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Review

Hallmarks of Tissue-Resident Lymphocytes

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Although they are classically viewed as continuously recirculating through the lymphoid organs and blood, lymphocytes also establish residency in non-lymphoid tissues, most prominently at barrier sites, including the mucosal surfaces and skin. These specialized tissue-resident lymphocyte subsets span the innate-adaptive continuum and include innate lymphoid cells (ILCs), unconventional T cells (e.g., NKT, MAIT, γδ T cells, and CD8αα$^+$ IELs), and tissue-resident memory T (T_{RM}) cells. Although these diverse cell types differ in the particulars of their biology, they nonetheless exhibit important shared features, including a role in the preservation of tissue integrity and function during homeostasis, infection, and non-infectious perturbations. In this Review, we discuss the hallmarks of tissue-resident innate, innate-like, and adaptive lymphocytes, as well as their potential functions in non-lymphoid organs.

Recirculating and Tissue-Resident Lymphocyte Subsets

From an evolutionary perspective, the mammalian adaptive immune system is the pinnacle of metazoan immune defenses in terms of its complexity and potential for molecular specificity. In contrast to innate immune systems, which rely on germline-encoded receptors to recognize stereotypic motifs associated with broad classes of pathogens, the hallmark of adaptive immunity is the generation of near-limitless antigen receptor diversity through somatic recombination, which in turn provides the foundation for immunological memory through the differentiation, expansion, and persistence of long-lived antigen-specific lymphocytes (Janeway, 1989; Medzhitov and Janeway, 2000; Medzhitov, 2009). Although they serve as direct effectors of immunity by elaborating cytotoxic function and antibody production, cells of the adaptive immune system act foremost as principal controllers, amplifying or limiting the responses of diverse cell types through positive and negative feedback loops.

At a basic level, the mammalian adaptive immune response is initiated by antigen-presenting cells (APCs) migrating from the site of infection to the draining lymph node to present captured microbial antigens to naive T cells, which constitutively recirculate between lymph nodes to survey presented antigens. When a naive T cell encounters its cognate antigen, it undergoes clonal expansion, a process that takes several days and results in the differentiation of both effector and memory T cells. While effector T cells home to the site of the primary infection and contribute to pathogen clearance, circulating memory T cells persist and are poised to mount a superior response to secondary infection. Teleologically, this efficient system of naive lymphocyte recirculation is necessitated by the minute frequencies at which individual lymphocyte clones are present, such that a given clone, incapable of being in all anatomical locations at once, instead patrols strategically positioned lymph nodes, which collect information on the statuses of tissues and organs—i.e., the antigenic landscape (Jenkins et al., 2010; Maryanski et al., 1996; von Andrian and Mackay, 2000). In contrast to this classical view of adaptive lymphocytes, studies in the last 10 years have led to a characterization of lymphocyte populations that are non-recirculating residents of non-lymphoid tissues and organs. These populations include tissue-resident memory T cells (T_{RM}); "unconventional" T cells such as invariant natural killer T (iNKT) cells, mucosal-associated invariant T (MAIT) cells, γδ T cells, and intestinal intraepithelial lymphocytes (IELs); and the emerging family of innate lymphoid cells (ILCs) (Artis and Spits, 2015; Clark, 2015; Eberl et al., 2015; Godfrey et al., 2015; Schenkel and Masopust, 2014). These tissue-resident lymphocytes span the innate-adaptive continuum but nonetheless share a number of particular features pertaining to their tissue-resident functions. In this Review, we will discuss the properties and functions of lymphocytes residing in non-lymphoid tissues. Just as manipulation of lymphocyte recirculation has resulted in effective therapies for autoimmune diseases such as multiple sclerosis (Pelletier and Hafler, 2012; Ransohoff, 2007; von Andrian and Engelhardt, 2003), a better understanding of tissue-resident lymphocytes may reveal new cellular mechanisms of organ dysfunction in a multitude of inflammatory, infectious, and neoplastic processes and suggest novel approaches for their treatment.

Definition of Tissue-Resident Populations

The discovery of tissue-resident lymphocytes owes to experimental approaches that allow for discrimination of circulating and tissue-resident populations. One of the most commonly used means of assessing tissue residency is parabiosis, whereby two congenic mice expressing distinct allelic markers of hematopoietic cells are surgically conjoined through adjacent skin, such that they develop a shared anastomotic circulation (Wright et al., 2001). This approach pinpoints tissue-resident cell populations by their exclusive expression of the host

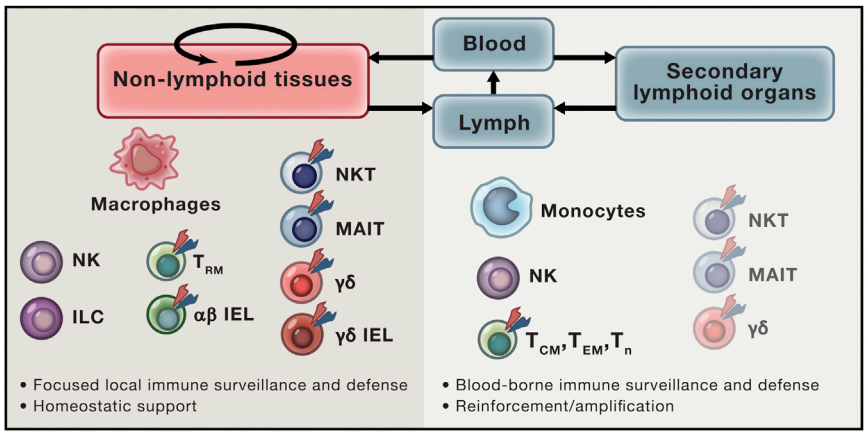

Figure 1. Tissue-Resident versus Recirculating Lymphocytes and Their Functions

Tissue-resident lymphocytes are principally found in barrier tissues, where they serve as sentinels and frontline defenders of tissue integrity in response to infection and non-infectious insults. Recirculating lymphocyte subsets actively survey the body for similar perturbations of homeostasis by patrolling the lymphatic and blood circulatory systems and associated secondary lymphoid organs (lymph nodes and spleen). While some lymphocyte subsets, most prominently ILCs, display almost exclusively tissue-resident behavior, circulating counterparts to other adaptive lymphocyte subsets, including NK, NKT, MAIT, γδ T, and αβ T cells can also be found in peripheral blood, albeit at lower frequencies.

congenic marker, in contrast to actively recirculating cells and their progeny, which exhibit both host and donor markers in equal proportion. It must be noted that the extent and kinetics of equilibration between circulating cells originating from the two parabionts is dependent on the turnover rate of a given cell subset. While two populations may be similarly replaced by circulating precursors, the longer-lived population is replaced more slowly and, thus, appears to be tissue-resident to a greater extent. Furthermore, failure of a population to exchange in parabiosis does not imply that cells of that population are sessile and static. For example, in the absence of inflammation, Langerhans cells remain overwhelmingly host-derived in parabiotic mice (Merad et al., 2002), although they migrate continuously and unidirectionally from the epidermis to skin-draining lymph nodes (Bajaña et al., 2012; Ohl et al., 2004; Tomura et al., 2014). Additionally, imaging studies have shown that liver-resident iNKT cells, epidermis-resident $CD8^+$ T_{RM} cells, and intestine-resident ILCs exhibit dynamic behavior within their respective tissues (Gebhardt et al., 2011; Geissmann et al., 2005; Mackley et al., 2015; Pearson et al., 2016; Zaid et al., 2014) but self-renew locally and are not replaced by circulating precursors (Gasteiger et al., 2015; Jiang et al., 2012; Thomas et al., 2011). Thus, cell tracking and imaging approaches offer an essential complement to the "10,000-foot view" provided by parabiosis. The mobile or sessile "styles" of tissue residency, and signal-dependent waves of migration to and from the tissue, have been elucidated through methodologies such as photo-switchable or constitutive cell tagging, direct visualization of cellular behavior using intravital imaging, and analysis of tissue explants or transplants into congenically marked mice.

The Spectrum of Tissue-Resident Lymphocytes

A combination of these approaches has revealed that a variety of tissue-resident lymphocytes, representing the innate and adaptive branches of immunity, differ in their distribution in non-lymphoid tissues yet exhibit common "innate"-like properties. These tissue-resident lymphocytes represent an integral part of a network of cells whose connections and hierarchy are poorly understood. However, it is reasonable to assume that they act as sensors of perturbed tissue integrity stemming from infection, injury, and potentially other forms of deviation from the homeostatic norm. In parallel to the role of their circulating counterparts in amplifying or suppressing innate immunity, tissue-resident lymphocytes likely support the functioning of non-lymphoid tissues by serving as sentinels of tissue integrity, recruiters of bloodborne reinforcements, and amplifiers of homeostatic mechanisms through feedback on parenchymal cells and non-lymphoid accessory cells (e.g., macrophages, fibroblasts, and endothelial cells) (Figure 1) (Medzhitov, 2008). Below, we will briefly review features of innate and adaptive tissue-resident lymphocytes and discuss experimental observations supporting this hypothetical model.

Innate Lymphoid Cells

Toward the "innate"-most end of the innate-adaptive spectrum are ILCs, a diverse family of lymphocytes, including natural killer (NK) cells, lymphoid tissue inducer (LTi) cells, and the "helper-like" ILCs. Like other lymphocytes, all ILCs develop from the common lymphoid progenitor. Helper-like ILCs develop through a common helper-like ILC precursor (ChILP) shared with LTi but not NK cells and, subsequently, through an intermediate expressing transcription factor PLZF with only helper-like ILC potential (Constantinides et al., 2015, 2014; Klose et al., 2014b; Wong et al., 2012). Long-term parabiosis experiments suggested that ILC and NK subsets residing in the non-lymphoid tissues and secondary lymphoid organs of adult mice are likely maintained through self-renewal with minimal contribution from hematogenous precursors under physiologic and inflammatory conditions (Gasteiger et al., 2015; Peng et al., 2013; Sojka et al., 2014). Consistent with these findings, distinct features have been reported for salivary-gland-resident NK cells and ILCs with the key properties of the latter coordinately evolving with the development of their "home" organ (i.e., salivary gland) (Cortez et al., 2014; M. Colonna, personal communication). Likewise, mature ILCs appear in the lung as early as day 8 of postnatal life, and intestinal ILCs appear to derive from a precursor present early in life (Bando et al., 2015; Nussbaum et al., 2013). Lending further support to the notion that ILCs serve important homeostatic functions in support of organs and tissues, the first characterized subset of ILC with a defined function were RORγt and lymphotoxin-expressing LTi cells essential for