COMMENTARY

Sophisticated Strategies for Information Encounter in the Lymph Node

The Reticular Network as a Conduit of Soluble Information and a Highway for Cell Traffic

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The lymph node is the crossroad in which soluble signals and cells carried by lymph meet lymphocytes emigrating from blood. Efficient interactions among these elements depend on the reticular network, which comprises reticular fibers, related extracellular matrix components, and associated fibroblastic reticular cells. This network provides a three-dimensional scaffold for attachment of APCs and pathways for the migration of T cells to these APCs. In addition, the network constitutes a miniature conduit system for bulk flow delivery of soluble molecules to distinct sites in the paracortex, particularly the high endothelial venule. The delivered mediators, such as chemokines, regulate the phenotype of the high endothelial venule, the recruitment of lymphocytes, and the behavior of the recruited lymphocytes. Thus, the reticular network is a multifunctional infrastructure that facilitates encounters of cells with other cells and factors necessary for effective and efficient immune surveillance. ***The Journal of Immunology,*** **1996, 157: 495–499.**

The extraordinary progress in molecular biology has shifted much of the emphasis in biology from organ systems to the subcellular level. However, the newly acquired understanding of dynamic molecular events triggering activation and expression of gene products has now made it possible to form more complete images of in vivo function. In vitro experiments have elucidated many of the principles in activation of T and B cells. Nevertheless, the extraordinary efficiency of immune responses depends on higher level orchestration that occurs in vivo. Secondary lymphoid tissues are not simply a system to filter lymph (or blood, in the case of the spleen), but rather play a central role in this orchestration. Therefore, the time has come to review the unique cellular organization, compartmentalization, and structure that make up an organ system that only as an integrated whole performs its complex functions. This brief review focuses on the lymph node (LN)[2] as a remarkably sophisticated point of convergence of essential elements of the immune response. Such elements brought in by afferent lymph include: Ag-bearing cells, soluble factors, cellfree Ags, and lymphocytes returning from tissues (1–4). Concurrently, large numbers of recirculating lymphocytes enter the LN from the blood (3). The organized convergence of these elements and the subsequent transfer of information between them are highly dependent on the molecular and cellular architecture of the LN.

Because of the very low number of T cells specific for any given Ag, initiation of a primary immune response requires that many T cells have access to Ag on an appropriate APC. Such responses occur in vivo primarily in lymphoid tissue (5–7). How does the LN make this possible? One could envision a simple arrangement in which incoming lymph and recruited lymphocytes meet and mix in a fluid-filled cavity. In reality, the arrangement is far more elegant and efficient. The LN provides: 1) highways with huge surface area to facilitate migration, 2) structured environments to foster interactions between particular cell types, and 3) a delivery system to direct soluble mediators to critical sites. These functions are performed by the reticular network, a system that, generally, has been assigned a pedestrian role in providing and maintaining LN structure. The term reticular network is a firmly established tautology since "reticulum" derives from the Latin "net." The network consists of reticular fibers with associated extracellular matrix (ECM) and fibroblastic reticular cells (FRCs). This review seeks to illustrate the importance of the reticular network in efficient and effective immune interactions. We develop the concept of LN function primarily as it relates to naive T cell activation, both because it is our primary interest and because it may be somewhat simpler than the events in B cell activation.

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[2] Abbreviations used in this paper: LN, lymph node; ECM, extracellular matrix; FRC, fibroblastic reticular cell; IDC, interdigitating dendritic cell; HEV, high endothelial venule; HRP, horseradish peroxidase.

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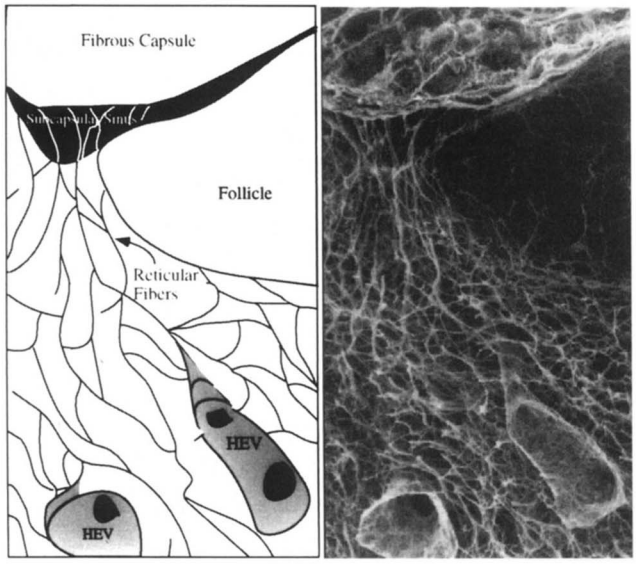

FIGURE 1. Reticular fiber meshwork in the rat LN. *Right,* scanning electron micrograph (×340) of LN cortex following alkali-water maceration. Photograph courtesy of T. Ushiki. *Left,* Tracing of micrograph on *right,* with key features labeled.

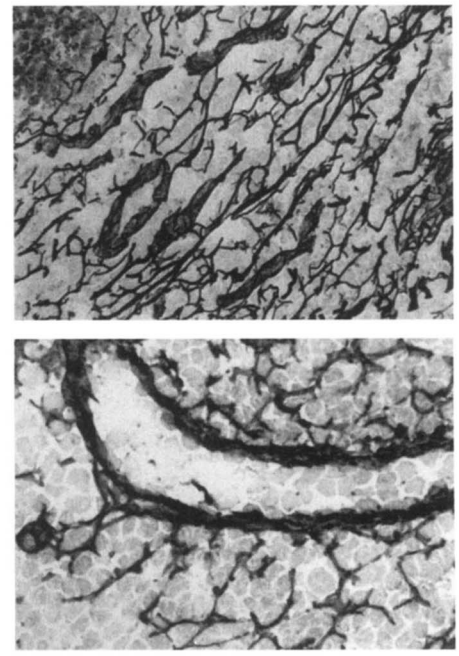

FIGURE 2. Light micrographs of the reticular network in the human LN. *Top,* reticulin silver stain delineating reticular fibers and high endothelial venules in paracortex. Follicle in *upper left corner* shows lack of fibers (×400). *Bottom,* frozen section immunoperoxidase stain with anti-fibronectin Ab showing similar network to that above, including termination of network on HEV. Counterstained cells between fibers are primarily lymphocytes (×600).

The reticular network orchestrates T cell contact with APCs

To understand the design of the reticular network, we start with the fibers themselves. The fibers are bundles of type I and type III collagen (8) and associated matrix components (9, 10), with diameters ranging between 0.5 and 5.0 μm (11). Figure 1, a scanning electron micrograph kindly provided by T. Ushiki (Niigata University School of Medicine, Japan), shows the three-dimensional arrangement of the fibers following removal of cells (FRCs, lymphocytes, and other cells). Notice how fibers interweave throughout the LN, with the density of the resulting meshwork varying between different compartments (12). As described by Ushiki et al. (11), many of the fibers that cross the sinus continue across the superficial cortex between follicles into the denser meshwork of the deep cortex, hereafter referred to as paracortex. In addition, fibers of this meshwork form a basket weave around blood vessels. In contrast, the follicle appears outlined due to the paucity of fibers within it.

Efficient T cell encounter with APCs is easiest to understand by analogy to the receiving line at a wedding: T cells migrate past stationary APCs, interacting with them as they pass by. Consider first how APCs come together to form the receiving line. The most important APCs in the paracortex are the abundant interdigitating dendritic cells (IDC). These cells originate from dendritic cells in tissue (such as Langerhans cells in skin) that have been stimulated within tissue to take up and process Ag (1, 13–16). They leave their tissue residence, enter initial lymphatics, and are carried via lymph to the draining LN. Upon arriving in the subcapsular sinus, the APCs adhere to the sinus floor and transmigrate through the interfollicular regions to the paracortex, where they cling to the reticular network. T cells, the guests in the receiving line, come from the opposite direction, by transmigrating into the paracortex from distinctive postcapillary venules known as high endothelial venules (HEV). They then migrate along the reticular network, studded with APCs, thus participating in a lengthy receiving line. The meshwork of intertwining fibers in Figure 1 clearly shows that the infrastructure of the reticular network could facilitate T cell contact with APCs in the paracortex, where initial T cell activation is believed to occur.

How do we know that T lymphocytes migrate along the reticular network and the APCs that line it? This inference is based on two lines of simple but fairly compelling logic. First, lymphocytes must have adhesion ligands along which to migrate; they do not swim. These ligands could be either part of the ECM or on apposing cells. The reticular network is the place where virtually all of the nodal ECM is found (9, 10, 17, 18). Figure 2 presents light micrographs of the reticular network labeled histochemically and by immunoaffinity. A classical reticulin stain of the paracortex reveals the pervasive tight weave of the reticular network in the *upper panel.* In the *bottom panel,* Ab conjugated with peroxidase labels abundant fibronectin in a similar pattern. Fibronectin is a particularly good substrate for T cell adhesion and migration, as well as being one of many ECM components concentrated along the reticular network (19). Thus, the LN is not filled with a jelly of ECM within which lymphocytes swim, but rather is structured by the reticular network that functions like a "jungle gym" coated with ECM and other adhesive molecules for lymphocyte migration (17). Migration ligands may also be on cells, such as the APCs studding the reticular network (1, 20, 21).

The second line of reasoning is that contact with and migration along the reticular network is almost unavoidable because of its geometry. Typical distances between fibers in the paracortex are approximately 10 to 20 μm (Figs. 1 and 2). Given an average inter-fiber distance of 15 μm, a lymphocyte (7 μm in diameter) is likely to be in contact with the network and APCs decorating it. Thus, the reticular network is an organizing structure that establishes an optimal geometry and molecular milieu in which T cell/APC interactions occur.

The reticular network rapidly delivers soluble information from lymph to HEV

In addition to cellular elements such as APCs, the afferent lymph is rich in soluble molecules derived from the tissue (4). These molecules regulate the LN in important ways. Of particular importance to our considerations of T cell activation is the role of soluble factors in regulating emigration of T cells via HEV. The classic example is the finding that continuous input of afferent lymph is critical for maintaining recirculation of T cells via HEV. Under normal conditions, at any instant, more than 95 lymphocytes can be found migrating across the endothelium along the length of each HEV (22). When afferent lymphatics are ligated, lymphocyte influx into the node rapidly decreases, and the high endothelium of the HEV subsequently reverts to a flattened endothelium (23, 24). Conversely, when the cytokine IL-8 arrives via the lymph, the rate of transmigration at the HEV increases measurably within 3 min and is threefold higher at 30 min (25). Thus, the critical process of T cell recruitment is influenced by soluble information in a rapid and sustainable way.

How does information reach the endothelium? The conventional view is that soluble molecules (such as cytokines) in the afferent lymph percolate from the subcapsular sinus through the LN cortex, eventually reaching the HEV. This concept, however, does not withstand scrutiny. When one considers that just the distance from the nearest sinus to an HEV is as much as 100 μm, diffusion is not a viable option for rapid message transfer. Therefore, one must consider bulk flow. However, the floor of the subcapsular sinus consists of sinus-lining cells (ultrastructurally similar to FRCs (26)) in an almost continuous monolayer, overlaying a collagen-based mesh that parallels the capsule (Fig. 1). Although small pores in this floor can be visualized with electron microscopy, often with cells squeezing through them (11, 26–28), functional studies suggest that the floor of the subcapsular sinus is a rather effective barrier. Carbon particles, with a nominal diameter of 0.04 μm, pass inefficiently from lymph into paracortex (29, 30). Such a carefully controlled boundary between lymph and paracortex implies that free fluid exchange across the interface may not occur. We infer that this allows a tightly regulated microenvironment within the paracortex. Therefore, the prevailing concept that percolation is the mechanism for rapid delivery of soluble molecules to the LN parenchyma requires reassessment.

Indeed, tracers in afferent lymph do not distribute diffusely in the paracortex. Studies of the progression of lymph through the LN using intralymphatic tracers, such as horseradish peroxidase (HRP), ferritin, Friedlander's bacillus, FITC BSA, and FITC globulins, have shown these labels in the cortical parenchyma as fine threads, with the majority of the tracer moving through the sinuses (29, 31–34). It is increasingly clear that this exquisitely localized movement of tracers within LN parenchyma is via the reticular network. Understanding how this can occur demands a more detailed understanding of the morphology of reticular fibers and FRCs.

The concept that reticular networks may be specialized compartments for molecular transport was proposed as early as 1930 (35). This view was reinforced with electron microscopy in the LN, leading to the statement, made by Moe in 1963, that "... it seems reasonable to hypothesize that the entire reticular interstitium may provide pathways for movement of nutrients, Ags, and hormones..." (27); similar views have been proposed by others (36–38). Based on refinements of such anatomic studies combined with functional studies, it has been proposed that the reticular network is a conduit that transports cytokines and other molecules from sinus to HEV (22, 29, 34, 39, 40). Our current hypothesis is that bulk flow carries cytokines and other molecules in the conduit. To understand such flow one needs to understand: 1) how fluid is confined in the conduit, 2) where fluid enters, and 3) where fluid exits.

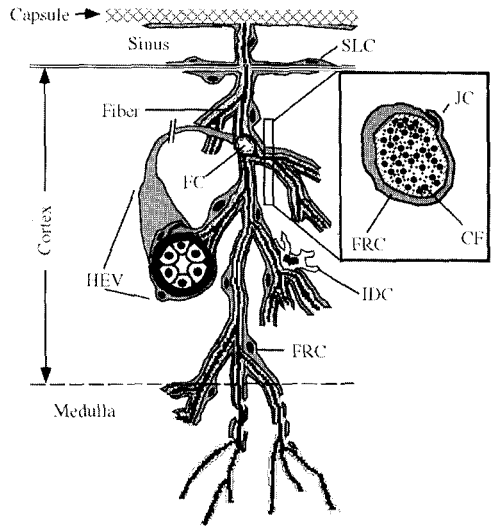

FIGURE 3. Schematic of reticular network conduit. Fibers (black) and associated ECM (stippled gray) are ensheathed by fibroblastic reticular cells (gray, FRCs) in the sinus and cortex, whereas the cellular investment is patchy to nonexistent in the medulla. Other abbreviations: high endothelial venules (HEV), fenestrated capillaries (FC), interdigitating dendritic cells (IDC), sinus-lining cells (SLC). Detail: cross-section of reticular network conduit shows fiber (CF) bundle enwrapped by FRC processes joined by a junctional complex (JC).

We begin with a simplified description to convey the general idea of flow within the reticular network conduit and then refine it. The first issue is fluid confinement. Reticular fibers crossing the sinus and in the superficial cortex are not bare, but are enveloped by tightly associated FRCs (Fig. 3) (26, 27, 38, 41). The cross-sectional view presented in Figure 3 illustrates that the fiber is enclosed within the FRC, yet is separated from FRC cytoplasm by plasma membrane. Long fibers are ensheathed by successive FRCs that isolate their contents (fibers and associated molecules) by providing a continuous privileged extracellular compartment distinct from the LN sinus and paracortical interstitial space.

Given the seemingly complete enclosure of the fibers, how does fluid enter the conduit? We infer that there are two mechanisms based on static anatomic evidence. The first and primary mechanism is transcytosis. Endocytic uptake of materials by the fibroblastic cells from sinuses has been observed in a variety of contexts. One of the most striking is the uptake of gold-labeled albumin by reticular cells in the sinus. Surprisingly, they ingest more than do the adjacent macrophages; furthermore, some of the gold label is deposited in the fibers (42). Other tracers, including HRP (29) and metachromatic mast cell granule contents (39, 43), are also endocytosed and appear within the conduit. This uptake and deposition are most appropriately referred to as transcytosis, since the fluid is transported from one extracellular space (the sinus) to another (the conduit); we view this as closely analogous to the transcytosis performed by endothelial cells. Thus, transcytosis of afferent lymph by FRCs in the sinus provides one mechanism of fluid and cytokine transport into the conduit. The volume introduced into the conduit by transcytosis may not seem large; however, the volume of the conduit, excluding the fibers, is quite small.

A secondary mechanism of fluid entry into the conduit is via fenestrated capillaries. Such capillaries can be observed passing through some of the fibers just below the subcapsular sinus (29). In

addition, tracer studies demonstrate that fluid outflow (transudation) can occur from these fenestrated capillaries into the conduit (29). Unlike the material transcytosed by FRCs in the sinus, this transudate will not contain soluble information from the draining tissue. The predicted advantage of this mode of fluid entry is that the additional volume introduced into the conduit will augment the flow of transcytosed material through the conduit; a corresponding drawback is that it may dilute the concentration of soluble information. The magnitude of this mode of fluid entry is uncertain. On the one hand, such capillaries have been found in a minority of the fibers; on the other hand, a single vessel may have effects on many fibers since the network is so thoroughly interconnected.

Where does fluid exit the conduit? Functional and anatomic evidence indicates that a major site is at the HEV (29, 34). The intersection of the conduit with the HEV has been described previously (29). Briefly, the fibers of the reticular network create a collagen sleeve surrounding both the HEV and its basement membrane (Fig. 1). The FRCs ensheathe only the outer surface of this sleeve. Thus, the conduit can deliver its contents to the ablumenal side of the high endothelium in an enclosed space. Presumably, the soluble factors coming down the conduit would act on cells at this site (29, 34, 44). Some factors will affect the endothelium directly (39, 45, 46). In addition, lymph-borne cytokines will reach the endothelial lumen and either in solution or immobilized on the lumenal endothelial surface they will act directly on lymphocytes (47, 48). Indeed, chemotactic factors MIP-1β and IL-8 have been localized to the reticular network in frozen sections (E. P. Kaldjian, unpublished observations). Soluble factors may reach the lumenal surface of the HEV by endothelial transcytosis or via the unique flap valve design of the interendothelial junctions of HEV, which provides a mechanism for unidirectional flow from the ablumenal to lumenal surface (22, 49).

We have presented a hypothesis suggesting that soluble factors from afferent lymph are carried to the HEV by a miniaturized system via a conduit formed by the reticular network. This system differs from established vertebrate vascular and tubular systems of bulk flow in two ways. First, the size of the conduit lumen is much smaller. Second, the lumen is occupied substantially by fibers, rather than being entirely hollow. While flow in the conduit is not yet fully understood, lymph-borne elements have repeatedly been shown to trace the reticular network from the sinus to the HEV. In addition, evidence of flow along unsheathed fibers has been obtained in other tissues (50, 51). This phenomenon and the mechanism by which it occurs merit further investigation.

Refinements of the conduit concept

Three related topics will be addressed only briefly here: 1) variations in cellular investment of the reticular fibers, 2) regions of sparse reticular network, and 3) implications of exposure of lymphocytes to conduit fluid. In the foregoing presentation, the reticular network has been presented as an enclosed system, apart from the termini at HEVs. This perspective is substantiated by the exhaustive studies by Hayakawa, in which he found complete investment of fibers in the paracortex (41). Of particular importance in his studies is the finding that 10% of the fiber surface area is invested by cells other than FRCs, such as IDCs, macrophages, and lymphocytes. It is plausible that soluble factors in the conduit would provide signals via these specialized contacts. Indeed it has been proposed that soluble Ag might be delivered to APCs via the reticular network (27, 29, 36, 37, 52). Likewise, soluble signals from these directly connected cells might be delivered to the conduit and thereby to the HEV. In contrast to Hayakawa's results, gaps in investment of paracortical fibers have been found (11). It remains to be determined whether a gap may reflect temporary exposure of a site that is normally occupied. Clearly, the network is a dynamic infrastructure that is constantly made and modified by the FRC (53). The investment of the fibers by the FRC takes place within the first few days of postnatal development (54) and appears to be a remarkable adaptation of the reticular system that is peculiar to the paracortex, since within the medullary cords the FRCs interact with the fiber but rarely envelop it (11).

Thus far, we have emphasized the areas of the LN that are rich in reticular network. However, in areas of lymphocyte proliferation, such as the follicles (Fig. 1) and the deep cortical units (11, 55), the reticular network is of a looser mesh than is found in the paracortex (these areas are believed to be sites of B and T cell proliferation, respectively). Insofar as the fine mesh is designed to facilitate migration, it makes sense that the network would be sparser in these regions. In addition, cell activation here has progressed sufficiently that rapid access to soluble information (via the conduit) from the tissue is not required.

Finally, as noted above, the ablumenal side of the HEV will be bathed in the conduit contents. All cells entering the LN from blood pass through this space and therefore will be exposed to the mix of cytokines and soluble Ag present in conduit fluid; this contrasts with the conventional view of lymph percolation, in which lymphocytes presumably would be bathed in lymph only later in the emigration. Since many soluble mediators influence T and B cell activation, exposure to conduit fluid at the time of arrival in the node could influence their subsequent migration, activation, and differentiation. For example, many soluble agents, including chemokines, are chemokinetic for T cells, increasing their rate of motion. Exposure to such agents would influence rates of subsequent migration properties in the node.

Conclusions

We have presented the reticular network of the LN as a multifunctional system designed to maximize the efficiency of the immune response. The reticular network is essential in the directed migration of lymphocytes through the LN and provides structured environments for cell/cell interactions. In addition, the function of the reticular network as a conduit system in the LN, if correct, provides an efficient and rapid local physiologic control of lymphocyte homing and recirculation. Overall, we hope to have stimulated a renewed appreciation for the unique architectural design of the LN, which enables it to augment the cellular encounters and information flow necessary for immune responses.

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