but are not key for the generation of a specific humoral response [13]. CD169$^+$ MΦ are also able to crosspresent tumor antigens to CD8$^+$ T cells after they phagocytose dead tumor cells transported via the lymphatic flow. Their depletion using mice expressing the diphtheria toxin (DT) receptor under the control of the *cd169* gene impairs tumor specific CD8$^+$ T cell activation and subsequent antitumor immunity [14]. As cell free antigens reach the subscapular sinus of the LN few hours before migratory DC arrive, SSM are ideally positioned to capture incoming material and act as early antigen presenting cells (APC). The medullary MΦ are also quickly exposed to free antigens flowing in the lymph, yet their APC capacity remains largely unexplored.

2. Macrophages residing in the lymph node parenchyma

Besides lymph bathed SSM and MSM, MΦ are also positioned in the LN parenchymal structures that emerge upon immunisation. Tingible body MΦ (TBM) are located in the germinal centre (GC) of reactive LN and are easily recognizable by their morphology [15]. They harbour numerous vesicles containing apoptotic cells in various states of degradation. This phagocytic ability largely depends on the mer receptor tyrosine kinase (MERTK), since its deficiency induces prolonged accumulation of apoptotic B cells in splenic GC, leading to autoimmune symptoms [16]. An additional MΦ subset populates the parenchyma adjacent to the medullary sinuses known as medullary cords [17]. These structures develop during an immune response when the medulla massively enlarges. The medullary cord MΦ (MCM) express F4/80 but not CD169, in contrast to their sinus counterparts (Table 1). The morphological features, the enzymes they produce and the nature of apoptotic cells they engulf are additional distinguishing features of the two medullary MΦ subsets. For instance, after gastrointestinal inflammation, MSM in rat LN contain apoptotic polymorphonuclear cells such as eosinophils and stain strongly for acid phosphatase. In contrast, MCM stain weakly for acid phosphatase but strongly for non-specific