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Review

Innate Lymphoid Cells in Inflammation and Immunity

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Innate lymphoid cells (ILCs) were first described as playing important roles in the development of lymphoid tissues and more recently in the initiation of inflammation at barrier surfaces in response to infection or tissue damage. It has now become apparent that ILCs play more complex roles throughout the duration of immune responses, participating in the transition from innate to adaptive immunity and contributing to chronic inflammation. The proximity of ILCs to epithelial surfaces and their constitutive strategic positioning in other tissues throughout the body ensures that, in spite of their rarity, ILCs are able to regulate immune homeostasis effectively. Dysregulation of ILC function might result in chronic pathologies such as allergies, autoimmunity, and inflammation. A new role for ILCs in the maintenance of metabolic homeostasis has started to emerge, underlining their importance in fundamental physiological processes beyond infection and immunity.

Introduction

The innate lymphoid cell (ILC) family includes group 1 ILCs (ILC1s) that predominantly express interferon-γ (IFN-γ), ILC2s that predominantly express interleukin-5 (IL-5), IL-9, and IL-13, and ILC3s that predominantly express IL-22 and/or IL-17 (Halim and McKenzie, 2013; Licona-Limón et al., 2013; Spits et al., 2013; Walker et al., 2013). They play roles in protective immunity against bacteria (ILC1s and ILC3s) (Sanos et al., 2009; Sawa et al., 2011; Sonnenberg et al., 2012), intracellular parasites (ILC1s) (Klose et al., 2014), fungi (ILC3) (Gladiator et al., 2013), and parasitic worms (ILC2s) (Moro et al., 2010; Neill et al., 2010; Price et al., 2010), and in autoimmune disorders (ILC1s and ILC3s) (Buonocore et al., 2010), allergic disease (ILC2s) (Barlow et al., 2012), and obesity (ILC2s) (Hams et al., 2013; Molofsky et al., 2013). Here we focus on the most recent advances in our understanding of the role of ILCs in inflammation and immunity, highlighting their essential roles in maintaining immune homeostasis.

ILC2s in Type-2 Immunity

ILC2s represent a critical innate cellular source of type 2 cytokines (including very high amounts of IL-5 and IL-13, but also IL-9, IL-4, and GM-CSF) (Moro et al., 2010; Neill et al., 2010; Price et al., 2010). The early expression of these effector cytokines potently induces eosinophilia, mucus production from goblet cells, activation of alternatively activated macrophages (AAM), muscle contractility, mastocytosis, and contribute to tissue repair (Allen and Sutherland, 2014; Fallon et al., 2002) (Figure 1). The critical importance of ILC2s in type 2 immunity has been revealed recently using gene-targeted mouse models in which ILC2s are transferred, deleted genetically, or ablated temporally (Liang et al., 2012; Neill et al., 2010; Oliphant et al., 2014). ILC2s comprise the predominant source of IL-13 during parasitic helminth infection (Moro et al., 2010; Neill et al., 2010; Price et al., 2010) and expand in allergic lung inflammation (Barlow et al., 2011; Chang et al., 2011; Halim et al., 2012; Klein Wolterink et al., 2012; Mjösberg et al., 2011; Monticelli et al., 2011). Recent reports have also associated ILC2s with metabolic homeostasis, obesity, and dietary stress (Hams et al., 2013; Molofsky et al., 2013; Stanya et al., 2013).

Control of ILC2s in the Transition from Innate to Adaptive Immunity

Early characterization of ILC2s demonstrated that IL-2 and IL-7 potently induced their proliferation and that hematopoietic cytokine γc receptor (a subunit of the IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptors) signaling was critical for ILC2 development (Moro et al., 2010; Neill et al., 2010; Price et al., 2010). Subsequently, IL-4 and IL-9 have also surfaced as regulators of ILC2 activation (Motomura et al., 2014; Turner et al., 2013), and a more complex pattern of γc-ligand control of ILC2 function has begun to emerge. Consequently, the cellular sources and temporal secretion profiles of specific ILC2-modulating cytokines appear to evolve and fluctuate during the maturation of the immune response. The in vivo sources of IL-7 required for ILC development are unknown, but IL-7 is critical for the generation and maintenance of all lymphocytes and is expressed by stromal cells in the bone marrow and the lymphatic endothelial cells in lymph nodes, skin, and intestine (Hara et al., 2012). This suggests that IL-7 is an early signal in ILC2 development and also a regulator of ILC2 activity at sites where the stromal cell-derived cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), which induce ILC2 growth and type 2 cytokine production, might also be released. Basophil-derived IL-4 has also been proposed to play a role in the ILC2 response to acute papain challenge (Motomura et al., 2014), though a role for IL-4 was less clear in other papain models (Halim et al., 2014). Although a number of studies have reported little IL-4 expression by ILC2s, in vivo antigen challenge can induce IL-4 (Oliphant et al., 2014), which raises the possibility that it might also act as an autocrine factor. Certainly autocrine IL-9 production by ILC2s is of importance, being produced transiently by activated ILC2s to augment ILC2 survival and cytokine expression (Wilhelm et al., 2011). Indeed, the absence of IL-9 results in reduced ILC2-derived amphiregulin expression and impaired tissue repair (Turner et al., 2013).

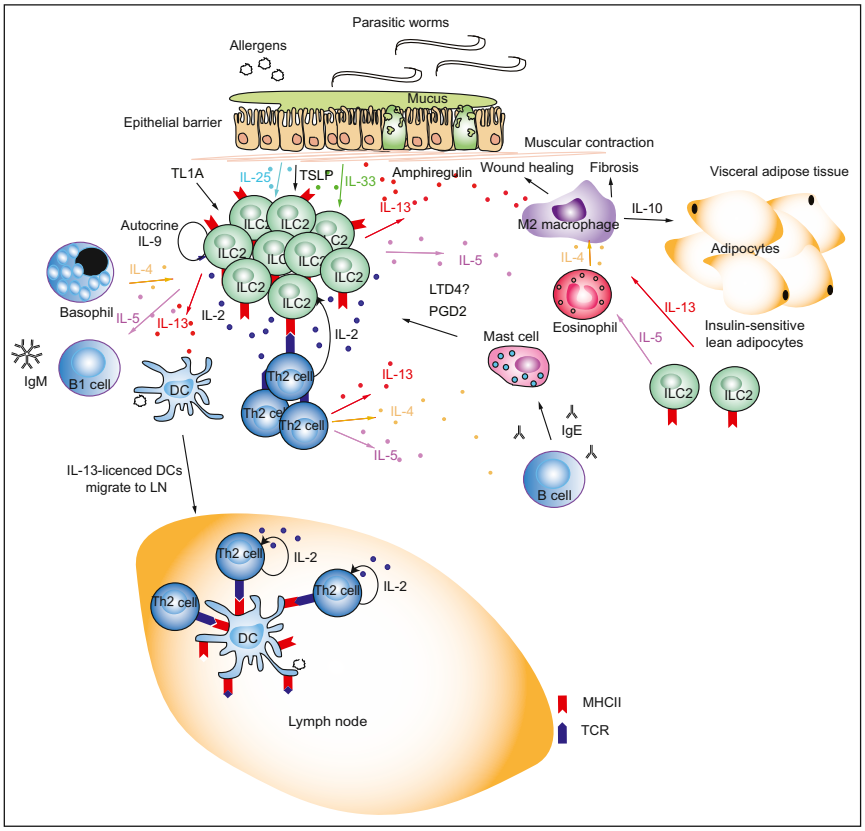

Figure 1. ILC2s in Type 2 Immunity and Homeostasis

Stimuli such as allergens or parasitic worms lead to the release of ILC2-inducing factors from the epithelium and infiltrating inflammatory cells. These cytokines cause ILC2s to proliferate and produce type 2 cytokines and activate type 2 effector pathways. This leads to the transition from innate to adaptive immunity. ILC2s also contribute to maintaining metabolic homeostasis. PGD2, prostaglandin D2 receptor; LTD4, leukotriene D4. See main text for details on differences between human and mouse.

A new role for ILC2s in directly regulating T cell activation has been proposed recently (Drake et al., 2014; Mirchandani et al., 2014; Oliphant et al., 2014). Through their expression of major histocompatibility complex II (MHCII), ILC2s can present antigen to T cells, though less efficiently than dendritic cells (DCs), inducing T cell-derived IL-2 production. Consequently, ILC2s, which express IL-2 receptors, proliferate and generate a highly enriched type 2 cytokine environment. This crosstalk between ILC2s and T cells is functionally important, because, in contrast to wild-type ILC2s, transfer of MHCII-deficient ILC2s into *Il13*$^{-/-}$ mice resulted in a delay in expulsion of parasitic helminth worms (Oliphant et al., 2014). IL-4 and OX40 ligand (OX40L) have also been suggested to contribute to the stimulatory crosstalk between ILC2s and T cells (Drake et al., 2014). Such T cell- and ILC2-derived signals appear to be important for maintaining ILC2s at the site of inflammation (Neill et al., 2010) and suggest that as the immune response matures ILC2s move from stromal and autocrine cytokine dependence to cytokines produced by the adaptive response. In addition to this dialog between ILC2s and T cells, ILC2s can also influence the onset of the adaptive T helper 2 (Th2) cell-mediated response by modifying DC function. ILC2-derived IL-13 was critical for rapid induction of Th2 cells, not by acting directly on naive CD4^{+} T cells, but by licensing the migration of activated DCs to the lung-draining lymph node (Halim et al., 2014). Therefore it was suggested that the deficit in primed DCs in the secondary lymphoid organs, in the absence of ILC2-produced IL-13, led to impaired Th2 cell priming (Halim et al., 2014). The involvement of ILC2s in the maturation of adaptive type 2 immunity appears to be limited to local mucosal surfaces since systemic antigen exposure was not perturbed by the absence of ILC2s (Gold et al., 2014). It waits to be determined whether ILC2 might also indulge in an antagonistic discourse with T cells leading to dampened responses such as those reported for ILC3 interactions with T cells (Hepworth et al., 2013).

Importantly, and perhaps consistent with an enduring dialog with the adaptive immune system, ILC2s are associated with chronic human diseases, such as asthma, cirrhosis, idiopathic pulmonary fibrosis, and atopic dermatitis, where they correlate with IL-25, IL-33, and/or TSLP cytokine profiles. Experimental mouse models have confirmed the functional involvement of ILC2s in these diseases; for example, IL-25 was sufficient to induce IL-13-secreting ILC2s and the onset of collagen deposition in the lungs of mice challenged with type 2 response-inducing schistosome eggs (Hams et al., 2014). Similarly, IL-33-deficient mice and ILC2 depletion strategies were used to demonstrate that IL-33-induced ILC2s were required for tissue remodeling and fibrosis in a mouse model of hepatic fibrosis (McHedlidze et al., 2013). However, the IL-33-ILC2-IL-13 axis has also been reported to mediate tissue repair functions in a mouse model of biliary injury by promoting epithelial restoration (Li et al., 2014). Similarly, lung ILC2s expressed amphiregulin to regulate wound healing after infection with the H1N1 influenza virus, where they initially exacerbate viral-induced airway hypersensitivity (Monticelli et al., 2011). Together these data illustrate that ILC2s, depending on the disease and experimental model, can contribute both to pathology and tissue repair.

ILC2s in Allergy and Asthma

Consistent with the identification of a gene signature (*IL1LR1* [IL-33R], *RORA*, *IL2RB*, and *IL13*) in human asthma that implicates ILC2 involvement (Moffatt et al., 2010), ILC2s have been shown to expand in experimental models of allergic lung inflammation in mice, and their production of type 2 cytokines contributes to disease pathology (Barlow et al., 2011; Chang et al., 2011; Halim et al., 2012; Klein Wolterink et al., 2012; Mjösberg et al., 2011; Monticelli et al., 2011). Induction of ILC2s during the early phase of mucosal immune responses is achieved through the actions of the epithelium-derived cytokines IL-25, IL-33, and TSLP, which

have variously been reported to associate with airway remodeling and viral asthma exacerbation (Gorski et al., 2013; Gregory et al., 2013; Hong et al., 2014; Saglani et al., 2013). These cytokines show redundancy in the induction of ILC2s to various stimuli (Neill et al., 2010; Salimi et al., 2013; Van Dyken et al., 2014) and are now joined by TL1A (*Tnfsf15*), a tumor necrosis factor (TNF)-family member that can also directly activate ILC2s to produce type 2 cytokines (Meylan et al., 2013; Yu et al., 2013). Although these cytokines display a degree of redundancy, the signaling pathways for these molecules are discrete and functional differences have been reported. For example, IL-33 has been shown to have a more potent effect on ILC2 activity than IL-25 in response to ragweed and *Alternaria alternata* challenge (Barlow et al., 2013; Hardman et al., 2013). Furthermore, induced steroid resistance of ILC2s was recently reported as TSLP dependent (Kabata et al., 2013), where IL-33 in combination with antigen resulted in ILC2s with increased resistance to steroid treatment than T cells. This required STAT5 and could be inhibited with pimozide (a STAT5-inhibiting antipsychotic drug).

Atopic dermatitis (AD) is a common pruritic inflammatory skin disease associated with barrier dysfunction and adaptive immune responses to common environmental allergens, characterized by the presence of Th2 cells and high amounts of IL-13 and IL-4 and often associated with asthma (Kim et al., 2012; Leung et al., 2004). Increased transcripts encoding IL-33 and IL-25 have been detected in acute lesional atopic dermatitis skin (Hvid et al., 2011; Miller, 2011), and ILC2s have been reported recently to arise with increased frequency in mouse and human atopic lesional skin (Kim et al., 2012; Salimi et al., 2013).

Notably, Ogg and colleagues proposed a mechanism for ILC2 sensing of barrier dysfunction in humans through the inhibitory receptor KLRG1. They demonstrated in vitro that the presence of E-cadherin, a known ligand of KLRG1, downregulated ILC2 cytokine expression (Salimi et al., 2013). As E-cadherin expression is reduced in AD lesions, this pathway might contribute to cytokine hyperproduction by skin ILC2s. A calcipotriol-induced mouse model of atopic dermatitis-like inflammation supported a role for ILC2s, independently of T cells, in the initiation of skin inflammation and the involvement of IL-25, IL-33, or TSLP in ILC2 induction in the skin (Kim et al., 2013; Salimi et al., 2013). Thus, ILC2s are regulated by a spectrum of epithelium-derived factors that influence their threshold of activation in response to infection or tissue damage.

Inhibiting ILC2s

In addition to biologics, such as antibodies against IL-25, IL-33, and TSLP that might be used to inhibit ILC2 proliferation and function (Ballantyne et al., 2007; Coyle et al., 1999; Gauvreau et al., 2014; He et al., 2008), a number of small molecule inhibitors have been shown to block ILC2 function by inhibiting arachadonic acid metabolites. For example, blocking prostaglandin D_2 (PGD_2) binding to chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2), which is highly expressed on human ILC2s, inhibits ILC2 chemoattraction and expression of IL-4, IL-5, IL-9, and IL-13 (Barnig et al., 2013; Chang et al., 2013; Xue et al., 2014). As mast cells produce PGD_2 predominantly after immunoglobulin E (IgE)-high-affinity IgE receptor (FcεRI) crosslinking, ILC2s might be attracted and activated by this pathway during adaptive type 2 immune responses. Notably, intravital imaging of mouse skin indicated that ILC2s interact with mast cells and produced IL-13 (Roediger et al., 2013). Similarly ILC2s express cysteinyl leukotriene receptor 1 (CysLT1R) and respond to leukotriene D_4 (LTD_4) by expressing type 2 cytokines, which can be inhibited by Montelukast, a leukotriene receptor antagonist (Doherty et al., 2013; Xue et al., 2014). Human ILC2s also bind the resolvin, lipoxin A_4, an anti-inflammatory derivative of arachadonic acid that partially inhibited ILC2-produced IL-13 in vitro (Barnig et al., 2013). Thus, to-date potential therapeutic strategies have focused on targeting soluble mediators that activate ILC2s. In future, a better understanding of the factors required for ILC2 development and maintenance might facilitate more specific approaches to directly target ILC2s.

ILC2s in Diet and Obesity

Growing evidence links ILC2s and type 2 cytokines with metabolic homeostasis, obesity, and dietary stress (Hams et al., 2013; Molofsky et al., 2013; Stanya et al., 2013). ILC2s are widely distributed in tissues of the body and are found constitutively in visceral adipose tissue (VAT). Here they provide IL-5 and IL-13 for the maintenance and induction of eosinophils and AAM, with deficiency of IL-5 and IL-13 leading to increased adiposity and insulin resistance (Molofsky et al., 2013). ILC2s have also been reported recently to coexpress IL-5 and IL-13 during the daily cycle of caloric intake and respond to the circadian synchronizer, vasoactive intestinal peptide via the VPAC2 receptor, resulting in cytokine expression associating with daily circadian rhythms (Nussbaum et al., 2013). Notably, administration of both IL-25 and IL-33 increased ILC2 cell numbers in mice fed a high-fat diet (HFD) and maintained a lean phenotype (Hams et al., 2013). However, the mechanisms by which eosinophils and AAM regulate glucose homeostasis and weight gain remain to be fully elucidated.

Just as overindulgence can destabilize the balance of ILC2-mediated cytokine regulation of metabolic homeostasis, so malnutrition can also disrupt ILC-regulated immunity. Vitamin A deficiency has been associated with immunodeficiency (Hall et al., 2011). Indeed, dietary deprivation of vitamin A in mice resulted in reduced frequencies of intestinal ILC3s, and this led to increased susceptibility to gastrointestinal bacterial infection with *Citrobacter rodentium* (Spencer et al., 2014). By contrast, intestinal ILC2s actually increased in frequency following vitamin A restriction and the mice displayed enhanced resistance to parasitic helminth infection. Administration of retinoic acid (a metabolite of vitamin A) to *Rag2*$^{-/-}$ mice induced ILC3, while a retinoic acid inhibitor stimulated ILC2 accumulation, probably through effects on retinoic acid sensitive ILC precursors. Thus, micronutrient deficiency might selectively provoke specific immune pathways that promote survival during periods of malnutrition. The authors suggest that although a deficiency in ILC3s might expose the host to acute intestinal pathogens, an increase in ILC2s might lessen the impact from commensals and helminth parasites when nutrients are limiting.

Thus ILC2s appear to be critically positioned to respond to environmental cues including metabolic stress and nutrient intake to maintain homeostasis and poised to rapidly respond to damage in multiple tissues. Upon epithelial damage, ILC2s become activated and provide immune stimulatory and wound healing signals. If injury continues, they might contribute to chronic pathology such as fibrosis and potentiate adaptive

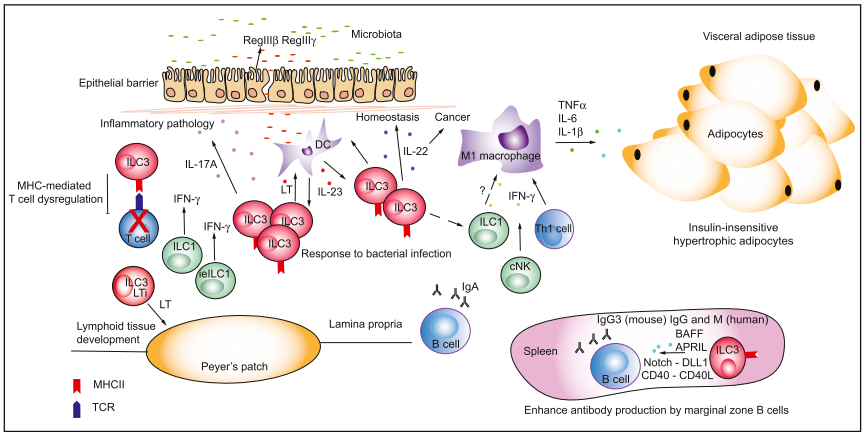

Figure 2. ILC1s and ILC3s in Immunity and Homeostasis

ILC3s maintain homeostasis in the presence of intestinal symbionts, but respond by inducing epithelial cell release of defensins such as RegIII upon mucosal invasion. ILC3s in the spleen induce antibody production. LTi initiate lymphoid tissue development. LT, lymphotoxin; ieILC1, intestinal epithelium ILC1; DC, dendritic cell; TCR, T cell receptor, DLL1, delta-like ligand 1; LTi, lymphoid tissue inducer. See main text for details on differences between human and mouse.

T cell responses. Although ILC2s are paramount in driving type 2 immune responses, other members of the ILC family have been shown to be central in type 1 and Th17 cell-mediated immunity and disease.

ILC3s in Homeostasis and Immunity

Group 3 ILCs are defined by their expression of RORγt and include lymphoid tissue inducer (LTi) cells (the first ILC3 subset that was discovered in the late 1990's; Adachi et al., 1997; Mebius et al., 1997) and ILC3s that express natural cytotoxicity triggering receptors (NCRs) and predominantly secrete IL-22 (Spits et al., 2013; Walker et al., 2013) (Figure 2). ILC3s express cytokines that play a central role in the development of lymphoid tissues and in the equilibrium between host and microbes at mucosal surfaces (Philip and Artis, 2013). Expression of membrane lymphotoxin (LT) $\alpha_1\beta_2$ by LTi cells, expressing chemokine receptor 6 (CCR6) (Adachi et al., 1997; Mebius et al., 1997), is required in the fetus to induce the development of lymph nodes and Peyer's patches through LTβ receptor (LTβR) expressed on stromal cells (De Togni et al., 1994; Eberl et al., 2004). After birth, a similar pathway leads to the formation of isolated lymphoid follicles (ILFs) in the intestinal lamina propria (Bouskra et al., 2008). Through $LT\alpha_1\beta_2$, ILC3s also activate intestinal epithelial cells to produce the chemokines chemokine (C-X-C motif) ligand 1 (CXCL1) and CXCL2 in response to infection by *Citrobacter rodentium* (Wang et al., 2010). These chemokines are associated with neutrophil recruitment and improved bacterial clearance.

The $LT\alpha_1\beta_2$ pathway is further involved in the positive regulation of IL-22, a cytokine produced by ILC3s, which plays a fundamental role in mucosal immunity through its effects on epithelial cells. Both LTi cells and the other major subset of $CCR6^-$ $NKp46^+$ ILC3s are the major producers of IL-22 (Cella et al., 2009; Cupedo et al., 2009; Satoh-Takayama et al., 2008), because mice lacking ILC3s largely recapitulate the phenotype of IL-22-deficient mice (Zheng et al., 2008). IL-22-production by ILC3s is induced by IL-23 produced by DCs in a STAT3-dependent manner, whereas ILC3s enhance IL-23 production by DCs through activation of LTβR in a positive feedback loop (Tumanov et al., 2011). Upon activation by IL-22, epithelial cells express antimicrobial proteins (AMPs) such as RegIIIβ and RegIIIγ, which establish a gradient of resistance to bacterial colonization in the intestinal lumen (Liang et al., 2006). In the absence of IL-22, susceptibility to *C. rodentium* infection (Zheng et al., 2008) and dextran sodium sulfate (DSS)-induced colitis (Zenewicz et al., 2008) is increased, and containment of invasive symbionts is significantly decreased (Sonnenberg et al., 2012).

ILC3s in Disease

In contrast to their protective role in producing IL-22, ILC3s can also promote pathology. IL-22 can contribute to colon cancer in susceptible 129SvEv.*Rag*$^{-/-}$ mice infected with *Helicobacter hepaticus* and treated with the genotoxin 2-azoxymethane (AOM) (Kirchberger et al., 2013). Thus, IL-22 is a double-edged sword, induced to protect from intestinal damage, but promoting tumorigenesis when uncontrolled (Huber et al., 2012). Thus, IL-22 activity must be tightly controlled, at least in part, by the DC-produced IL-22-binding protein that neutralizes IL-22 (Huber et al., 2012). Interestingly, IL-22-producing $CD3^-$ cells were found within human colorectal carcinoma (CRC) tumors, and these cells might constitute ILC3s. However, a role for IL-22 in human carcinogenesis has yet to be determined (Kirchberger et al., 2013).

The frequencies of ILC3s are significantly increased in skin lesions and also in peripheral blood of psoriasis patients (Teunissen et al., 2014; Villanova et al., 2014). Interestingly, one patient who showed a therapeutic response to anti-TNF antibodies, as evidenced by reduction in psoriatic plaques, had an associated decrease in circulating NCR^+ILC3 (Villanova et al., 2014). IL-17- and IL-22-producing NCR^+ILC3s were also induced in skin lesions of mice that develop a psoriasis-like disease following treatment with Aldara cream, and loss of IL-17 and IL-22 reduced the severity of the disease (Pantelyushin et al., 2012). These findings together suggest a role of NCR^+ILC3 in psoriasis.

IL-17-production by ILC3s has now also been linked with obesity-associated asthma, through a mechanism that involves the induction of IL-1β expression by macrophages after feeding mice a high-fat diet (Kim et al., 2014). Notably, IL-22 produced by ILC3s favors the development of obesity, although this occurs indirectly by controlling the composition of the intestinal microbiota (Upadhyay et al., 2012). Because the ratio of type 2 to type 1 cytokines appears to play a key role in regulating obesity, it will be informative to determine whether IFN-γ-expressing ILC1s (or "ex-ILC3s") influence weight gain by skewing macrophage polarization to an M1-phenotype.

A correlation between ILC3s and multiple sclerosis (MS) has also been reported recently (Perry et al., 2012). An increased frequency of ILC3s was shown to associate with MS and treatment

with the anti-CD25-blocking antibody, daclizumab, resulted in the reduction of ILC3s in peripheral blood and a decrease in intrathecal inflammation. However, the effects of anti-CD25 treatment extend beyond ILC3s, and an initial report using a mouse model of experimental autoimmune encephalomyelitis (EAE) failed to show a causative role for ILC3s in this disease (Mair and Becher, 2014).

ILC3s Crosstalk with Adaptive T and B Cells

New functions for ILC3s in influencing adaptive immunity have recently been discovered. In Th17 cells, the production of GM-CSF has been associated with autoimmune inflammation in the models of EAE and collagen-induced arthritis (CIA) (Codarri et al., 2011; El-Behi et al., 2011). However, during intestinal homeostasis, another role for GM-CSF has been uncovered. Microbiota activate the production of IL-1β by macrophages, which induces GM-CSF production by ILC3s. GM-CSF then feeds back on macrophages to produce retinoic acid (RA) and induce the differentiation of regulatory T (Treg) cells, thereby promoting oral tolerance (Mortha et al., 2014). Earlier, it was shown that RA promotes the generation of Tregs that express RORγt, the signature transcription factor for ILC3s and Th17 cells (Lochner et al., 2008). An association between RA and ILC3-mediated responses has been further documented during the fetal maturation of LTi cells through RA receptors (RAR) or retinoid X receptors (RXR) binding to RA response elements in the *Rorgt* locus (van de Pavert et al., 2014), and the lineage decision between ILC2s and ILC3s (Spencer et al., 2014).

Even though ILC3s were known to express MHCII (Eberl et al., 2004; Mebius et al., 1997), only recently have they been shown to produce the antigen-processing machinery for class II presentation and be able to regulate T cell responses to microbiota (Hepworth et al., 2013). Whether antigen presentation by ILC3s can also induce T cell effectors in an inflammatory context remains to be assessed. In return, lymphocytes negatively regulate the number and function of ILCs. In RAG-deficient mice, the expression of IL-22 by ILC3s is increased (Korn et al., 2014; Sawa et al., 2011). However, it is unclear whether this results from the direct inhibition of ILC3s by T or B cells or whether it is due to decreased competition for a common stimulating factor, such as IL-23. In addition, DCs have been found to negatively regulate the activity of ILC3s during homeostasis by relaying type 2 signals such as IL-25, induced by microbiota and produced by epithelial cells (Sawa et al., 2011).

Gut ILC3s also interact with B cells. They promote the production of IgA through both membrane $LT\alpha_1\beta_2$ and soluble $LT\alpha_3$, the former regulating DC activity through LTβR, and the latter promoting the recruitment of T cells through TNF receptors (Kruglov et al., 2013). In both mice and humans, ILC3s are located in the perifollicular zone of the spleen, where they communicate with marginal reticular cells via TNF and $LT\alpha1\beta2$ (Magri et al., 2014). Human splenic ILC3s express the plasma cell survival factor B cell activating factor (BAFF), CD40 ligand (CD40L), and Delta-like ligand (DLL) 1, which collaborate to activate marginal zone B cells to produce IgM (Magri et al., 2014). Human ILC3 co-opt neutrophils, probably through IL-8, that have marginal zone (MZ) plasma cell helper function to sustain T cell-independent antibody production. In mice, splenic ILC3s do not express BAFF or CD40L but do express DLL1 and the BAFF-related molecule a proliferation-inducing ligand (APRIL) and enhance IgG3, rather than IgM production. Mice do not express IL-8 and in their spleen neutrophils are recruited through GM-CSF (Magri et al., 2014). Thus in both mice and humans ILC3s aid T cell-independent antibody production, but through different mechanisms. Thus, in addition to providing innate regulation of intestinal homeostasis, ILC3s can influence T and B cells through a variety of mechanisms to either suppress or activate adaptive immunity.

ILC1 in Immunity and Pathology

NK Cells and ILC1s. Recent studies have provided more insight in the relationship of NK cells and other IFN-γ-producing ILCs. Initially, conventional (c) NK cells were classified in group 1 ILCs because they produce vast amounts of IFN-γ and express the transcription factor T-bet. However, cNK cells turn out to differ from other group 1 ILC subsets because they are developmentally dependent on Eomesodermin (Eomes, a T box transcription factor related to T-bet) and not on T-bet. Moreover, in contrast to other ILC1 subsets, NK cells express molecules, such as perforin, that mediate cytotoxic activity. Based on this and on studies into the developmental pathway of cNK cells and ILCs, it has been proposed that ILC1s, ILC2s, and ILC3s are the innate counterparts of $CD4^+$ T helper cells, whereas NK cells are the innate equivalents of $CD8^+$ cytotoxic T cells (Fuchs et al., 2013; Klose et al., 2014).

A T-bet-dependent Eomes-independent ILC1 subset was recently identified by RORγt cell-fate mapping in combination with a reporter allele for the transcription factor Eomes; these cells expressed NK1.1 and T-bet, but not Eomes, and were negative by RORγt lineage fate mapping. Like cNK cells, the $NK1.1^+$ILC1s are dependent on IL-15, although they do express the IL-7Rα chain (CD127). The $NK1.1^+$ ILC1s also expressed CD27 and produced high amounts of IFN-γ and TNF and protected mice against infection with the protozoan intracellular parasite *Toxoplasma gondii* (Klose et al., 2014).

Plasticity of ILC1s and ILC3s. A $Tbet^+Eomes^-CD127^+$ ILC1 subset, which is RORγt-dependent, was found in the mouse gut (Vonarbourg et al., 2010). A similar ILC1 subset was identified in lymphoid organs, tissues, and peripheral blood of humans (Bernink et al., 2013). In both humans and mice, these cells may arise from ILC3s downregulating RORγt and upregulating T-bet under the influence of inflammatory stimuli such as IL-12, IL-18, and IL-15 (Bernink et al., 2013; Vonarbourg et al., 2010). The ILC3-derived ILC1s (which are also referred to in some studies as ex-ILC3s) are therefore distinct from the $NK1.1^+$RORγt fate-map-negative ILC1s that never expressed RORγt during their development (Klose et al., 2014). In the mouse, development of ILC3s into ILC1s occurs gradually. $NKp46^-$ILC3s acquire the capacity to produce IFN-γ when they develop into $NKp46^+$ ILC3s in a T-bet-dependent way. Expression of T-bet results in a lower expression of RORγt and the ratio of RORγt and T-bet can be decreased further under the influence of cytokines such as IL-12 and IL-18, resulting in loss of the capacity to produce IL-17 and IL-22. Thus a gradient of RORγt and T-bet determines the phenotype and cytokine production of ILC3s and ILC3-derived ILC1s (Klose et al., 2013).

A similar differentiation of ILC3s into ILC1s was observed in humans but the transition of $IL\text{-}22^+$ and/or $IL\text{-}17^+$ ILC3s into IFN-γ-producing ILC1s was clearly distinguished by their downregulation of c-Kit and NKp44 expression (Bernink et al., 2013).

The c-Kit$^+$NKp44$^+$ ILC3s expressed RORγt, but no T-bet, whereas the ILC1s that developed from these cells lacked NKp44 and c-Kit, and expressed T-bet, but minimal amounts of RORγt (Bernink et al., 2013). ILC3s that adopt characteristics of ILC1s or differentiate into ILC1s (producing IFN-γ variably with IL-17 and/or IL-22) have been reported in the context of colitis in mouse and human and associated with intestinal pathology (Bernink et al., 2013; Buonocore et al., 2010; Coccia et al., 2012; Ermann et al., 2014; Geremia et al., 2011). Similar functions are expressed by CCR6$^-$ ILC3s during infection by *Salmonella enterica*, which also drive enterocolitis through T-bet-controlled production of IFN-γ as a result of the infection (Klose et al., 2013).

Another member of group 1 ILCs was described to be present specifically in the intestinal epithelium (ie) in both mice and humans and are termed ieILC1s (Fuchs et al., 2013). In humans, these cells expressed the NK marker CD94 and perforin, suggesting that they are closely related to cNK cells, but the mouse equivalent of these cells appears to develop in an IL-15-independent manner (Fuchs et al., 2013). Like ILC3-derived ILC1s, ieILC1s are also expanded in the intestine of Crohn's disease patients (Bernink et al., 2013, Fuchs et al., 2013), and in mice these ILC1 subsets promote colitis, presumably through their production of IFN-γ (Fuchs et al., 2013; Vonarbourg et al., 2010).

Perspectives

Recent work has led to a better understanding of the diversity of ILC subsets and their plasticity. Whereas ILCs were originally associated with acute innate immune responses to infection and tissue remodeling, it is now clear that ILCs play a much broader role as they are also involved in the regulation of adaptive immunity, chronic inflammation, and metabolic homeostasis. Although ILCs are present in small numbers in tissues, their strategic location at mucosal barriers in intimate proximity with epithelial surfaces enables them to regulate maintenance of immune homeostasis by balancing destructive immunity and "constructive" repair responses. It is clear that excessive activation may lead to ILCs contributing to chronic pathologies such as allergies, autoimmunity and inflammation, and the activation of adaptive immunity. Future research should be directed at understanding the mechanisms underlying the extensive array of biological activities of ILCs, especially in disease, and open new preventive and therapeutic avenues based on the modulation of ILC activity.

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