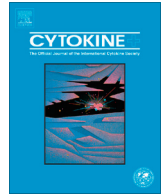




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Regulation of group 2 innate lymphoid cells

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ABSTRACT

Group 2 innate lymphoid cells (ILC2) exert critical roles in type 2 immune responses, epithelial repair at mucosal tissues and metabolic homeostasis. ILC2 rapidly provide large amounts of type 2 signature cytokines, thereby driving type 2 immune responses such as the defense against helminths. However, if deregulated, ILC2 facilitate tissue fibrosis and trigger unwanted type 2 immunopathologies such as allergies, asthma and atopic dermatitis. Therefore, ILC2 need to be tightly regulated and we are just beginning to understand which mediators activate or inhibit this rare but important cell population. In this review, we summarize current knowledge about positive and negative regulation of ILC2 and discuss its immunological consequences.

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1. Introduction

Innate lymphoid cells (ILC) are considered to be the innate counterparts of adaptive T helper cell populations. ILC can be subdivided into two main groups: cytotoxic and helper ILC. Whereas Natural Killer (NK) cells represent the group of cytotoxic ILC, the group of helper ILC is composed of ILC1, ILC2 and ILC3 [1]. Moreover, lymphoid tissue inducer cells (LTi) are helper ILC3 that are important in the organogenesis of secondary lymphoid organs [1]. ILC develop from a common lymphoid precursor (CLP) into a global innate lymphoid precursor (GILP) [2,3]. GILP give rise to cytotoxic ILCs (NK cells) and the common helper innate lymphoid progenitor (CHILP) that serves as a precursor for LTi, ILC1, ILC2 and ILC3 [4] (Fig. 1).

Similar to their adaptive T helper cell counterparts, ILC are defined by the production of signature cytokines as well as their transcription factor requirements, but unlike T cells, are activated independent of antigen recognition. As such, ILC are especially important in the onset and amplification of an immune challenge, thereby linking innate and adaptive immune responses. Moreover, ILC are involved in diverse processes of an immune response, from building the first line of defense against infectious pathogens to tissue repair, organogenesis as well as chronic inflammatory processes [5].

ILC2 act as central regulators of type 2 immune responses through the instruction of diverse effector pathways (Fig. 2). ILC2

have been first described as a non-B/non-T (NBNT) cell population [6] and were further defined in 2010 by independent laboratories as nuocytes [7], natural helper cells [8] and fat-associated lymphoid cluster cells (FALC) [9], which are now collectively referred to as group 2 innate lymphoid cells (ILC2) [10]. Development and maintenance of ILC2 requires different transcription factors such as GATA3, ROR α , TCF1 and GFI1 [11–15]. ILC2 are generally defined as lineage negative cells expressing CD127 (IL-7R α), CD25 (IL-2R α), ICOS, Sca-1, Thy1 (CD90), ST2 (IL-33R/ST2), IL-17RB, KLRG-1, and c-Kit [10,16]. However, depending on the ILC2 subtype, developmental stage and tissue localization, expression levels for some of these cell surface molecules vary [10,16] and the mechanisms responsible for these variations are largely unknown [17]. Interestingly, several of these surface receptors (e.g., CD25 and KLRG1) are shared with other lymphocytes such as T and NK cells and their expression level has been shown to vary with the cellular activation status [18–20]. It is becoming increasingly evident that the location and the microenvironment of ILC2 are important for their phenotype and function. ILC2 are induced upon different challenges including infections by viruses, helminths and fungi, but also upon exposure to different allergens such as house dust mite or papain [21] (see Fig. 3).

ILC2 are tissue-resident cells that are maintained and expanded locally under physiologic conditions, upon systemic perturbation of immune homeostasis and during acute infection [17,22]. These observations indicate that ILC2 are maintained by self-renewal in broadly different microenvironments and physiological settings and therefore suggest an extreme “sedentary” lifestyle that is consistent with the proposed roles of ILC as sentinels and local keepers of tissue function.

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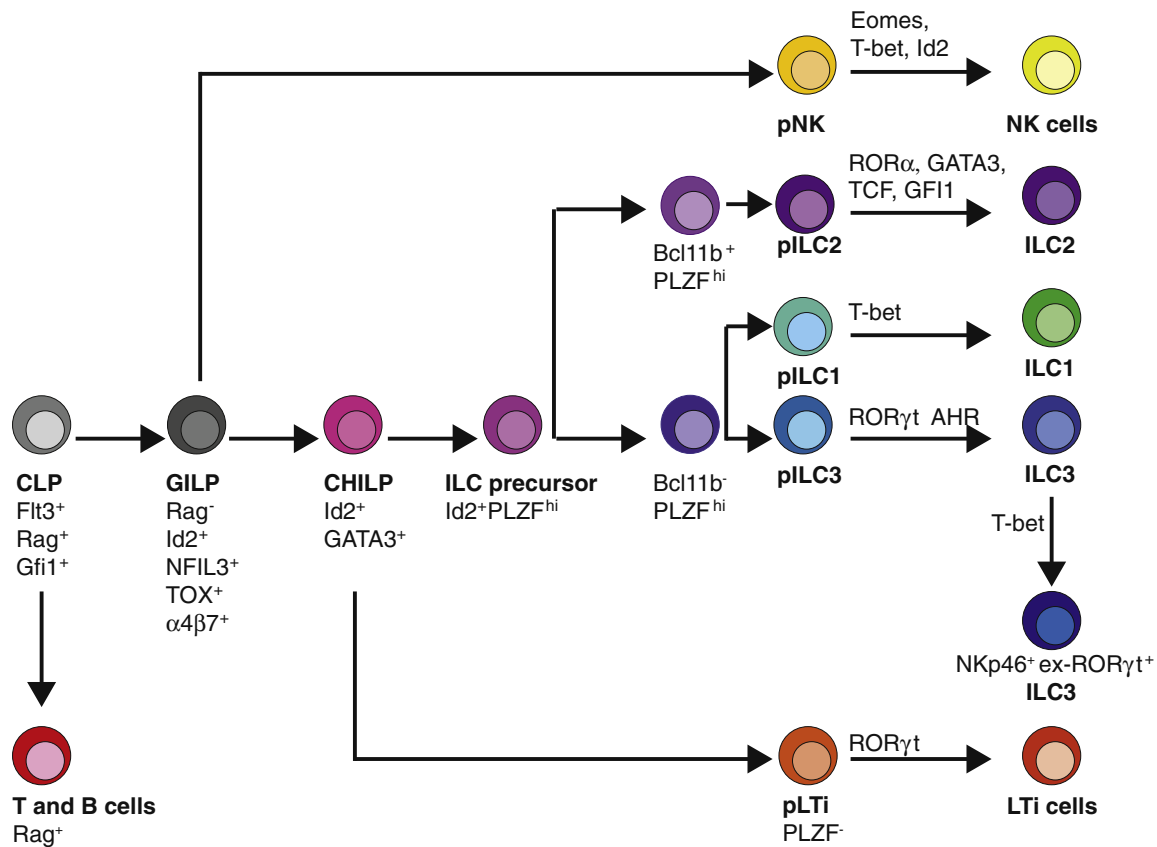


Fig. 1. Differentiation of innate lymphoid cells (ILCs). ILC develop from a common lymphoid precursor (CLP) into a global innate lymphoid precursor (GILP). GILP give rise to cytotoxic ILCs (NK cells) and the common helper innate lymphoid progenitor (CHILP) that serves as a precursor for LTi, ILC1, ILC2 and ILC3.

Overall, ILC2 are important players to defend the host against pathogens but can also lead to unwanted pathologies through the production of high levels of type 2 signature cytokines. Therefore, ILC2 need to be tightly regulated and fine-tuned. In this review, we summarize the latest work on modulation of ILC2 activation covering mediators of positive and negative regulation.

2. Positive regulation

2.1. IL-25, IL-33 and TSLP

IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) were the first cytokines described to induce ILC2 proliferation and cytokine production [1]. These ILC2-activating cytokines are expressed by tissue resident non-hematopoietic stromal cells as well as by cells of hematopoietic origin [23].

IL-25 (IL-17E) is a member of the IL-17 family and signals through a heterodimeric receptor, consisting of IL-17RB (IL-25 receptor) and IL-17RA. In addition, IL-17RB is able to form homodimers to transduce signals [24]. IL-17RA is also engaged in the signaling of IL-17A and IL-17F. Moreover, IL-17RA can pair with IL-17RD [24], however the ligand of this receptor combination has not yet been identified. IL-25 signaling leads to NF-κB translocation and activation involving TRAF6 and Act-1 [24]. While IL-25 has been shown to activate ILC2, it remains unknown if other IL-17 family members can regulate ILC2.

IL-33 (IL-1F11) is a member of the IL-1 family and stimulates ILC2 through the IL-33 receptor, which consists of ST2 and IL-1 receptor accessory protein (IL-1RAcP) [25]. ST2 can also be found as a soluble form (sST2), which has been suggested to act as a

decoy receptor [25]. However, the effect of sST2 on ILC2 regulation has not yet been addressed. IL-33 transduces downstream signaling similar to other members of the Toll-like receptor/IL-1 receptor superfamily, utilizing MyD88 to activate NF-κB and MAPK signaling [25].

The effect of TSLP on ILC2 is exerted through binding to a high-affinity TSLP receptor complex that consists of a TSLP-binding chain and the IL-7Rα subunit (CD127) [26]. IL-25 and IL-33 are the main cytokines currently known to drive expansion and cytokine production by ILC2. Although TSLP induces cytokine production by human but not by mouse ILC2, it reinforces GATA3 expression in a STAT5-dependent manner and therefore helps to sustain IL-25- and IL-33-induced activation [12]. In a murine model of atopic dermatitis, both, TSLP as well as IL-33 were shown to contribute to disease, indicating that these cytokines synergistically activate skin ILC2 [27].

Intraperitoneal (i.p.) IL-25 challenge of mice led to the discovery that this cytokine can prime a lineage negative cell population during type 2 immune responses [28]. In 2010, ILC2 were characterized in more detail, demonstrating that these cells express IL-17RB and ST2 as well as intermediate levels of c-Kit when isolated from mesenteric lymph nodes (mLN) [7]. Interestingly, ILC2 from mLN and spleen show differences of ST2 expression [7]. Moreover, utilizing an IL-13 reporter mouse line, differences in the location of IL-25-elicited versus IL-33-elicited ILC2 were observed. While ILC2 induced by IL-25 were detected predominantly in the villi of the small intestine, IL-33-elicited ILC2 were found to be more prominent in the crypt region [7]. Although IL-25 and IL-33 are the main cytokines driving expansion and cytokine production by ILC2, the relationship between IL-25- and IL-33-responsive ILC2 is still not clear, as ILC2 populations with different tissue distribution and

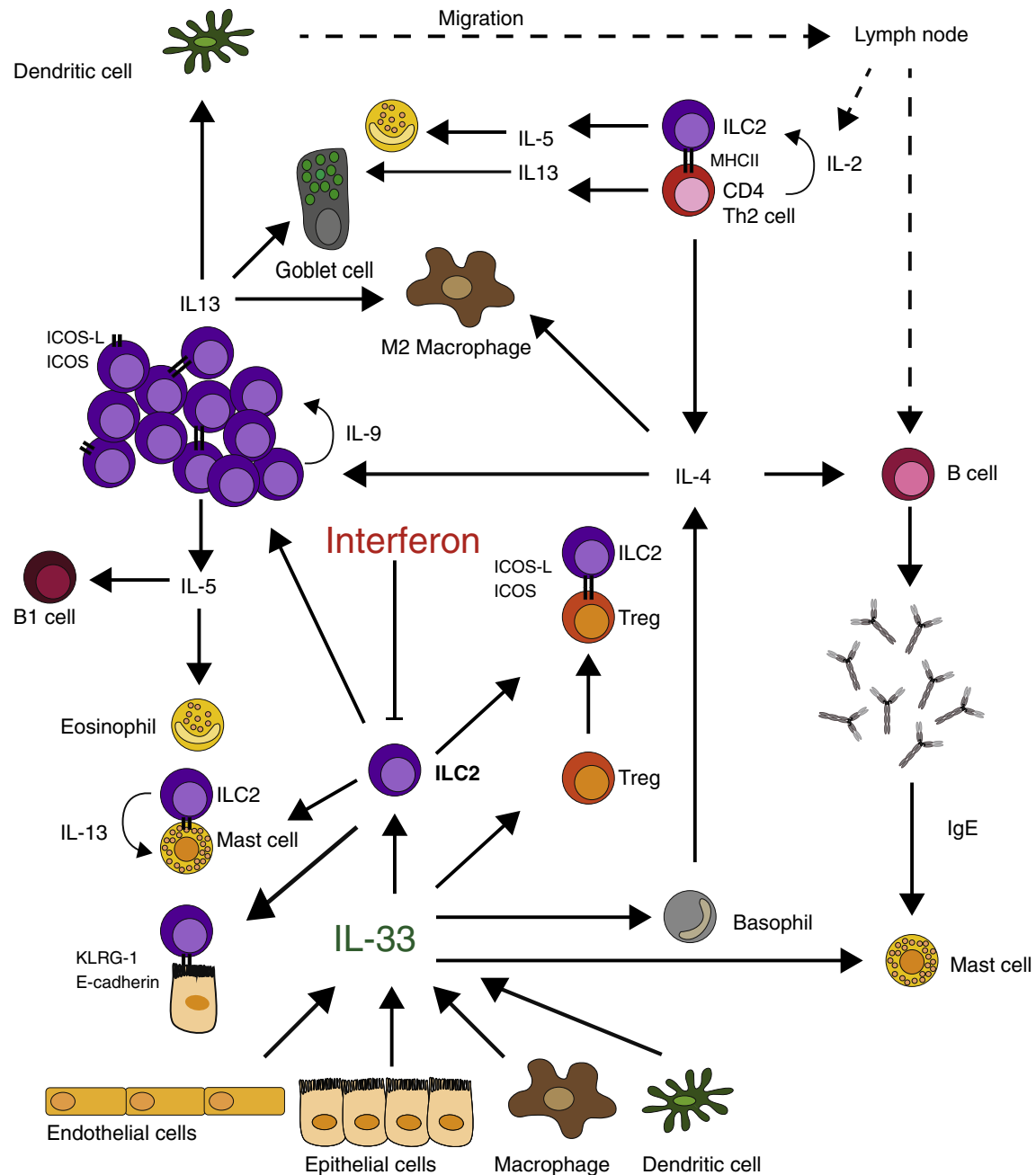


Fig. 2. The role of ILC2 for the regulation of type 2 immunity. ILC2 are induced by IL-33 and IL-25 released by stromal cells (e.g. endothelial and epithelial cells) and/or myeloid cells (e.g. macrophages). ILC2 activation is further sustained by ICOS/ICOS-L ligation and IL-4 and IL-9 stimulation. The secretion of type 2 cytokines by ILC2 induces mucus secretion by goblet cells (IL-13). In addition, IL-13 stimulates dendritic cell migration. Moreover, IL-13 activates tissue resident lung stellate cells to become fibrogenic myofibroblasts, thereby contributing to tissue fibrosis. Secretion of IL-9 and IL-5 by ILC2 leads to the recruitment and activation of mast cells and eosinophils, respectively. IL-5 further activates B1 B cells and is responsible for eosinophil homeostasis and activation. The activation of T helper (Th) cells in lymphoid organs further amplifies the secretion of type 2 cytokines, and the production of IL-4 by Th2 cells and basophils in lymphoid organs leads to the production of IgE by B cells. IL-4 and IL-13 collectively can further activate tissue-resident macrophages to acquire a type 2 polarization pattern. Together, the responses triggered by secretion of type 2 cytokines from both ILC2 and Th2 cells orchestrate type 2 immunity and its associated pathologies.

cytokine receptor-expression patterns have been reported. For example, in mLN, lower levels of ILC2 are induced upon IL-33 injection compared to IL-25 challenge [7]. However, in the lung, IL-33 elicits a stronger ILC2-inducing effect when compared to IL-25 upon intranasal challenge [29]. The distinct potential of IL-25 and IL-33 to induce ILC2 was followed by the identification of two separate pulmonary ILC2 populations, natural ILC2 (nILC2) and inflammatory ILC2 (iILC2) [30]. While nILC2 are characterized by their responsiveness to IL-33, iILC2 are triggered by IL-25, show

high KLRG1 expression and exert multipotent plasticity as they release IL-17A in addition to type 2 cytokines. However, recent evidence suggests that iILC2 may also depend on IL-33 as iILC2, elicited upon intraperitoneal administration of IL-25, are not induced to the same extent in lungs of T1/ST2-deficient mice when compared to WT controls [30]. These observations suggest that the relationship between IL-25 and IL-33 and their ability to induce ILC2 is not yet completely understood. Interestingly, iILC2 were only found in lungs after intraperitoneal but not intranasal

administration of IL-25 and are not induced upon challenge in the bone marrow [30,31]. As recently suggested [31], this may indicate that progenitors of iILC2 are not present in the lung. Therefore, the tissue tropism of the infectious and inflammatory challenge may determine the grade of nILC2 vs iILC2 elicitation.

2.2. IL-2 and IL-7

IL-2 and IL-7 are both essential regulators of ILC2 development and maintenance [9] and ILC2 constitutively express CD25 (IL-2R α) and CD127 (IL-7R α) [10]. ILC2 are highly dependent on the IL-7R α (CD127) chain [11], which pairs with the common γ chain (γ c) to transduce IL-7 signaling. IL-2 signaling can be initiated in different ways: (i) engaging CD25, together with CD122 and γ c as a trimeric receptor, (ii) independent of CD25, utilizing only CD122 and γ c, or (iii) involving trans-stimulation of CD25 by the heterodimeric receptor CD122 and γ c [32]. Both, IL-2 and IL-7 can activate STAT5 upon ligation of their respective receptors [32,33]. The γ c chain is involved in a variety of different cytokine signaling pathways including IL-2 and IL-7, and mice that are deficient for γ c lack ILC2 [1]. Animals double-deficient for Rag and γ c (*Rag2*^{-/-}*Il2rg*^{-/-}) lack mature T and B cells as well as ILC populations and therefore are frequently used as a recipient mouse model for transfer studies of ILC populations.

IL-2 is mainly secreted by CD4⁺ T cells but is induced in additional subsets such as CD8⁺ T cells [32]. In addition, dendritic cells (DC) can produce IL-2 under inflammatory conditions [32]. IL-33 has recently been shown to induce IL-2 production by DC, thereby acting as a positive feed-forward regulator for ILC2 stimulation [34]. Interestingly, ILC2 are elicited in IL-2 therapy aiming for regulatory T cell (Treg) induction and are responsible for the unwanted accumulation of eosinophils in this setting [35]. In contrast to IL-2, IL-7 is not produced by lymphocytes but is released mainly by tissue resident non-hematopoietic stromal cells, epithelial cells or neurons at different locations including the bone marrow, lymph node, thymus and spleen [36].

2.3. ICOS and ICOS-L

Inducible T cell costimulator (ICOS, CD278) belongs to the CD28-superfamily and is expressed on T cells including activated and memory T cells as well as regulatory T cells (Treg) and serves as a co-stimulatory molecule. ICOS binds to ICOS-Ligand (ICOS-L, B7-related protein-1 (B7RP-1)), which is expressed on B cells, macrophages and dendritic cells (DC) [37]. Since the first reports describing ILC2, ICOS expression was shown to be a characteristic surface marker [7]. Recent reports further demonstrate that human as well as mouse ILC2 express not only ICOS but also ICOS-L, which plays a critical role in ILC2 functions [38–40]. Markedly reduced numbers of ILC2 are present in lung, small intestine and bone marrow of ICOS-deficient mice. ICOS was further shown to be critical for ILC2 function in models of allergic lung inflammation. Less ILC2 and eosinophils and an improved lung function were observed in ICOS-deficient mice when compared to wild-type animals. In addition, ICOS-deficient ILC2 express less Bcl-2 and are more prone to cell death, leading to lower type 2 cytokine levels. Adoptive transfer experiments confirmed that ICOS expressed by ILC2 is needed to induce airway hyper-responsiveness and eosinophil accumulation *in vivo*. Moreover, blocking ICOS interaction ameliorated lung inflammation independent of the adaptive immune system in a model of fungal allergen challenge [38–40].

In addition, ICOS has recently been shown to be important for the interaction of ILC2 with Treg. IL-33 stimulated ILC2 interact through ICOS-L with ICOS expressed by Treg, and this interaction is needed for the IL-33-mediated induction of Tregs [41]. Co-

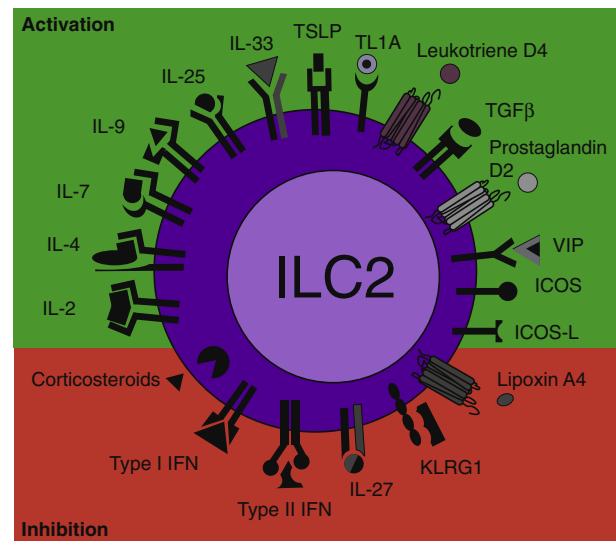


Fig. 3. ILC2 homeostasis and function is regulated by different activating and inhibitory factors. Activating factors for ILC2 are IL-2, IL-4, IL-7, IL-9, IL-25, IL-33, TSLP, TL1A, TGFβ, Leukotriene D4, prostaglandin D2, VIP, ICOS and ICOS-L signaling as well as caloric intake. In contrast, Lipoxin A4, type I and type II interferons, IL-27, KLRG1 and corticosteroids function as negative regulators of ILC2.

culture experiments of ILC2 and Treg further revealed that ICOS-L/ICOS interaction is important for Treg survival [41].

Interestingly, a recently developed mouse model to deplete ILC2 makes use of the fact that ILC2 express ICOS. This inducible ILC2-deficient mouse line utilizes an insertion of a floxed diphtheria toxin (DTx) receptor gene into the ICOS locus, resulting in a null allele [42]. Importantly, not only ILC2 but also ILC3 including LT α i cells express ICOS [40,43]. As such, the role of ICOS on ILC populations other than ILC2 needs to be addressed in future experiments.

2.4. IL-4

Besides IL-5 and IL-13, Th2 cells of the adaptive immune system also express and secrete IL-4. As an early report utilized IL-4 mRNA reporter mice to identify and characterize ILC2 [8], expression of IL-4 has been initially linked to murine ILC2 activation. However, although IL-4 mRNA is expressed by mouse ILC2, the actual amount of IL-4 protein produced and released by murine ILC2 stimulated with ILC2-activating cytokines alone is very low [7,8]. In contrast, upon non-specific stimulation with PMA/ionomycin, IL-4 release can be potently induced in murine ILC2 [9]. Interestingly, a recent study demonstrates that the eicosanoid inflammatory lipid leukotriene D4 (LTD4) is a potent stimulator of IL-4 production and release by murine ILC2 [44]. In contrast, human ILC2 express and release large quantities of IL-4 upon stimulation with ILC2-activating cytokines alone (e.g., IL-33 or IL-25) [12], suggesting that murine and human ILC2 utilize distinct molecular pathways to induce IL-4 production.

Importantly, aside from being produced by ILC2, IL-4 is also utilized as a positive feed-forward loop for ILC2 activation. Recent observations demonstrate that ILC2 express IL-4R α and that its ligation by IL-4 is a potent positive regulator of ILC2 [45]. IL-4 alone or in combination with IL-33 or IL-2 activates ILC2, leading to the enhanced release of type 2 signature cytokines. Basophil-derived IL-4 was shown to be the dominant source of IL-4 in a model of cysteine protease induced pulmonary inflammation, highlighting a key functional crosstalk between ILC2 and basophils for the regulation of type 2 immunity [45].

2.5. IL-9

IL-9 was identified as a factor that stimulates proliferation of T cells and mast cells and has been linked for a long time to type 2 immune responses [46]. IL-9 can be produced by different T cell subsets, mast cells and ILC2, and utilizes the IL-9R and γc to transduce downstream signaling through Jak1 and Jak3 kinases, leading to the recruitment and subsequent activation of STAT1, 3 and 5 [46]. As ILC2 express the IL-9R, a regulatory role of this cytokine has been suggested [8,47]. Utilizing IL-9 reporter animals, helminth infection and models of allergic lung inflammation it was recently shown that ILC2 are a major source of IL-9, which acts in an autocrine fashion to positively regulate cell survival of and cytokine production by ILC2 [47–50]. Upon infection with *Nippostrongylus brasiliensis*, CD4⁺ T cells as well as ILC2 were shown to express and release IL-9. Interestingly, more IL-9 expressing ILC2 than CD4⁺ T cells are observed in the lung but not in the mediastinal lymph node [49], suggesting a role for the microenvironment for IL-9-producing cells. Moreover, IL-9 expression by ILC2 was reported to be dependent on IL-2 and IL-33 and of transient nature followed by a strong and dominant expression of IL-5 and IL-13 [48]. In addition, using IL-9R deficient mice, it was observed that not only ILC2 accumulation but also type 2 signature cytokine production requires IL-9R signaling [47]. Furthermore, ILC2-derived IL-9 was shown to be critical for tissue repair in infected lungs by promoting cell survival and proliferation [47]. In addition, IL-33 and TSLP were found to synergistically induce an interferon regulatory factor 4 (IRF4)-IL-9 program in ILC2, and autocrine IL-9 promotes rapid IL-5 and IL-13 production by ILC2 required for optimal responses in the conducting airways [50].

2.6. TL1A

ILC2 have been identified through the administration of the cytokines IL-25 and IL-33 [7–9,28]. However, the observation that mice with deletions in IL-25R and IL-33R are still able to elicit some ILC2 led to the discovery of ILC2 responsiveness to TL1A (TNFSF15), a member of the tumor necrosis factor (TNF) superfamily (TNFSF) [51,52]. Similar to ICOS, TL1A can serve as a co-stimulatory molecule of T lymphocytes [53]. Interestingly, genome-wide association studies (GWAS) reported single-nucleotide polymorphisms in TL1A to be linked to inflammatory bowel disease [54,55]. Moreover, TL1A is expressed by epithelial and endothelial cells as well as by activated myeloid cells at barrier surfaces including lung and gut [52]. Two recent studies demonstrate that murine and human ILC2 express the receptor for TL1A [51,52], the tumor necrosis factor (TNF)-receptor superfamily member DR3 (TNFRSF25) [56]. Similar numbers of ILC2 were found in DR3-deficient mice, suggesting that TL1A signaling does not influence the development of ILC2 [51]. In contrast, ILC2 activation is positively regulated by TL1A signaling *in vivo* and *in vitro*. ILC2 numbers and cytokine production are increased upon *in vivo* stimulation of TL1A in a DR3-dependent but T and B cell-independent manner. Moreover, DR3-deficient mice display impaired innate immunity when infected with *N. brasiliensis* that was associated with lower ILC2 numbers and reduced IL-5 and IL-13 levels in the bronchoalveolar lavage, while no differences in CD4⁺Th2 cells were observed. Similar results were obtained upon intranasal challenge using papain. Furthermore, TL1A acts in synergy with IL-25 and IL-33 to enhance proliferation and cytokine production by ILC2 *in vitro*. However, DR3-deficiency results in lower ILC2 numbers upon IL-25 challenge but not upon IL-33 challenge, indicating that the situation *in vivo* is more complex. Importantly, GATA3 was reduced in DR3^{−/−} ILC2 upon IL-25 administration, suggesting that DR3 regulates GATA3 maintenance [51]. Another recent study made use of the IL-13 reporter mouse to demonstrate ILC2 activation by TL1A [52].

IL-25-elicited ILC2 show increased production of IL-5, IL-6, IL-9, IL-13 and IL-17A in response to TL1A and IL-7. However, administration of TL1A does not elevate ILC2 proliferation or IL-13 mRNA expression in ILC2 *in vivo*. In addition, CD2-TL1A transgenic mice show upregulation of IL-25 and to a lesser extent IL-33 mRNA. In contrast to the paper by Yu et al. [51], Meylan and colleagues observed no differences in proliferation of ILC2 in DR3-deficient mice when treated with IL-25 or IL-33, or infected with *N. brasiliensis* or *Schistosoma mansoni* [52]. However, both studies observe that challenge of DR3-deficient mice using papain results in a reduction in ILC2 numbers [51,52]. The observed differences in these two reports might result from the use of distinct experimental approaches and readouts (IL-13 eGFP reporter mice vs intracellular IL-13 staining; steady state versus cytokine elicited ILC2). However, the importance of TL1A for ILC2 regulation is clearly demonstrated and warrants studies to test whether other members of the tumor necrosis factor superfamily can also influence ILC2 functions.

2.7. Lipid mediators – PGD2 and LTD4

Prostaglandins are a group of physiologically active lipid mediators that exert diverse hormone-like effects [57]. Prostaglandin D2 (PGD2) binds to the receptors PTGDR (DP1) and chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2, DP2) [58]. Although expression of CRTH2 is mainly found in the central nervous system, mast cells and Th2 cells [58], the first report of human ILC2 identified CRTH2 as one of the key surface markers on human ILC2 [59]. PGD2 in combination with IL-2, IL-33 and IL-25 synergistically stimulates IL-13 production by ILC2 [60]. In addition, CRTH2 regulates the *in vivo* accumulation of ILC2 in the lung [61]. Although a significant proportion of ILC2 in human peripheral blood express CRTH2, a smaller proportion of ILC2 from human lung expressed CRTH2, suggesting that regulation of CRTH2 expression by ILC2 might influence migration into tissues. Murine ILC2 express CRTH2, migrate toward PGD2 *in vitro*, and accumulate in the lung in response to PGD2 *in vivo*. Furthermore, mice deficient in CRTH2 exhibit reduced ILC2 responses and inflammation upon helminth-induced pulmonary type 2 inflammation, suggesting a role for the PGD2-CRTH2 pathway in regulating the *in vivo* accumulation of ILC2 [61].

A recent study demonstrates that the eicosanoid inflammatory lipid leukotriene D4 (LTD4) is a potent stimulator of IL-4 production and release by murine ILC2 [44]. Future studies will have to address whether LTD4 selectively influences IL-4 release or can also regulate other ILC2 functions. Moreover, it remains to be explored if lipid mediators other than PGD2 and LTD4 can positively regulate ILC2.

2.8. TGF β

Global genetic deletion of TGF- β results in early death from multi-organ inflammation, highlighting the crucial role TGF- β plays in maintaining peripheral tolerance [62]. In contrast, targeted deletion of TGF- β signaling in CD4⁺ T cells results specifically in inflammation at mucosal sites, including the airways [63]. However, at mucosal surfaces, TGF- β is expressed constitutively by a wide variety of leukocytes and stromal cells. Within the lung, alveolar macrophages, smooth muscle cells, fibroblasts as well as epithelial cells produce TGF- β [64,65] and expression of TGF- β is increased in the lung after both viral and allergen challenge [66–68]. Interestingly, systemic neutralization of TGF- β has variable effects on lung remodeling, inflammation, and airway hyperactivity (AHR), depending on the route of allergen exposure [69,70]. Moreover, manipulation of epithelial genes to promote TGF- β signaling results in an exacerbation of house dust mite

(HDM)-induced allergic inflammation and its associated pathology and loss of tolerance to inhaled antigen [71,72]. Animals that specifically lack epithelial-derived TGF- β 1 displayed no baseline immune defects but were protected from the effects of allergen exposure, exhibiting markedly reduced airway inflammation and improved lung function. Pulmonary IL-13⁺ Th2 cells were unaffected but the frequency of IL-13⁺ ILC2s was significantly reduced. IL-33 was shown to increase bioactive TGF- β 1 levels *in vivo*. Bone marrow and pulmonary ILC2 express TGF- β R1 and show increased cell chemoactivity that leads to increased IL-5 and IL-13 production [73]. In contrast, TGF- β has been shown to negatively regulate Th2 development [74,75]. Therefore, it will be of interest to explore of whether IL-33 signaling can alleviate TGF- β -mediated Th2 suppression. The interaction between ILC2 and epithelial-derived TGF- β constitutes a crucial pathway for the generation of early allergic immune responses and reinforces the concept that resident tissue stromal cells are key regulators of local mucosal immunity.

2.9. Circadian clock and calorie intake

The influence of circadian rhythm on cell populations of the immune system has been of interest since a long time [76]. In a recent publication, cytokine expression of gut and lung ILC2 was analyzed at steady state and upon food intake or inflammation [77]. Using cytokine reporter mice, it was observed that gut and lung ILC2 constitutively express IL-5. However, intestinal ILC2 also constitutively express IL-13. Moreover, IL-13 in pulmonary ILC2 needs to be induced by an inflammatory challenge such as infection with *N. brasiliensis*. Importantly, upon food intake intestinal ILC2 increase cytokine expression while the number of cells remains constant. Moreover stimulation of the VPAC2 receptor by vasoactive intestinal peptide (VIP), an important synchronizer of circadian rhythm [78], triggers cytokine expression by ILC2. However, if VPAC2 signaling is not intact, increased cytokine release can be compensated by food intake, demonstrating that ILC2 are regulated by the circadian clock and calorie intake [77]. Future studies are needed to elucidate the molecular mechanisms underlying calorie intake-mediated ILC2 activation.

3. Negative regulation

3.1. Lipid mediators

3.1.1. Lipoxin A₄

Lipoxins, are derived from arachidonic acid and exhibit anti-inflammatory effects [79]. Lipoxin A₄ binds to its receptor ALX/FPR2, which is regarded as its main receptor and responsible for its anti-inflammatory activity. Studying human ILC2, lipoxin A₄ has been shown to decrease IL-13 release [60]. Lipoxin A₄ and possibly other lipid mediators are interesting candidates to negatively regulate ILC2 function. However, further studies are required to decipher the underlying molecular mechanisms and *in vivo* relevance.

3.1.2. Corticosteroids

Corticosteroids are without doubt an important group of mediators that efficiently suppress allergic inflammation [80]. In the clinics, corticosteroids are widely used to inhibit pro-inflammatory immune reactions including diseases such as asthma and allergies [80]. Many cells of the innate and the adaptive immune system respond to corticosteroids. However, some patients are unresponsive to such a therapy [81]. A recent report demonstrated that ILC2 can be negatively regulated by corticosteroids [82]. However, stimulation of ILC2 by TSLP induces phosphorylation of STAT5 and Bcl-xL expression and confers

resistance to corticosteroid inhibition, a process that is reversed by the STAT5 inhibitor Pimozide [82]. It therefore remains to be tested of whether TSLP could also confer resistance to other negative regulators of ILC2.

3.2. KLRG1

Like NK cells and antigen-experienced T cells [18–20], mouse and human ILC2 can express the co-inhibitory receptor killer-cell lectin like receptor G1 (KLRG1) [11,83]. Of note, in contrast to tissue resident ILC2, bone marrow progenitors exert no KLRG1 expression [11]. Interestingly, KLRG1 binds to E-Cadherin, which is expressed by epithelial cells, Langerhans cells and keratinocytes [84]. Importantly, human ILC2 exert reduced levels of GATA3, IL-5 and IL-13 when co-cultured with recombinant E-Cadherin [83]. As ILC2 have been found in close proximity to epithelial layers within mucosal tissues such as the skin, small intestine and lung [7,77,85–87], KLRG1-E-Cadherin ligation might constitute an important tissue-intrinsic mechanism to restrain ILC2 activity.

3.3. Interferons and IL-27

The mammalian interferon family comprises three different subtypes; type I interferons, type II interferon and type III interferons [88]. Type I interferons consist of more than 10 members including the different α subtypes and interferon β and all signal through a heterodimeric receptor of IFNAR1 and IFNAR2. IFN γ , the only type II interferon, engages IFN γ R1 and IFN γ R2 to induce its downstream effects. Type III interferons, which are also referred to as interferon lambda, bind to the IL-28R α together with the IL-10R2 receptor [88]. In general, IFN signaling via STAT proteins mediate immunity against viruses and bacteria and also exert important immunomodulatory functions [89,90].

Type I and type II IFNs have been shown to inhibit anti-parasitic type 2 immunity already 20 years ago [91]. Following these observations, it was shown that type I and type II IFNs interfere with Th2 cell differentiation [92]. Moreover, type I IFNs were shown to suppress allergic inflammatory processes by blocking granulocyte activation and IL-4-mediated B cell isotype switching to IgE [92]. Three recent publications further revealed that type I and type II IFNs as well as IL-27 act as critical negative regulators of ILC2 [17,41,93].

Recent observations reported the confluence of innate cells associated with type 2 immunity, including ILC2, eosinophils, and alternatively activated macrophages (AAM) with Treg in visceral adipose tissue (VAT) of resting mice [94]. It has been demonstrated that this cellular network is necessary for metabolic homeostasis, and its loss during obesity is associated with increased inflammatory T cells, macrophages, and the development of insulin resistance and type 2 diabetes [94]. Although VAT IL-33 is increased in obesity [95], ILC2, Treg, eosinophils, and AAMs decline [96], suggesting that loss of IL-33 does not account for this effect. However, IFN γ -producing T cells and NK cells increase in obese VAT and IFN γ can promote inflammation and systemic insulin resistance [41]. IFN γ was shown to directly repress ILC2 activation, cytokine production, and proliferation *in vitro* [55]. *In vivo* studies using heterozygous Yeti mice in which the 3' untranslated region (UTR) of IFN γ is stabilized by a YFP-bovine growth hormone poly-A construct, leading to constitutive increases in IFN γ [97] revealed that ILC2 express lower levels of cytokines and ICOS-L. IFN- γ inhibited ILC2 activation and Treg accumulation in adipose tissue, where repression increased with aging and high-fat diet-induced obesity [41].

Type I and type II IFNs as well as IL-27 were further shown to directly suppress ILC2 activation *in vitro* and during parasitic infection and models of allergic inflammation *in vivo*, thereby reducing

anti-parasitic type 2 immunity and pulmonary lung pathology, respectively [17,41,93]. Receptor chains for type I and type II IFNs and IL-27 are expressed by bone marrow and pulmonary ILC2 [17,41,93]. While IFN γ chains are expressed at steady state by ILC2, IFNAR was not detectable. However, expression of IFNAR by ILC2 was found to be induced upon culture with IL-2 and IL-25 as well as with IL-33 [17]. In Yeti mice, clearance of *N. brasiliensis* was delayed and pulmonary ILC2 showed decreased proliferation and cytokine expression profiles. Interestingly, in coinfection experiments with *N. brasiliensis* and *Listeria monocytogenes*, pulmonary ILC2 as well as IL-5 expression were reduced [41]. IFN γ as well as IL-27 effectively suppressed the function of ILC2 during lung inflammation induced by the fungus *Alternaria*, thereby negatively regulating type 2 immunity [17].

Viral respiratory infections are the dominant cause of type 2 immunity-mediated asthma and asthma exacerbations, and are associated with very high frequencies of pediatric and adult disease that remains mechanistically unexplained [98]. Asthma is associated with a type 2 immune response-mediated disease that is characterized by the presence of chronic inflammation in the lower airways, resulting in airflow obstruction and airway hyper-responsiveness (AHR) [99]. Interestingly, viral respiratory tract infections, archetypal triggers of potent innate and adaptive type 1 immune responses, which are characterized by the production of type I and type II IFN [100], frequently give rise to pulmonary type 2 immunopathology [101]. We have recently demonstrated that deficiency in signaling via type I interferon receptor leads to deregulated activation of ILC2 and infection-associated type 2 immunopathology. It was observed that type I IFN directly regulates mouse and human ILC2 in a manner dependent on ISGF3, leading to diminished cytokine production and cell proliferation and increased cell death [93]. These observations demonstrate that type I IFNs are important negative regulators of ILC2 to restrict type 2 immunity and its associated pathologies.

4. Conclusion

ILC2 have only been recently identified, but the study of their development and maintenance has lead to an immense knowledge about this important cell population in recent years. Moreover, the regulation of ILC2 is becoming more and more complex. As summarized in this review, cytokine release, transcription factor gradients and the expression of diverse surface receptors modulate ILC2 homeostasis, activation and functions. Onset and amplification of an immune response is of high importance and ILC2 are essential regulators in this process. Therefore, a better understanding of how ILC2 are regulated will ultimately result in improved treatments and tailored therapeutics against unwanted type 2 immune responses such as asthma and allergy as well as tissue fibrosis.

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