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Hallmarks of Tissue-Resident Lymphocytes

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Abstract

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

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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 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 the organogenesis of lymph nodes and Peyer's patches (Adachi et al., 1997; Eberl et al., 2004; Kelly and Scollay, 1992; Mebius et al., 1997; Sun et al., 2000).

Lacking classical antigen receptors, ILCs are instead activated by cytokines, whereas NK cells are additionally stimulated through activating receptors such as NKG2D and Ly49H, or through a receptor for the immunoglobulin constant region (FcγRIII/CD16). Mirroring the T-helper polarization of conventional $CD4^+$ T cells, helper-like ILCs can be subdivided into types 1, 2, and 3 (ILC1, ILC2, and ILC3) based on differential expression of the lineage-specifying transcription factors T-bet, GATA-3, and RORγt (respectively) and production of the corresponding effector cytokines interferon-γ(ILC1), IL-5 and IL-13 (ILC2), and IL-17 (ILC3) (Artis and Spits, 2015; Eberl et al., 2015). Besides producing cytokines that orchestrate and amplify antimicrobial defenses, ILCs also elaborate soluble factors that promote tissue maintenance. Different ILC subsets respond to the pro-inflammatory cytokine IL-23 or the alarmin IL-33 by producing tissue-protective factors IL-22 or amphiregulin, respectively (Cella et al., 2009; Monticelli et al., 2015, 2011; Sanos et al., 2009).

"Innate-like" T Cells

In contrast to ILCs, "unconventional" or "innate-like" T cells express T cell receptors (TCRs) of limited diversity, which recognize antigens in the context of non-classical, non-polymorphic MHC-like molecules, or independently of MHC-related presenting molecules altogether (Godfrey et al., 2015). Lymphocytes belonging to this group include αβTCR-expressing iNKT, MAIT, and γδ T cells.

iNKT cells express an invariant TCRα chain (Vα14-Jα18 in mice, Vα24-Jα18 in humans) paired with a TCRβ chain of limited diversity (Brennan et al., 2013; Salio et al., 2014). Unlike most αβTCRs, iNKT TCRs recognize glycolipid antigens presented by the MHC class I-like molecule CD1d (Bendelac et al., 1994, 1995). Functionally, iNKT cells can be activated by potent bacterial ligands, such as cell wall sphingolipids from *Sphingomonas*, *Borrelia*, or *Streptococcus* (Kinjo et al., 2006, 2011; Sriram et al., 2005). They can also sense changes in host lipid metabolism through recognition of transiently expressed, less potent, rare, or unstable endogenous lipids, a number of which have been proposed (Brennan et al., 2011, 2014; Facciotti et al., 2012; Kain et al., 2015; Zhou et al., 2004). This endogenous lipid sensing, which may in fact be the dominant mode of iNKT cell activation in vivo, allows iNKT cells to indirectly detect the breach of tissue integrity resulting from infection with viruses, fungi, and bacteria like *Salmonella typhimurium*, which lack potent agonist ligands (Cohen et al., 2011; Mattner et al., 2005). As with ILCs, NKT cell subsets analogous to T_H1, T_H2, and T_H17 conventional T cells have been described. These subsets express the corresponding cytokines and transcriptional regulators of their T-helper counterparts and have been shown to localize to different tissues (Constantinides and Bendelac, 2013; Coquet et al., 2008; Lee et al., 2013; Lee et al., 2015b; Michel et al., 2007; Watarai et al., 2012).

Like iNKT cells, MAIT cells express a semi-invariant TCR combining a unique TCRα chain (Vα19-Jα33 in mice, Vα7.2-Jα33 in humans) with a restricted set of TCRβ chains and reside in the liver but also in the intestine (Dusseaux et al., 2011; Le Bourhis et al., 2011; Salio et al., 2014). MAIT TCRs, however, are activated by bacterial riboflavin biosynthesis intermediates presented by the MHC class I-like molecule MR1 (Corbett et al., 2014; Kjer-Nielsen et al., 2012; Treiner et al., 2003). Additionally, it seems likely from the MR1 crystal structure that its ligand-binding groove can accommodate other ligands. In fact, it has been shown that pterin derivatives can bind MR1 but fail to stimulate MAIT cells (Kjer-Nielsen et al., 2012). Distinct subsets of MAIT cells can produce IFN-γ and IL-17 (Dusseaux et al., 2011; Rahimpour et al., 2015). Although MAIT cells have been suggested to play a role in antibacterial immunity through sensing of MR1-bound microbial products (Chua et al., 2012; Georgel et al., 2011; Kjer-Nielsen et al., 2012; Le Bourhis et al., 2010; Meierovics et al., 2013), it is tempting to speculate that these cells may also be involved in mediating beneficial host-commensal interactions in the intestine and, potentially, the skin or lung. Such interactions could be reminiscent of the previously proposed roles of commensal-derived short-chain fatty acids in maintaining colonic immune homeostasis through the de novo differentiation of Treg cells and the tolerogenic imprinting of APCs (Arpaia et al., 2013; Chang et al., 2014; Furusawa et al., 2013; Smith et al., 2013).

T cells expressing the γδTCR represent another prominent innate-like T cell subset that resides in barrier tissues and is especially enriched among IELs. In mice, specific Vγ and Vδ segment rearrangements within the γδTCR locus occur in a highly ordered fashion during embryonic development (Chien et al., 1987; Ito et al., 1989; Itohara et al., 1989). This results in the sequential appearance of distinct waves of γδ T cells bearing oligoclonal or monoclonal TCRs that populate different epithelial tissues (Havran and Allison, 1988; Itohara et al., 1990). For example, dendritic epidermal T cells (DETCs), which are the only lymphocytes to reside in the epidermis of naive mice, are a monoclonal population of intraepithelial γδ T cells that arise from fetal thymic precursors between embryonic days 14 and 16 and exclusively express the Vγ3Vδ1 TCR (Asarnow et al., 1988; Havran and Allison, 1990; Havran et al., 1989). Unlike the αβTCR, the γδTCR exhibits a longer, immunoglobulin-like CDR3 structure, and several modes of antigen recognition by γδ T cells have been elucidated, in contrast to the strict MHC restriction of conventional αβ T cells (Rock et al., 1994). Different subsets of γδ T cells have been shown to recognize ligands as diverse as lipids presented on CD1 family members; a conformational change in butyrophilin-3A induced by prenyl pyrophosphate derivatives; MHC class I-like molecules (e.g., MICA, ULBP4, T10, T22), which may be induced by cellular stress; conventional MHC molecules irrespective of loaded peptide; and even some soluble ligands in the absence of presenting molecules (Chien et al., 2014; Sandstrom et al., 2014). As with MAIT cells, IFN-γ and IL-17 are produced by different γδ T cell subsets (Jensen et al., 2008).

It must be noted that intestinal IELs, unlike their epidermal counterparts in mice—monoclonal Vγ3Vδ1$^+$ DETCs—consist of a heterogeneous assortment of αβ T cells, γδ T cells, and ILCs united by their localization (Cheroutre et al., 2011; Fuchs et al., 2013). A distinguishing feature of many αβ and γδ IELs is their expression of the CD8αα homodimer, as opposed to the CD8αβ heterodimer expressed by conventional cytotoxic T cells. In addition to recognizing MHC class I, CD8αα also binds the non-classical MHC class I

molecule, thymus leukemia antigen (TLA), which is expressed by intestinal epithelial cells (Leishman et al., 2001). Thymocytes can differentiate into $CD4^{-}$ $CD8\alpha\beta^{-}$ "natural" IELs by escaping from negative selection after experiencing agonist signaling in the thymus (Gangadharan et al., 2006; Leishman et al., 2002; McDonald et al., 2014, 2015; Pobezinsky et al., 2012; Rocha et al., 1992; Yamagata et al., 2004). Alternatively, mature T cells can be induced to become IELs in the periphery, in which case they may retain expression of CD4 or CD8αβ. The strong self-reactivity of TCRs from natural IELs thus explains the likely function of CD8αα as a repressor of activation and the concomitant expression of a variety of inhibitory receptors (e.g., LAG-3, PD-1, and Ly49 family NK inhibitory receptors) on natural IELs (Cheroutre et al., 2011; Denning et al., 2007; Mayans et al., 2014; Shires et al., 2001). After exiting the thymus, natural IEL precursors mature upon IL-15-induced upregulation of T-bet in the periphery, and a similar differentiation pathway has been demonstrated for induced IELs, which can develop from $CD4^{+}$ T cells after upregulation of T-bet and Runx3, and loss of ThPOK (Klose et al., 2014a; Mucida et al., 2013; Reis et al., 2014). However, induced IEL differentiation appears to be driven by exogenous antigen rather than self-antigen, and these cells may therefore be the antigen-specific "adaptive" counterparts of innate-like natural IELs (Mucida et al., 2013). Consistent with a role of antigen in this process, germ-free mice and mice fed an elementary diet free of protein antigens show decreased intestinal IEL numbers (Bandeira et al., 1990; Menezes et al., 2003; Helgeland et al., 1996; Umesaki et al., 1993).

Hallmarks of Tissue-Resident Lymphocytes

Besides their ability to self-renew in tissues independently of circulating precursors, there are other important properties shared by tissue-resident lymphocytes (Box 1). Importantly, far from being rare, tissue-resident lymphocytes are among the most abundant lymphocyte populations. First, taking into consideration the large surface areas of barrier tissues, a careful accounting of the absolute number of epidermal and intestinal IELs shows that each population comprises a substantial fraction of the total lymphocyte pool (Beagley et al., 1995; Clark et al., 2006). However, common methods of isolation are inefficient for lymphocytes residing in non-lymphoid tissues, causing their numerical importance to be underappreciated (Steinert et al., 2015). Second, tissue-resident lymphocytes often comprise a large percentage of lymphocytes in the tissue compartments that they inhabit and may localize to specific niches that are relatively inaccessible to recirculating cells that enter the same tissue. For example, in the absence of challenge, DETCs are the only lymphocytes in mouse epidermis, and resident γδ T cells also comprise a large fraction of lymphocytes in the mouse dermis (Gray et al., 2011; Sumaria et al., 2011). Intestinal IELs are mostly resident lymphocytes, and iNKT or MAIT cells are abundant among liver lymphocytes in mice and humans, respectively (Dusseaux et al., 2011; Poussier et al., 1992; Rahimpour et al., 2015; Sugahara et al., 1999; Suzuki et al., 1998). Importantly, the antigen specificities of semi-invariant tissue-resident T cells are abundant relative to the individual clonal frequencies of naive T cells. While roughly one in a million naive T cells possesses the antigen specificity to respond to a given pathogen-derived peptide-MHC complex (Jenkins et al., 2010), innate and innate-like lymphocytes are present in populations in which nearly all cells can respond in the presence of signal. This means that the appropriate stimulus can

activate large numbers of innate lymphocytes to produce significant effector function during the time in which the few reactive clones of adaptive lymphocytes must be expanded.

The second hallmark of innate tissue lymphocytes is their recognition of a wide variety of microbial ligands and host-derived signals that collectively signify infection, inflammation, and tissue injury (Figure 2). These signals activate tissue lymphocytes through the aforementioned semi-invariant antigen receptors, NK activating receptors, and alarmin and cytokine receptors to elicit the rapid production of effector cytokines. The semi-invariant TCRs of iNKT cells recognize glycolipids, the most potent of which possess an α-anomeric glycosidic linkage and can be produced by pathogenic bacteria (Brennan et al., 2013; Salio et al., 2014). αβ T cells restricted for other CD1 molecules (CD1a, CD1b, CD1c) have been described in humans, and some of these cells respond most strongly to lipids from mycobacteria (Godfrey et al., 2015). As noted above, the most potent activating antigens for MAIT cells (riboflavin derivatives) and for human Vγ9Vδ2$^+$ T cells (“phosphoantigens”) are also bacterial products (Corbett et al., 2014; Hintz et al., 2001; Kjer-Nielsen et al., 2012; Le Bourhis et al., 2010). Thus, because of their direct activation by microbial products, the invariant TCRs of unconventional T cells functionally resemble pattern recognition receptors. However, in the absence of potent microbial antigens, these cells can also be activated by lower-affinity endogenous ligands with concurrent cytokine stimulation, most notably from IL-12 and IL-18 (Brigl et al., 2003; Nagarajan and Kronenberg, 2007; Tyznik et al., 2008). This may be a major mode of iNKT activation even for pathogens that make suitable TCR ligands (Brigl et al., 2011). It is appealing to think that glycolipid-sensing iNKT cells, with their prominent enrichment in the liver and adipose tissue, may also be triggered in response to sterile metabolic stresses, which are accompanied by altered glycolipid synthesis and turnover. Indeed, iNKT cells decrease in the adipose tissue, liver, and omenta of obese humans or mice (Ji et al., 2012; Kotas et al., 2011; Lynch et al., 2009, 2012; Schipper et al., 2012). CD1d-deficient mice on a high-fat diet show exacerbated metabolic abnormalities (Kotas et al., 2011; Lynch et al., 2012; Schipper et al., 2012), though reports conflict as to whether this phenotype is recapitulated in mice specifically deficient in Jα18-expressing iNKT cells. Besides iNKT cells, recognition of self-ligands is also a feature of other unconventional T cell types: Vγ9Vδ2$^+$ T cells can be activated by endogenous prenyl intermediates that accumulate in cells upon inhibition of the isoprenoid biosynthesis pathway (Gober et al., 2003), and various IEL subsets are also thought to primarily recognize self-ligands. For example, DETCs recognize a self-ligand whose precise molecular identity is unknown but is expressed transiently by injured keratinocytes within an hour of cutaneous wounding (Havran et al., 1991; Komori et al., 2012). Natural IELs exhibit self-reactive TCRs that result from thymic agonist selection and may be kept in a unique “activated yet resting” state by the regulated expression of co-stimulatory and co-inhibitory molecules (Shires et al., 2001). Accordingly, IELs, along with iNKT cells, MAIT cells, γδ T cells, and several other tissue-resident subsets, express NK activating receptors such as NKG2D, which detect molecules present on stressed epithelial cells. Some γδ T cells may additionally recognize these or other stress ligands through their TCR (Kong et al., 2009; Wu et al., 2002). Thus, besides reacting to pathogens, tissue-resident lymphocytes also directly monitor the condition of tissue parenchymal cells.

Another hallmark of tissue-resident lymphocytes is their “memory”-like phenotype—specifically, their ability to rapidly produce effector cytokines, cytolytic molecules, and growth factors upon activation at early time points during infection (Figure 2). Innate lymphocytes can respond on the order of hours, which is in contrast to the days that are required for the activation and clonal expansion of naive conventional T cells during a primary immune response. For example, vaccinia virus infection induces IFN-γ production by γδ T cells as early as day 2 post-infection (Selin et al., 2001), NKT cells produce IFN-γ at day 2 after BCG infection (Chiba et al., 2008), and ILC2s are early producers of IL-13 after infection with the helminth *Nippostrongylus brasiliensis* (Fallon et al., 2006; Moro et al., 2010; Neill et al., 2010; Price et al., 2010; Saenz et al., 2010; Voehringer et al., 2006). After intraperitoneal injection of *E. coli*, γδ T cells serve as the major producers of IL-17, peaking at 6 hr post-infection; antibody-mediated depletion of γδ T cells or IL-17 impairs neutrophil recruitment to the peritoneal cavity (Shibata et al., 2007). The importance of this early cytokine production is further borne out by the phenotypes of mice that lack certain innate lymphocyte populations. For example, mice lacking γδ T cells show increased bacterial burden in the spleen at 3–4 hr (but not beyond 24 hr) after oral *Salmonella* infection, as well as increased viral load and mortality early after vaccinia infection (Ismail et al., 2011; Selin et al., 2001). The memory-like properties common to innate tissue-resident lymphocytes may have their basis in the shared expression of the transcription factor PLZF by many of these cell types, including iNKT cells, MAIT cells, some γδ T cells, and ILC precursors (Alonzo et al., 2010; Constantinides et al., 2014; Kovalovsky et al., 2008; Lu et al., 2015; Rahimpour et al., 2015; Savage et al., 2008). Indeed, PLZF-deficient mice show a profound deficiency of iNKT cells and MAIT cells, and the few iNKT cells remaining exhibit aberrant function and localization (Kovalovsky et al., 2008; Savage et al., 2008; Rahimpour et al., 2015). Conversely, forced expression of PLZF is sufficient to confer certain features of iNKT cells on conventional T cells (Kovalovsky et al., 2010; Raberger et al., 2008; Savage et al., 2011; Thomas et al., 2011). A history of PLZF expression may therefore explain the superficial similarities between ILCs lacking antigen receptors and unconventional T cells that arise from agonist TCR selection. In accordance with these shared functional features, the cell-surface phenotype of tissue-resident lymphocytes also resembles that of antigen-experienced memory T cells. For example, many tissue-resident lymphocyte subsets express CD44, a receptor for hyaluronan; integrin α_E (CD103), which recognizes E-cadherin; and integrin α_1 (CD49a), which binds type IV collagen. These markers mediate adhesion to extracellular matrix, reflecting their probable function in controlling cellular localization and motility in non-lymphoid tissues.

Given their close association with parenchymal cells, often beginning early in development, tissue-resident lymphocytes are well poised to sense dysfunction of parenchymal cells and to produce factors that contribute to tissue protection and maintenance. Cytokines and alarmins released by myeloid, stromal, and parenchymal cells are important signals that convey the presence of infection and the perturbation of tissue homeostasis to resident lymphocytes. Myeloid cells integrate inputs received through various pattern recognition receptors into a distinct combination of cytokine outputs (e.g., IL-12 or IL-23), thereby activating specific subsets of innate lymphocytes while also shaping the polarization of the adaptive response. Collectively, cytokine and alarmin signals appear to be the most important stimuli for the

activation of ILCs, which lack antigen receptors. Epithelial cells appear to be the major source of the cytokines that initiate type 2 immune responses—namely, IL-33, IL-25, and thymic stromal lymphopoietin (TSLP). By producing their own cytokines in turn, innate lymphocytes comprise an important amplification loop in this process (Figure 3). For example, IL-33 released from dying epithelial cells, and IL-25 from chemosensory tuft cells, are both potent activators of ILC2s during helminth infection (Gerbe et al., 2016; Howitt et al., 2016; Moro et al., 2010; Neill et al., 2010; Price et al., 2010; Saenz et al., 2010; von Moltke et al., 2016). Activated ILC2s produce IL-13, which acts on the intestinal stem cell compartment to facilitate goblet cell and tuft cell hyperplasia, two functional adaptations that promote worm expulsion and additional IL-25 production, respectively. Mice deficient in IL-25, IL-33, or tuft cells (*Pou2f3*$^{-/-}$) are unable to sustain this feed-forward loop and are less able to expel *Nippostrongylus brasiliensis* (Fallon et al., 2006; Hung et al., 2013; Gerbe et al., 2016; Neill et al., 2010; von Moltke et al., 2016). Notably, Rag1-deficient mice, which lack adaptive lymphocytes, are less efficient at expelling worms, but mice, in which T cells are unable to produce IL-4 and IL-13, show no such defect (Voehringer et al., 2006; von Moltke et al., 2016). These findings illustrate the role of the adaptive immune system in amplifying and reinforcing the responses of innate tissue-resident lymphocytes to clear an infection.

Notably, tissue repair is a prominent feature of type 2 immunity, which may have evolved to defend mammalian hosts from the widespread tissue damage associated with migrating helminth larvae (Allen and Sutherland, 2014; Gause et al., 2013). In further support of this notion, the major type 2 cytokines IL-4 and IL-13 activate collagen deposition by fibroblasts, as well as epithelial remodeling of the intestinal mucosa, skin, and airways. IL-33 stimulation of tissue-resident T_H2 cells, ILC2 cells, and regulatory T (Treg) cells also results in the production of the EGFR ligand amphiregulin (Areg), which promotes epithelial cell proliferation. Tissue Treg cells are an important source of Areg (Burzyn et al., 2013), and mice in which Treg cells lack Areg exhibit impaired pulmonary function and exacerbated tissue pathology during influenza infection (Arpaia et al., 2015). However, production of trophic factors is not restricted to type 2 immune responses; the pro-inflammatory cytokine IL-18 can also stimulate Areg production from Treg cells (Arpaia et al., 2015). In addition, IL-22 produced by ILC3s and T_H17 cells has been demonstrated to act as a major tissue-protective factor in a number of settings, including thymic radiation damage and intestinal inflammation or infection (Aujla et al., 2008; Dudakov et al., 2012; Hanash et al., 2012; Lindemans et al., 2015; Zenewicz et al., 2008; Zheng et al., 2008). IELs also produce a number of trophic or regulatory factors, including keratinocyte growth factor, IGF-1, and TGF-β, and mice lacking γδ T cells experience delayed epithelial repair (Boismenu and Havran, 1994; Chen et al., 2002; Jameson et al., 2002; Sharp et al., 2005; Shires et al., 2001). Finally, recent studies have suggested that ILC2 cells regulate the conversion of white adipose tissue into thermogenic beige adipose tissue, possibly through the production of neuropeptides (Brestoff et al., 2015; Lee et al., 2015a). Resident T cells that synthesize acetylcholine as part of a neuroimmune circuit have also been identified (Rosas-Ballina et al., 2011). These diverse observations suggest the centrality of tissue repair and maintenance functions to tissue-resident lymphocyte biology. Collectively, these hallmarks of innate and innate-like tissue-resident lymphocytes—abundance, especially at

barrier tissues and seeding early in development; sensing of microbial products, cytokines, and stress-induced self-ligands; and rapid “memory”-like provision of antimicrobial and tissue reparative effector function—endow these cells with the ability to detect infection or injury and to coordinate protective responses. Furthermore, restoring and safeguarding the integrity of barrier tissues is a critical function that goes hand in hand with the sensing and clearance of pathogens.

Redundancy and Unique Functions of Tissue-Resident Lymphocytes

Given the functional properties that tissue-resident lymphocyte subsets share, to what extent are these subsets redundant or essential? For example, in the mucosal tissues of healthy uninfected mice, αβ and γδ IELs, MAIT cells, and ILC1s are all innate tissue-resident cells potentially capable of producing IFN-γ or inducing cytolysis. Such a redundancy in innate and innate-like tissue-resident lymphocytes likely allows for the robustness of defense against infection and tissue protection. Therefore, tissue immune responses can be seen as multilayered, with an ordered involvement of different cell types with partially overlapping functions in a relay-like manner (“passing the baton”). For example, early during influenza virus infection, lung Treg cells represent the numerically most significant source of amphiregulin and are essential for protection against lung injury, whereas at later times, expanded pools of ILCs, myeloid cells, and effector T cells may provide sufficient protection (Arpaia et al., 2015). Yet, it is possible that such a “relay” of different cell types allows for non-redundant, still-to-be-recognized functions. Consistent with this idea, the different types of tissue-resident lymphocytes are present at different frequencies and may occupy distinct locations within the same non-lymphoid organ (e.g., intra- versus extravascular or connective tissue versus intraepithelial localization). Independently of their frequency and distribution, tissue-resident lymphocytes may also exhibit unique and non-redundant functions by being activated by an overlapping but distinct array of stimuli, presented on different molecules, potentially by different APCs. For example, iNKT cells are abundant in the mouse liver. *Borrelia burgdorferi*, the causal agent of Lyme disease, produces an α-linked glycolipid presented to liver-resident iNKT cells by CD1d expressed on Kupffer cells (Kinjo et al., 2006; Lee et al., 2010). Upon blood-borne dissemination of *Borrelia*, activated iNKT cells cease patrolling liver sinusoids, cluster on Kupffer cells, and produce IFN-γ. Importantly, Jα18- or CD1d-deficient mice lacking iNKT or all NKT cells, respectively, exhibit sharply increased microbial load in their joints upon *Borrelia* infection (Kumar et al., 2000; Lee et al., 2010; Tupin et al., 2008). Thus, in this infection, iNKT cells serve an early, non-redundant protective function, presumably due to their anatomical location within the sinusoids of the liver, their sensing of CD1d-presented antigen through their semi-invariant TCR, and their rapid production of a key protective cytokine.

The fact that several of the innate and innate-like lymphocyte subsets exhibit considerable species-specific variation in their abundance suggests that their functions are conserved, but not the particulars—i.e., the specific cell type responsible for these functions. As an illustration, iNKT cells, a major liver lymphocyte subset in mice, represent no more than 1% of liver lymphocytes in humans (Kenna et al., 2003). Conversely, MAIT cells comprise up to 45% of liver T cells in humans but only a small percentage in the common C57BL/6J strain of laboratory mouse (though they are 20-fold more abundant in wild-derived CAST/EiJ mice

than in C57BL/6J mice) (Cui et al., 2015). Species differences in tissue-resident lymphocytes are perhaps even more striking for γδ T cells; γδ T cells are less abundant in humans and mice than in cattle and swine, and the diversity or oligoclonality of γδ T cells differs significantly in different mammals (Hein and Dudler, 1997; Hein and Mackay, 1991; Mackay and Hein, 1989; Van Rhijn et al., 2007). Furthermore, $V\gamma3V\delta1^+$ DETCs are absent in humans, while $V\gamma9V\delta2^+$ T cells, which are the most abundant population of γδ T cells in human peripheral blood, are absent in mice. Going forward, a challenge will be to elucidate the relative contributions and non-redundant roles of individual tissue lymphocyte subsets, especially ILCs, for which specific genetic depletion strategies that preserve adaptive lymphocytes are only beginning to emerge. The first studies using such tools have suggested both redundant and non-redundant roles for ILCs in various experimental settings (Oliphant et al., 2014; Rankin et al., 2016; Song et al., 2015).

Superposition of Tissue-Resident Memory T Cells with Innate and Innate-like Lymphocyte Subsets

The innate and innate-like lymphocytes cohabit non-lymphoid organs with long-lived $CD4^+$ or $CD8^+$ tissue-resident memory T (T_{RM}) cells expressing conventional, diverse, MHC-restricted αβTCRs. T_{RM} cells seed tissues early during the immune response to infection and represent a subset distinct from recirculating memory T cells in blood and secondary lymphoid organs (Clark, 2015; Schenkel and Masopust, 2014; Stary et al., 2015). Like innate tissue-resident lymphocytes, T_{RM} cells are numerically prominent in the mucosal tissues where pathogen encounter first occurs, with the highest seeding of T_{RM} found at the site of infection; upon repeated infections, some degree of cross-protection of adjacent epithelium and distant epithelial tissues can also occur (Jiang et al., 2012). Tissue microenvironmental factors, mostly as yet undefined, likely have a role in shaping the phenotype of embedded T_{RM} cells. For example, epidermal T_{RM} cells adopt a dendritic morphology reminiscent of Langerhans cells and DETCs, which share the same niche, and distinct from T_{RM} cells of the same TCR specificity that have seeded the dermis (Zaid et al., 2014). In the absence of reinfection, these epidermal T_{RM} cells have been shown to scan swathes of epidermis in a matter of hours through slow, non-directed Brownian motion (Zaid et al., 2014). Upon encounter with cognate antigen, T_{RM} cells elaborate soluble factors, which rapidly engender an antimicrobial state in parenchymal cells, and recruit and activate other immune cells (Ariotti et al., 2014; Schenkel et al., 2013, 2014). Although the initial trigger for T_{RM} cell reactivation is cognate antigen, the generation of a nonspecific, tissue-wide state of alarm can offer protection against non-cognate pathogens. Thus, the differentiation of antigen-specific lymphocytes into T_{RM} cells enables them to mount an innate-like response with the rapidity and frontline surveillance features of innate lymphocytes. At the same time, T_{RM} cells retain the diversity, specificity, and amplifying function characteristic of adaptive T cells. It must be noted that tissue-resident innate and innate-like lymphocytes and T_{RM} cells may be differentially important at different stages of development. For example, it has been seen that after infection, T_{RM} cells displace DETCs from the skin (Zaid et al., 2014). Likewise, intestinal induced IELs gain numerical prominence over natural IELs with age (Cheroutre et al., 2011). Thus, lymphocyte subsets that seed tissues in fetal life and have limited regeneration potential may be functionally and

even physically superseded by adaptive cells later in life after exposure to serial infections or injuries.

Concluding Remarks

It seems reasonable to assume that, taken in isolation, T_{RM} cells function primarily in antimicrobial immunity and eschew the tissue-supportive roles of their innate and innate-like cousins. However, we favor the broader view of tissues as diverse “ecosystems” composed of multiple cell types, where T_{RM} and other tissue-resident lymphocytes, in coordination with macrophages and additional cell types, provide a robust and multifaceted protection of tissue function and integrity upon diverse inflammatory insults and injuries. A previously proposed crosstalk between tissue-resident innate and adaptive lymphocytes can be viewed as a part of the still poorly understood web of communications between parenchymal, immune, and other accessory cells in an organ (Carnaud et al., 1999; Gasteiger and Rudensky, 2014; Okabe and Medzhitov, 2014). Beyond the common hallmarks shared by diverse classes of tissue-resident lymphocytes, specific tissues may imprint resident lymphocytes with unique features tailored to those tissues. This imprinting has been well appreciated for specialized embryonic-derived macrophages (e.g., microglia versus Langerhans cells), but only a few examples have been observed for resident lymphocytes (Amit et al., 2015; Okabe and Medzhitov, 2015; Perdiguero and Geissmann, 2015). As one example, Treg cells in visceral adipose tissue express the transcription factor PPAR-γ, which contributes to their distinct transcriptional profile and enables their accumulation in adipose tissue (Bapat et al., 2015; Cipolletta et al., 2012, 2015). However, the environmental factors that drive this imprinting in the adipose tissue remain largely unknown, although IL-33 and TCR signaling may help maintain some aspects of this transcriptional program (Kolodin et al., 2015; Vasanthakumar et al., 2015). The specific mediators that imprint resident cells have been best worked out for the intestine. In the intestine and related organs, retinoic acid from dietary sources has a major role in imprinting naive T cells, ILCs, IELs, peritoneal macrophages, and tolerogenic dendritic cells, the last of which additionally support extrathymic Treg cell differentiation, IgA class switching, and expression of gut-homing molecules (Coombes et al., 2007; Iwata et al., 2004; Mora et al., 2006; Mucida et al., 2009; Okabe and Medzhitov, 2014; Reis et al., 2014; Spencer et al., 2014; Sun et al., 2007; Suzuki et al., 2010; van de Pavert et al., 2014). However, despite these advances in our understanding of tissue-associated factors, a comprehensive framework for understanding the tissue microenvironments that shape identity of resident lymphocyte subsets is still lacking. The elucidation of the relationships between parenchymal cells, tissue-resident innate and adaptive lymphocytes, and other cells in this complex ecosystem, their hierarchy, and their means of communication would inform an integrated view of tissue function in health and disease and may offer novel means of therapeutic intervention in diverse inflammatory disorders and cancer.

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Box 1

Hallmarks of Tissue-Resident Lymphocytes

- Long-term maintenance and self-renewal
- Abundance at barrier tissues
- Sensing of microbial products, cytokines, alarmins, and stress ligands
- Rapid provision of antimicrobial and tissue-protective factors

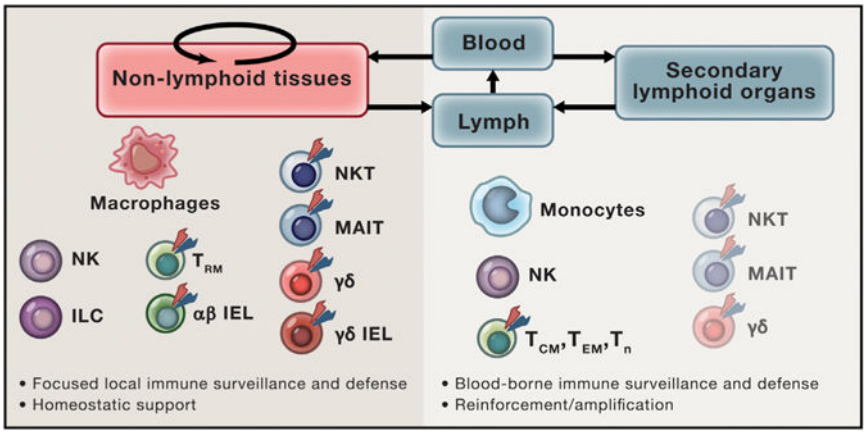

Figure 1. Tissue-Resident versus Recirculating Lymphocytes and Their Functions

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.

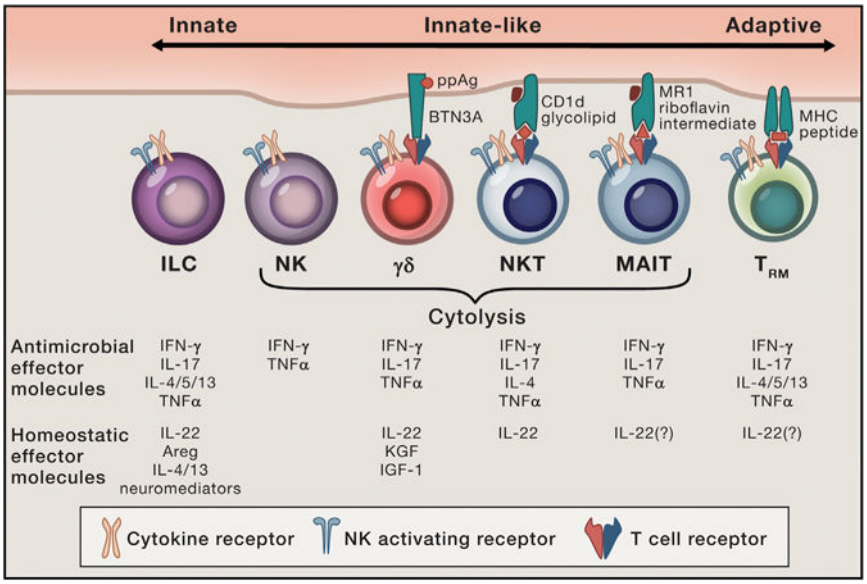

Figure 2. Modes of Sensing and Provision of Effector Function by Tissue-Resident Innate, Innate-like and Adaptive Lymphocytes

Note that γδTCRs can be activated by a variety of antigens with or without presenting molecules; only one mode of γδTCR activation is shown. Also, both CD4+ and CD8+ T_{RM} cells have been described, although only the former is depicted.

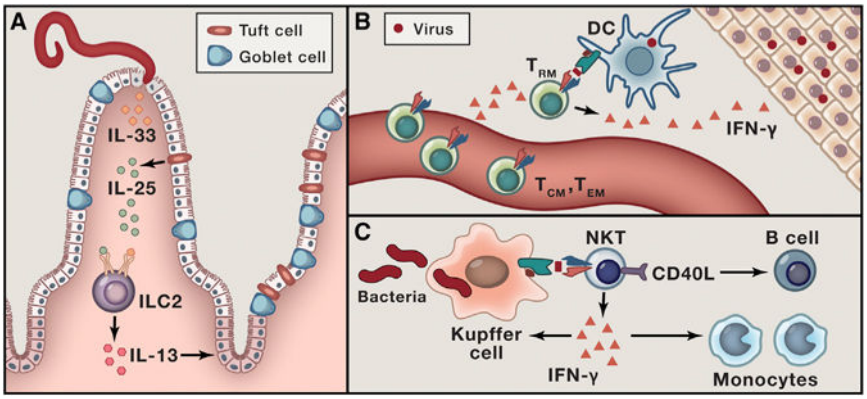

Figure 3. Amplification of Immune Responses by Tissue-Resident Lymphocytes

(A) Feed-forward loop in the early type 2 response to intestinal helminth infection. Helminth infection triggers release of IL-33 from dying epithelial cells and IL-25 from chemosensory tuft cells. These cytokines activate ILC2s to produce IL-13, which acts on the stem cell compartment to induce goblet and tuft cell hyperplasia.

(B) Triggered by cognate antigen, CD8+ T_{RM} cells release interferon-gamma, which initiates a tissue-wide state of alarm and recruits circulating memory cells.

(C) NKT cells rapidly produce cytokines and upregulate CD40L after being activated by Kupffer cells presenting CD1d-bound glycolipids derived from bloodborne bacterial pathogens.