Heterogeneity of type 2 innate lymphoid cells

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Abstract | More than a decade ago, type 2 innate lymphoid cells (ILC2s) were discovered to be members of a family of innate immune cells consisting of five subsets that form a first line of defence against infections before the recruitment of adaptive immune cells. Initially, ILC2s were implicated in the early immune response to parasitic infections, but it is now clear that ILC2s are highly diverse and have crucial roles in the regulation of tissue homeostasis and repair. ILC2s can also regulate the functions of other type 2 immune cells, including T helper 2 cells, type 2 macrophages and eosinophils. Dysregulation of ILC2s contributes to type 2-mediated pathology in a wide variety of diseases, potentially making ILC2s attractive targets for therapeutic interventions. In this Review, we focus on the spectrum of ILC2 phenotypes that have been described across different tissues and disease states with an emphasis on human ILC2s. We discuss recent insights in ILC2 biology and suggest how this knowledge might be used for novel disease treatments and improved human health.

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Just over a decade has passed since the first extensive descriptions of type 2 innate lymphoid cells (ILC2s) in mice[1–3] (in 2010) and humans[4,5] (in 2011), although there had been hints as to the existence of these cells in earlier papers from 2001 (REF.[6]) and 2006 (REF.[7]). At the time that ILC2s were discovered, an extensive body of knowledge on the biology of T helper 2 (T_H2) cells was already available. T_H2 cells and ILC2s have key transcription factors and cytokine production profiles in common, and these shared features were a major driver of research efforts that have propelled our understanding of the mechanisms of ILC2 development and function. For some time, it was thought that ILC2s, in contrast to other ILC subsets, were a homogeneous population of cells because, initially, no phenotypic or functional heterogeneity of ILC2s was noted, in contrast to the subsets of ILC1s and ILC3s that were identified at the time of their discovery. However, progress in the past couple of years has made clear that ILC2s differ in phenotype and function between and within tissues[8]. Different tissue microenvironments imprint the phenotypes and functions of ILC2s, which are, like other ILC subsets, highly plastic, thus facilitating adaptation to their microenvironment[9]. Furthermore, both in mice[10] and humans[11,12], regulatory, IL-10-producing ILC2s have been identified that can counteract the activities of canonical ILC2s producing IL-5 and/or IL-13 (REF.[13]). In addition, whereas ILC2s and the other ILC subsets were previously considered to be exclusively tissue resident, studies in mice[14] and humans[15] have shown that ILC2s can acquire the capacity to migrate following activation, thereby contributing

to systemic immunity. This Review discusses the diverse landscape of ILC2s that is emerging from these recent studies and the consequences of these new data for understanding the roles of ILC2s in cancer, metabolism, inflammation and infection.

Diversity of human circulating ILC2s

Initially, human ILC2s were defined by expression of CD127 (the IL-7 receptor α-subunit), CD161 (encoded by *KLRB1*) and CRTH2 (the receptor for prostaglandin D2)[4]. CRTH2 functionally regulates the migration of mouse ILC2s to the lung[16]. However, CRTH2 has proved less useful as a definitive marker for human ILC2s[17] because, as discussed below, human peripheral blood contains ILC2-like cells that lack CRTH2 expression[18,19]. TABLE 1 shows the ILC2 populations in humans whose lineage identity has been thoroughly confirmed not using transiently expressed markers.

In one study, it was observed that peripheral blood CD117+CRTH2− ILCs expressing another ILC2-associated marker, KLRG1, could upregulate CRTH2 expression in vitro following incubation with IL-7, which suggests that these CD117+CRTH2− cells are precursors of ILC2s or immature CRTH2− ILC2s[18] (TABLE 1; FIG. 1a). However, not all CRTH2+ ILC2s are functionally mature because CRTH2+ ILC2s expressing CD5 that are unable to produce type 2 cytokines were found in human cord blood and postnatal thymus[20]. Differentiation of CD5+CRTH2+ ILC2s to cytokine-producing ILC2s was accompanied by downregulation of CD5 expression[20]. Furthermore, CD5 is transiently expressed on ILC2s at an early stage during

Table 1 | **Phenotypes of type 2 innate lymphoid cells in humans**

ILC2 population	Surface markers						Activating signals[a]	Factors produced	Tissue distribution	Unique transcription factors
	CD127	CRTH2	CD117	KLRG1	CD45RA	CD45RO				
KLRG1+ immature or naive ILC2s	+	−	+	+	+	−	Type 2	IL-5, IL-13	Peripheral blood, nasal polyps, tonsil	TCF7
CRTH2+CD117+ ILC2s	+	+	+	+	ND	ND	Type 1	IL-13, IFNγ	Peripheral blood, nasal polyps	RORγt
							Type 2	IL-5, IL-13		
							Type 3	IL-13, IL-17A		
CRTH2+CD117− ILC2s	+	+	−	ND	+	−	Type 2	IL-5, IL-13	Peripheral blood	ND
CD45RO+ activated ILC2s	+	+	−	+	−	+	IL-2, IL-7, IL-33, TSLP	IL-5, IL-13	Peripheral blood, nasal polyps, bronchoalveolar lavage	BATF, IRF4
IL-10-producing ILC2s	+	+	−	+	ND	ND	IL-2, IL-7, IL-33, RA	IL-5, IL-10, IL-13	Peripheral blood, nasal polyps	ND

IFNγ, interferon-γ; ILC2, type 2 innate lymphoid cell; ND, not determined; RA, retinoic acid; TSLP, thymic stromal lymphopoietin. [a]Type 1: IL-1β, IL-2, IL-7, IL-12. Type 2: IL-2, IL-7, IL-25, IL-33, TSLP. Type 3: IL-1β, IL-2, IL-7, IL-23, transforming growth factor-β.

their in vitro differentiation from CD34+ haematopoietic stem cells in the presence of the Notch ligand Delta like 1 (REFS[20,21]). Together, these observations suggest that CD5 is a marker of functionally immature CRTH2+ ILC2s. Recently, it was found that CD5+ ILCs capable of differentiating to mature ILC2s are present in the intravascular spaces of immunodeficient mice containing immune cells that have developed from human CD34+ haematopoietic precursors, and it was suggested in this study that CD5+ ILCs follow a developmental path distinct from CD5− ILCs[22].

Whereas the CRTH2−KLRG1+ ILC2s seem to include ILC2 precursors[18], another study has identified ILC2s in human peripheral blood that lack expression of CRTH2 and/or CD127 but express multiple transcripts and proteins typically expressed by conventional mature CRTH2+ ILC2s, including the production of IL-5 and IL-13 (REF.[19]). Although their lineage identity has not been precisely confirmed, ILC2s lacking CRTH2 and/or CD127 were enriched in the blood and bronchoalveolar lavage (BAL) fluid of patients with asthma and could cause airway hyperreactivity when transferred to mice. Supporting these data, single-cell RNA sequencing of human lung ILCs has shown the presence of CRTH2− ILC2-like cells[8]. Such cells could be generated in vitro from blood CRTH2+ ILC2s upon alarmin stimulation, which suggests that lung alarmins induce the downregulation of CD127 and CRTH2, the latter likely via endogenous production of prostaglandin D2 (REF.[23]). Hence, in addition to CRTH2, CD127 and CD117, other markers, including KLRG1, CD30, TNFR2 and CD200R1 (REF.[19]), might be needed to appropriately assess ILC2 numbers and function in type 2 inflammatory settings. In summary, these studies show that ILC2s that lack CRTH2 expression may be either immature cells that have not yet gained CRTH2 expression or functionally mature cells that have downregulated CRTH2 as a result of activation.

In addition to the described diversity of CRTH2− ILC2s, more mature CRTH2+ ILC2s are also highly diverse. Recent data point to CD117 (stem cell factor receptor encoded by *KIT*) as a surface marker that distinguishes CRTH2+ ILC2s with different functions (TABLE 1; FIG. 1a). Circulating CRTH2+CD117− ILC2s have been described as cells that are committed to the ILC2 lineage with low propensity for transdifferentiation to ILC1s and ILC3s[24]. Expression of CD45RO, which is a well-known marker for human memory T cells, seems to define activated CRTH2+CD117− ILC2s as they can be generated from ILC2s expressing CD45RA, which is also expressed on naive T cells, by stimulation with IL-33 (REF.[15]) (FIG. 1a). Whereas a lack of CD117 expression seems to be a characteristic of several previously described populations of committed and activated CRTH2+ and CRTH2− ILC2s[15,18,19,24], CRTH2+CD117+ ILC2s have some features of ILC3s, including expression of the transcription factor RORγt (encoded by *RORC*) and the chemokine receptor CCR6 (REFS[24,25]) (TABLE 1). Indeed, CD117+ ILC2s can produce IL-17A when stimulated with cytokines, such as IL-23, that also strongly activate ILC3s but, in parallel, they mostly maintain their capacity to produce IL-5 and IL-13. CD117+ ILC2s are also prone to ILC1-like differentiation in the presence of IL-1β and IL-12[24]. These observations are in line with accumulating data that strongly suggest that ILC plasticity can account for flexible ILC responses within a tissue without the need for recruitment of ILCs from other tissue sources[11,24–31]. The plasticity of ILCs has recently been reviewed extensively[9,32] and information on the plasticity of ILC2s in particular is summarized in BOX 1.

In summary, the peripheral blood of healthy human donors contains a spectrum of ILC2 phenotypes, ranging from immature to mature. KLRG1+CRTH2− immature ILC2s and CD5+CRTH2+ ILC2s seem to be precursors of mature CRTH2+ ILC2s that have at least two phenotypes with distinct functionalities. Whereas CRTH2+CD117+

Alarmin
A type of damage-associated molecular pattern composed of endogenously produced proteins or peptides, including IL-33, that are released upon immune activation, degranulation, cell injury or death.

ILC2s represent a plastic state with increased propensity for differentiation to an ILC1-like or ILC3-like phenotype, CRTH2+CD117− ILC2s are less plastic, being more committed to the ILC2 lineage, and some of these CD117− ILC2s express CD45RO. CD45RO+ ILC2s produce the highest levels of type 2 cytokines among all described ILC2 phenotypes, which indicates that they are in a (pre-)activated state.

ILC2s with regulatory functions

Because ILC subsets have so many features in common with T cell subsets, it was long thought that there would be a FOXP3-expressing ILC subset as a counterpart to FOXP3+ regulatory T (T$_{reg}$) cells. However, despite extensive efforts, such cells have thus far not been found. Nonetheless, ILCs with regulatory activities have now been identified[33], and within the ILC2
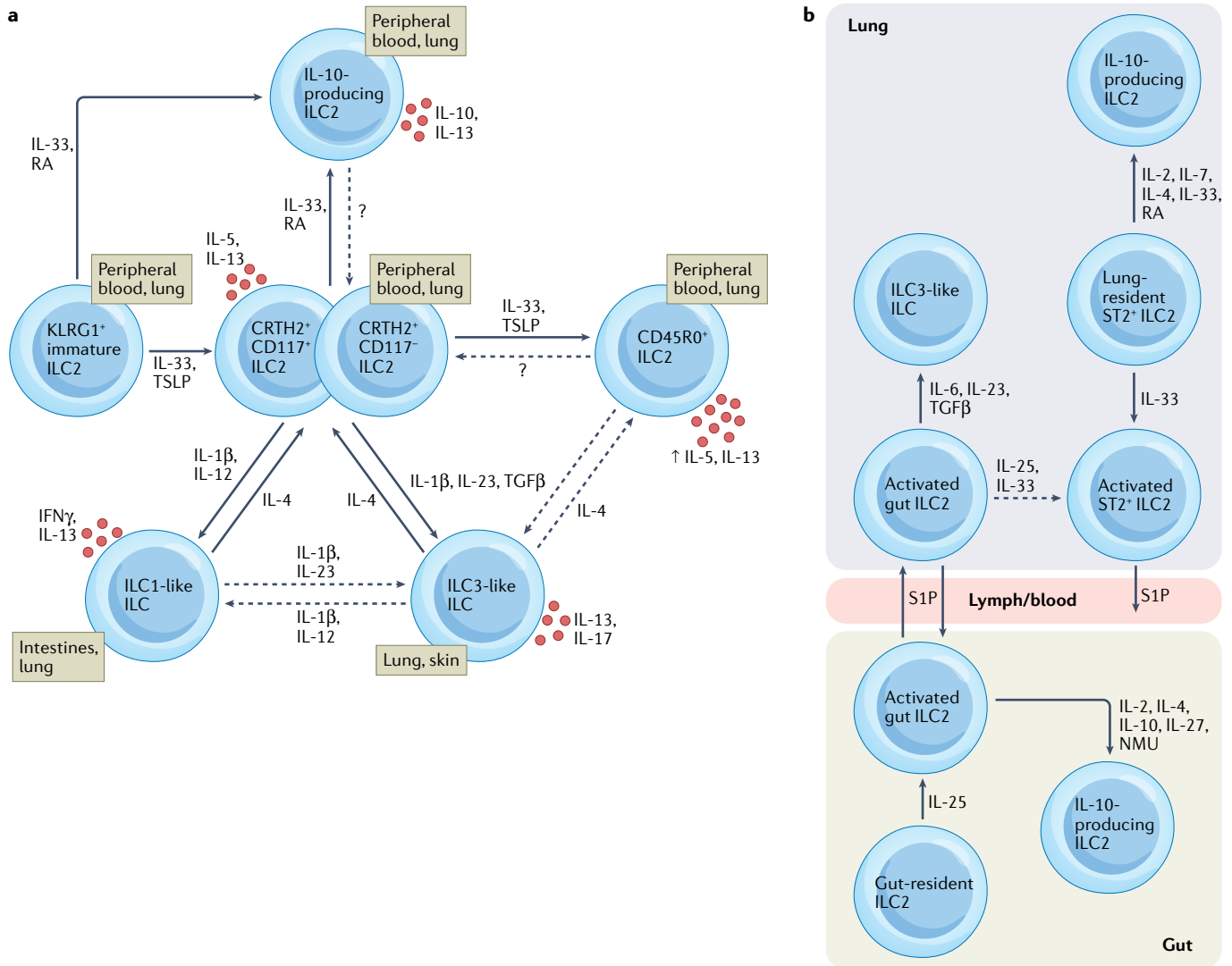

Fig. 1 | **The plasticity and migration of ILC2s generate phenotypic diversity in tissues. a** | KLRG1+ immature type 2 innate lymphoid cells (ILC2s) in humans can generate IL-10-producing regulatory ILC2s as well as IL-5-producing and IL-13-producing ILC2s (CRTH2+CD117+ ILC2s and CRTH2+CD117− ILC2s), depending on the tissue microenvironment and cytokine milieu. It is currently unknown if IL-10-producing ILC2s can lose the capacity for IL-10 production and become IL-5-producing and IL-13-producing ILC2s. Upon activation with IL-33 and thymic stromal lymphopoietin (TSLP), human ILC2s generate CD45RO+ ILC2s that are similar to activated gut ILC2s in mice, expressing CD45RO, BATF, IRF4 and increased levels of IL-5 and IL-13. CD117− ILC2s represent committed ILC2s, but it is currently unclear if such cells are the precursors of CD45RO+ ILC2s or if CD45RO+ ILC2s can revert to CD45RO−CD117− ILC2s. ILC2s, preferentially those expressing high levels of CD117, can generate ILC3-like cells producing IL-17 under the influence of IL-1β, IL-23 and transforming growth factor-β (TGFβ), or ILC1-like cells producing interferon-γ (IFNγ) under the

influence of IL-1β and IL-12. Such transdifferentiation is prevented, in both cases, by IL-4. It is currently unclear if ILC2–ILC1 plasticity involves an intermediate ILC3-like stage. **b** | In a mouse model of *Nippostrongylus brasiliensis* infection, IL-25-activated 'inflammatory' ILC2s in the gut can migrate via the lymphatic system and blood circulation to the lung in a sphingosine 1-phosphate (S1P)-dependent manner, adding to the pool of lung-resident ST2+ ILC2s. Gut-derived ILC2s can also generate ILC3-like cells in the lung in response to type 3 cytokines such as IL-6, IL-23 and TGFβ. Gut-derived ILC2s from the lung likely return to the gut, as such cells cannot be found in the lung after parasite clearance. Additionally, lung-derived, activated ST2+ ILC2s can leave the lung and enter the circulation but it is so far unclear where such cells migrate. IL-10-producing ILC2s can be generated in both the gut and lung but the migratory behaviour of these cells is still unclear. The migratory pattern of human ILC2s is unclear but data support the recirculation of ILC2s between blood and lung in individuals with asthma. NMU, neuromedin U; RA, retinoic acid.

Box 1 | **Plasticity of type 2 innate lymphoid cells**

Plasticity can be defined as the capacity of cells to change their destiny during differentiation as well as the capacity of differentiated, functionally mature cells to change their functions and phenotype. Several immune cell types, including T cells[108] and macrophage subsets[109], have been shown to be capable of plasticity. Recent reviews have discussed the plasticity of innate lymphoid cells (ILCs) in general[9,32]. Concerning type 2 ILCs (ILC2s) in particular, the Lineage⁻CD127⁺KLRG1⁺CRTH2⁻CD117⁺CD45RA⁺ precursor cells that are found in human peripheral blood[18] are transcriptionally more similar to mature ILC2s than to ILC1s or ILC3s, which indicates that they are biased towards the ILC2 lineage. Regardless, these ILC2 precursors not only give rise to CRTH2⁺ ILC2s but also to ILC1-like or ILC3-like cells in the presence of IL-1β and IL-12 or IL-23, respectively. Several studies, both in humans and mice, have shown that functionally mature ILC2s are also able to change their cytokine production profile and phenotype in the context of inflammation. Longitudinal single-cell RNA sequencing and assay for transposase-accessible chromatin (ATAC) sequencing, together with in vivo fate mapping experiments, have revealed the kinetics and mechanisms of how mouse skin-resident ILCs, including effector ILC2s, acquire ILC3-like features upon induction of IL-23-induced psoriasis-like inflammation[91]. Similarly, in humans, skin-resident ILC2s can transition into ILC3-like cells in psoriasis[25]. Moreover, in humans, the transition of ILC2s into ILC1-like cells has been observed in chronic obstructive pulmonary disease[26,31] and in Crohn's disease[29]. This ILC1-like differentiation process can be mimicked in vitro by the combination of IL-1β and IL-12. Mechanistically, IL-1β induces low levels of expression of the transcription factor T-bet and of IL-12 receptor-β2 on ILC2s, which enables IL-12 to stimulate the conversion of these cells into ILC1s[30]. As ILC2 plasticity seems to be prominent in the context of inflammatory diseases, it may also have a role in other diseases such as cancer, emphasizing the need for further studies in both mouse models and humans.

Chronic rhinosinusitis with nasal polyps (CRSwNP). A chronic inflammation of sinonasal tissues, resulting in the formation of inflammatory lesions and polyps, and manifested as rhinorrhoea, nasal congestion, and facial pressure and/or pain.

pool, regulatory activities have been associated with IL-10 production, which was indeed observed in one of the early reports of mouse ILC2s[1]. More recent work in mice has shown that IL-10-producing ILC2s can be generated following activation with alarmins, such as IL-33, and retinoic acid (TABLE 2; FIG. 1a) and that these cells counteract the recruitment of eosinophils in the lung mediated by canonical ILC2s[10]. IL-10-producing ILC2s were also found in the mouse intestine, where factors, including IL-2, IL-4, IL-10 and the neuropeptide neuromedin U, could increase IL-10 production, whereas TL1A (encoded by *TNFSF15*) suppressed this[34]. IL-10-producing ILC2s generated following activation with IL-33 and retinoic acid have now also been identified in human peripheral blood and the nasal polyps of patients with chronic rhinosinusitis with nasal polyps (CRSwNP)[12,13] (TABLE 1). IL-10-producing ILC2s from the inflamed nasal tissue of patients with CRSwNP[12] could inhibit the activation of IL-5-producing ILC2s and attenuate cytokine production by T$_H$2 cells[12,13]. IL-10-producing ILC2s in humans are derived from immature (CRTH2⁻) and mature (CRTH2⁺) ILC2s expressing KLRG1, as KLRG1⁻CRTH2⁺ ILC2s, which are yet to be properly defined, failed to produce IL-10 under stimulation with IL-2, IL-7, IL-33 and retinoic acid[13]. Notably, circulating KLRG1⁺ ILC2s from individuals with allergic disease were unable to produce IL-10, but the capacity of ILC2s to produce IL-10 was restored following successful allergen immunotherapy, which suggests that human IL-10-producing ILC2s might be involved in the control of allergic responses[13,35,36]. However, it has not yet been confirmed whether human IL-10-producing ILC2s reside in lung and intestine as well as nasal tissue as is the case in mice. It is also unclear

if IL-10 production is a feature of a subset of ILC2s or is part of an effector programme that functions to provide negative feedback during activation. How the differentiation of canonical ILC2s into IL-10-producing ILC2s is regulated is just beginning to be unravelled. Recent research has shown that BLIMP1 (encoded by *PRDM1*) and MAF regulate IL-10 production by ILC2s in mice[37] (TABLE 2) but whether this is also the case in human ILC2s remains to be determined.

ILC2 tissue residency and migration

A landmark paper in 2015 using adult parabiotic mice showed that ILCs, including ILC2s, are stably tissue resident in lung, small intestine and mesenteric lymph nodes over a period of several months, both during homeostatic conditions and in the presence of systemic inflammation in FOXP3-deficient mice, which lack inflammation-inhibiting T$_{reg}$ cells[38]. However, during the chronic phase of *Nippostrongylus brasiliensis* infection in these parabiotic mice, a fraction of the ILC2 population was found to be recruited from the donor mouse, which, together with local proliferation of host-derived ILC2s, generated an enlarged pool of ILC2s for clearance of the infection and tissue healing[38]. Since then, multiple reports have used the gut–lung axis-dependent immunity model of *N. brasiliensis* infection to study ILC2 migration between tissues. This model involves a robust type 2 immune response in both the gut and lung owing to the dynamics of the parasite, which initially infects the lung, then later infects the gut after having been expelled from the lung through coughing and swallowing. Using this model, studies support a migratory behaviour of gut ILC2s that are activated by the unique tissue microenvironment during *N. brasiliensis* infection[14,39]. Gut ILC2s, which express the IL-25 receptor component IL-17RB (TABLE 2), are activated by IL-25. Activated gut ILC2s (also referred to as 'inflammatory' ILC2s) then leave the gut in a sphingosine 1-phosphate receptor 1 (S1PR1)-dependent manner and migrate to the lungs to support a type 2 immune response in lung tissue, likely via migratory mechanisms involving the integrin LFA1 (REF.[40]) (FIG. 1b). Some, if only a small proportion, of the gut ILC2s that enter the lungs upregulate expression of the IL-33 receptor ST2 (also known as IL-1RL1), thereby taking on the phenotype of lung-resident ILC2s (also referred to as 'natural' ILC2s) (TABLE 2). It is currently unclear if gut ILC2s that enter the lung during *N. brasiliensis* infection also upregulate neuropilin 1 (NRP1), which was recently shown to be an activating receptor specifically expressed by lung ILC2s and upregulated on intestinal ILC2s following transfer to the lungs in mice[41]. In addition to the influx of gut ILC2s, recruited and tissue-resident precursors of ILC2s also contribute to the local population of ILC2s in the lung and have a role in the dynamic diversity of ILC2s observed in the lung during *N. brasiliensis* infection[42]. Whereas some gut-derived ST2⁺ ILC2s stay in the lung, some return to the gut; they enter the circulation together with activated lung-derived ST2⁺ ILC2s[14,39], using S1PR1 to exit the lung[39] (FIG. 1b). Gut ILC2s acquire migratory features early in *N. brasiliensis* infection, whereas lung ST2⁺ ILC2s become migratory at

later stages of infection[14,39], together suggesting that tissue-specific type 2 immunity can be systemically disseminated as has also been shown recently by others[43]. Further studies will be required to confirm whether ILC2s that migrate from tissues upon local activation indeed contribute to systemic type 2 immunity and to address whether these ILC2s have an increased propensity for returning to their tissue of origin as has been described for tissue-resident T cells[44].

The clinical translation of these findings from mice is complicated by the markedly different distribution of ILC2s in mice and humans. Humans have IL-25-responsive and IL-33-responsive, IL-13-producing ILC2s in peripheral blood at steady state[4]. By contrast, naive mice, possibly as a result of being kept under specific pathogen-free or germ-free conditions, lack circulating ILC2s, which are present in peripheral blood only after type 2 stimulation in tissues such as during *N. brasiliensis* infection as discussed above[39]. Furthermore, ILC2s are a prominent ILC population in the mouse intestine[14], whereas CD127+ ILC2s in the intestine of adult humans are mostly undetectable[8] unless it is severely inflamed[45]. Gut ILC2s increase in number in antibiotic-treated mice[46], and thus it is thought that the gut microbiota might suppress ILC2 numbers in human gut; indeed, CRTH2+ ILC2s can be found in human fetal gut[4] and ST2+ ILCs were identified in human paediatric gut[47]. However, there are also fundamental differences in the development of innate and adaptive lymphocytes in mice and humans that could explain the divergent distribution of ILC2s in the two species. In mice, fully mature T cells do not appear until the postnatal period[48], by which time intestinal ILC2s are being maintained and activated through a tuft cell–ILC2 circuit[49]. By contrast, in humans, naive T cells populate the thymus already at 6–9 weeks post conception, memory T cells are found in the gut at 14–21 weeks post conception[50] and T cells are the dominant lymphocyte population in the intestine at birth[51]. This raises the possibility that human intestinal ILC2s are regulated not only by microbial factors but also by adaptive lymphocytes, which might suppress intestinal ILC2 numbers by the time of birth. In support of this, it has been reported that ILC3s are inhibited by both regulatory and effector CD4+ T cells following weaning in mice[52]. It is also possible that ILC2s are present in human adult gut but at sites that have so far been difficult to sample, or that they lack expression of canonical ILC markers, such as CD127, as has been reported for blood and lung ILC2s[19], thereby complicating their identification. Hence, the dynamics, regulation, phenotype, location and role of gut ILC2s during the human lifespan require further research.

Assessment of BAL fluid of individuals with asthma stimulated with lung allergens provides a unique opportunity to gain insight into the kinetics of ILC2 composition in human tissues in a clinically relevant setting. Indeed, ILC2s that express ST2 (REF.[53]) and CRTH2 (REF.[54]) accumulate in BAL fluid within the first 24 h of allergen challenge. Interestingly, CRTH2+ ILC2s in BAL fluid have increased levels of *IL17RB* and *IL1RL1* (encoding ST2) transcripts as compared to peripheral blood ILC2s[54]. Further analysis revealed that ILC2s in BAL fluid also have increased expression of *BATF* and *IRF4* (REF.[54]), pointing towards a phenotype equivalent to that of gut ILC2s identified in mice (TABLE 2), which can migrate to the lung and acquire ST2 expression[15,55] (FIG. 1b). As the accumulation of ILC2s in BAL fluid occurred within 24 h of allergen challenge, likely preceding local proliferation of ILC2s, and correlated with the depletion of peripheral blood ILC2s[54], it is tempting to speculate that human ILC2s can leave the circulation and enter the lung upon allergen challenge, which is supported by mouse data[14] (FIG. 1b). In line with this, exposure of human peripheral blood ILC2s to alarmins leads to marked phenotypic changes, including increased protein expression of IL-17RB and ST2 and decreased expression of CRTH2, which is similar to the phenotype of lung ILC2s both at homeostasis[8] and during allergic inflammation[54]. Of note, similar results were recently obtained in patients with CRSwNP, where it was shown that peripheral blood CD45RA+ ILC2s exposed to alarmins undergo conversion to CD45RO+ activated 'inflammatory' ILC2-like cells similar to those found in nasal polyps[15]. In addition, as discussed above, CD45RO+ cells that have a transcriptional profile similar to activated and migratory gut ILC2s in mice[15] are found in the circulation of patients with asthma, particularly in steroid-resistant disease[15]. Consistent with this, CD45RO+ ILC2s are significantly more steroid-resistant than CD45RA+ ILC2s[15]. Hence, such data support a model in which circulating human CRTH2+CD45RA+ ILC2s that enter type 2 inflamed tissues convert to CD45RO+ ILC2-like cells that produce large amounts of IL-13 and IL-5, thereby contributing to type 2 pathophysiology. Such CD45RO+ ILC2s

Table 2 | **Phenotypes of type 2 innate lymphoid cells in mice**

ILC2 population	Surface markers				Activating signals	Factors produced	Tissue distribution	Unique transcription factors
	ST2	IL-17RB	CD90	KLRG1				
Tissue-resident 'natural' ILC2s	+	+/−	+	+/−	Type 2: IL-7, IL-33	IL-5, IL-13	Lung, fat, stomach	ND
					Type 3: IL-23, TGFβ	IL-13, IL-17A		
Activated 'inflammatory' ILC2s	−	+	−	+	IL-7, IL-25	IL-5, IL-13	Intestines	BATF
IL-10-producing ILC2s	+	+	+	+	IL-2, IL-4, IL-7, IL-33, RA	IL-5, IL-10, IL-13	Lung, intestines	BLIMP1, MAF

ILC2, type 2 innate lymphoid cell; ND, not determined; RA, retinoic acid; TGFβ, transforming growth factor-β.

in humans can later migrate out of inflamed tissues, thereby re-entering the circulation and potentially contributing to systemic type 2 immunity as observed in mice[39] (FIG. 1b).

However, alternative explanations for the enlarged population of ILC2s seen in asthmatic lungs and nasal tissue from patients with CRSwNP are possible. In BAL fluid, ILC2s may be mobilized from peribronchial areas, which contain IL-17RB⁺ST2⁺ ILC2s even during homeostasis[8]. Indeed, using intravital microscopy in live mice, ILC2s are seen to have significant CCR8–CCL1-mediated ameboid mobility and preferentially localize in perivascular and peribronchial spaces upon intranasal IL-33 administration[56].

In summary, studies of ILC2s in mice indicate that, under steady-state conditions, these cells are tissue resident, whereas ILC2s activated by cytokines in the local tissue environment, such as that induced by *N. brasiliensis*, can acquire migratory capacities. In humans, ILC2s can be found in the circulation of both healthy individuals and patients with type 2 inflammation but it is currently unclear from which tissues such cells derive and whether populations of tissue-resident ILC2s exist. As in mice, human ILC2s can adapt to their microenvironment to generate a diverse repertoire of cells (TABLE 1; FIG. 1), with recent studies suggesting that ILC2s have important functions in an increasing variety of disease types, as we discuss below.

ILC2s in cancer

Previous studies have shown a role for ILC2s in both tumour promotion and tumour rejection, which have been comprehensively summarized elsewhere[57]. However, over the past 2 years, considerable progress has been made in the understanding of how specific populations of ILC2s contribute to immunosurveillance in different types of cancer[58–62] (FIG. 2). Most of these mechanistic insights have been generated in mouse models, with supporting but still limited data derived from human cancer tissues.

In two studies of human hepatocellular carcinoma (HCC), numbers of intratumoural ILC2s were shown to be increased whereas levels of the ILC2-promoting cytokine IL-33 were decreased[58,59]. In a mouse model of HCC, the reduced level of IL-33 was shown to correlate with expansion of a population of KLRG1⁻ ILC2s with low levels of expression of ST2. To replace the function of IL-33 signalling through ST2, these cells relied on the lack of KLRG1-mediated inhibition to promote the production of IL-13 and of the chemokines CXCL2 and CXCL8; this led to the chemoattraction of neutrophils that, under the influence of IL-13, produced the immunosuppressive factor arginase 1 (ARG1), thereby reducing T cell responses and promoting tumour growth[58] (FIG. 2a). Therefore, the authors suggest that the presence of KLRG1⁻ ILC2s in HCC correlates with reduced survival. However, the other study showed that high intratumoural levels of IL-33 and high frequencies of ILC2s are associated with better survival in patients with HCC[59]. Stratifying patients according to their ILC2 to ILC1 ratio revealed that only those patients with increased ILC2s relative to ILC1s had a KLRG1⁺ ILC2

phenotype driven by IL-33 and associated with better survival. Patients with decreased numbers of ILC2s relative to ILC1s had an ILC2 phenotype with low levels of KLRG1 and high levels of expression of CXCL8, reminiscent of the KLRG1⁻ CXCL8-producing ILC2s described in the mouse study[58]. This raises the possibility that the two phenotypes of KLRG1⁻ and KLRG1⁺ ILC2s might have opposing functions in HCC, with KLRG1⁻ ILC2s being pro-tumorigenic and KLRG1⁺ ILC2s being anti-tumorigenic (FIG. 2a). Although both HCC studies show the therapeutic potential of targeting ILC2s, we urgently need to better understand the conditions that regulate KLRG1⁺ versus KLRG1⁻ ILC2s in this type of cancer and how to selectively target them.

The role of the IL-33–ILC2 axis in promoting tumour rejection has also been demonstrated in a mouse model of melanoma[60] (FIG. 2b), in which it was shown that IL-33-induced ILC2s produce granulocyte–macrophage colony-stimulating factor (GM-CSF) and thus attract eosinophils to the tumour site, which are crucial for tumour rejection. Unleashing the full capacity of ILC2s through anti-PD1 checkpoint blockade further enhanced tumour rejection in this model, involving the recruitment of eosinophils and CD103⁺ dendritic cells, and the priming of antitumour CD8⁺ T cells. In humans with melanoma, an intratumoural type 2 gene signature, including *KLRG1* expression, was associated with better survival[60]. Similarly, in patients with pancreatic cancer, ILC2 accumulation and IL-33 levels are associated with increased survival[61] (FIG. 2c). In a mouse model of pancreatic cancer, IL-33-induced expansion of ILC2 populations also led to CD103⁺ dendritic cell recruitment through CCL5 production and subsequent CD8⁺ T cell priming. In this model, ILC2s were important for optimal tumour rejection, which was further enhanced by anti-PD1 therapy that not only unleashed CD8⁺ T cell-mediated antitumour immunity but also prevented the intrinsic PD1-dependent inhibition of ILC2s[61] (FIG. 2c). These exciting data suggest additional, non-T cell-driven mechanisms underlying the antitumour effects of PD1 checkpoint blockade, which presents novel opportunities to increase the efficacy of this therapy.

The role of ILC2s in colorectal cancer (CRC) is complex (FIG. 2d). Whereas the total number of ILC2s is low and unaffected in colon tumours of humans[63,64], the frequency of intratumoural IL-13⁺ ILC2s is increased in humans[64] and mice[65] with CRC. A recent study highlighted the role of the peroxisome proliferator-activated receptor-γ (PPARγ) pathway in ILC2s in a mouse model of CRC[64]. Among ILCs, PPARγ is selectively expressed by ILC2s, and in a mouse model of CRC, deletion of PPARγ in ID2-expressing cells, which includes ILC2s (as well as other ILC subsets), reduced the tumour burden and increased survival. Although the exact mechanisms were not explored, the pro-tumorigenic effects of ILC2s have previously been linked to creating a type 2 cytokine-driven immunosuppressive tumour microenvironment involving myeloid-derived suppressor cells, T$_{reg}$ cells and the inhibition of natural killer cells[66–68]. As PPARγ was shown to directly regulate PD1 expression in ILC2s[69], it is possible that PPARγ inhibition results in

a subset of PD1⁻ ILC2s with antitumour effects. Indeed, PD1⁺ ILC2s accumulate in human CRC tumours, and mice engrafted with PD1⁺ ILC2-containing tumours had, compared with tumours not containing PD1⁺ ILC2s, an increased tumour mass, which was decreased upon PD1 blockade[70]. By contrast, using the same mouse model of colitis-associated CRC, another study showed that selective deletion of ILC2s increased tumour burden

and reduced survival[65]. Hence, whereas PD1⁺ ILC2s seem to be a tumour-promoting subset in CRC, the effect of the total ILC2 pool may be anti-tumorigenic as it is associated with improved survival[65].

In summary, subsets of ILC2s can have opposing roles within and across different cancers. Notably, whereas the role of IL-10-producing T_{reg} cells in suppressing antitumour immunity is well understood, a role
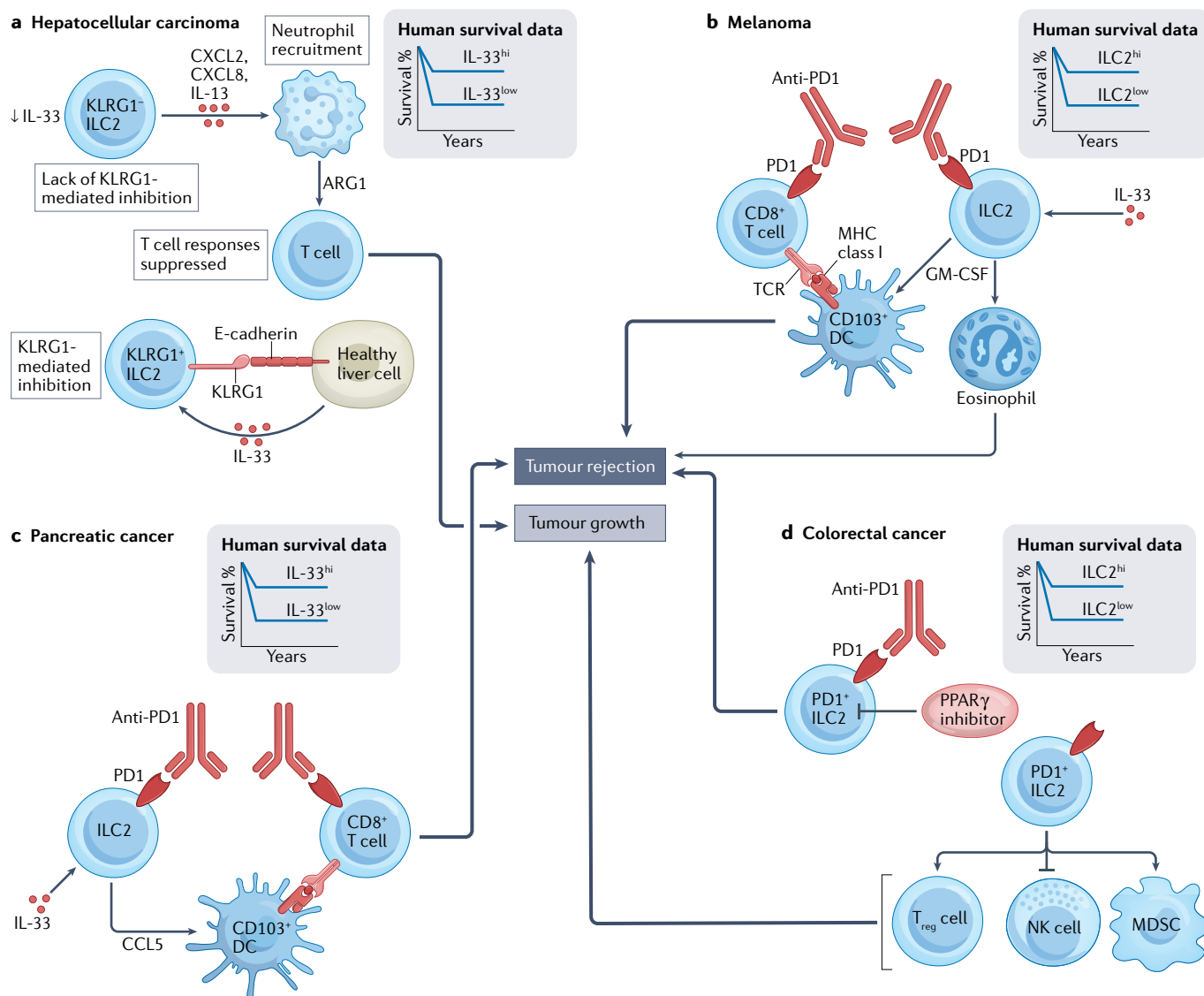
Fig. 2 | **ILC2s can contribute to tumour rejection or tumour growth.** In mouse models of hepatocellular carcinoma (part **a**), loss of KLRG1-mediated inhibition in a population of KLRG1⁻ type 2 innate lymphoid cells (ILC2s) results in the production of IL-13 as well as of the chemokines CXCL2 and CXCL8. CXCL2 and CXCL8 recruit neutrophils to the tumour site, which, under the influence of IL-13, produce the immunosuppressive factor arginase 1 (ARG1). ARG1 suppresses T cell responses, ultimately promoting tumour growth. In mouse models of melanoma (part **b**) and pancreatic cancer (part **c**), IL-33 induces ILC2s that subsequently activate CD103⁺ dendritic cells (DCs) to prime antitumour CD8⁺ T cells. In the case of melanoma, the production of granulocyte–macrophage colony-stimulating factor (GM-CSF) by ILC2s also recruits eosinophils to promote tumour rejection. Anti-PD1 therapy blocks cell-intrinsic inhibition of CD8⁺ T cells and ILC2s through the checkpoint molecule PD1 to further enhance tumour

rejection. In mouse models of colorectal cancer (part **d**), PD1⁺ ILC2s enhance tumour growth, for example through the inhibition of natural killer (NK) cell responses and enhancing the responses of regulatory T (T_{reg}) cells and myeloid-derived suppressor cells (MDSCs). Inhibition of PD1 signalling in ILC2s, through either pharmacological or genetic inhibition of the peroxisome proliferator-activated receptor-γ (PPARγ) pathway (which reduces PD1 expression) or anti-PD1 therapy promotes tumour rejection in colorectal cancer. These mechanistic insights from mouse models are supported by data derived from human cancer tissues (see inset schematic graphs). Genome-wide transcriptional data indicative of high intratumoural levels of *IL33* (in hepatocellular carcinoma (part **a**) and pancreatic cancer (part **c**)) or high levels of ILC2-associated gene expression (in melanoma (part **b**) and colorectal cancer (part **d**)) predict better survival in humans.

for IL-10-producing ILC2s in antitumour immunity has yet to be explored.

ILC2s in adipose tissue homeostasis

In mice, ILC2s in visceral adipose tissue are ST2^{+}ARG1^{+} cells and are transcriptionally, functionally and developmentally closely related to ILC2s found in the lung[71,72] (TABLE 2). Accumulating data in mice point to activated ILC2s as being regulators of adipose tissue homeostasis, preventing adiposity and promoting beiging of white adipose tissue (WAT) into thermogenic brown fat[73–75]. In support of these findings, ILC2s in human adipose tissue are also ST2^{+} and are reduced in number in adipose tissue from patients with obesity[73]. More recent mouse studies suggest that this function of ILC2s in adipose tissue homeostasis, and the development of adipose tissue ILC2s[76], are regulated in particular stromal cell niches, of which at least some are under neuronal control (FIG. 3). In a model of cold-induced beiging of WAT, it was shown that the increased number of ILC2s depended on IL-33 produced by a subset of mesenchymal adipose progenitor cells[77]. Mesenchymal adipose progenitor cells responded to β-adrenergic receptor signalling via cAMP response element-binding protein (CREB), which links neuronal stimulation to adipose tissue plasticity via ILC2s. In line with these observations, it was shown that the sympathetic nervous system controls mesenchymal adipose progenitor cells through the release of noradrenaline,

which acts on β-adrenergic receptors on these cells. In turn, these cells produce glial-derived neurotropic factor, the receptor for which, RET, is particularly highly expressed on visceral adipose tissue ILC2s. This interaction leads to the production of type 2 cytokines and enkephalins by ILC2s, which promotes beiging of WAT and counteracts the development of obesity following a high-fat diet[78]. In addition, it was recently shown that ILC2s regulate the downstream effects of obesity, namely metabolic syndrome, limiting both the onset of insulin resistance and established insulin resistance in a mouse model of obesity[79]. These preclinical data now warrant exploration in humans to determine the clinical relevance.

ILC2s in airway inflammation

Since their discovery, ILC2s have been shown to mediate airway inflammation in several mouse models of asthma, and increasing data correlate ILC2 numbers and function with asthma severity in humans (recently excellently reviewed elsewhere[80]). Recent data in mice[81–83] and humans[84] point towards metabolic factors that influence the role of ILC2s in lung homeostasis[84] and airway inflammation[81–83]. For example, glucose-dependent fatty acid uptake and metabolism in lung ILC2s in mice have been shown to fuel airway inflammation through ILC2 proliferation and cytokine production, which could be prevented by a ketogenic diet[82]. In parallel, the short-chain fatty acid butyrate has been shown to inhibit ILC2 functions and ameliorate airway inflammation in mice[83]. Furthermore, bilirubin, the catabolic end-product of haem, suppresses ILC2 function and airway inflammation in a mouse model of asthma, and human infants with hyperbilirubinaemia have reduced circulating ILC2 frequencies and cytokine production[81]. Hence, ILC2s are clearly not only involved in regulating whole-body metabolism through effects on adipose tissue homeostasis but are also themselves regulated by metabolic factors at a cellular level. The details of how metabolism regulates human ILC2s are beginning to be unravelled[84], showing a crucial role for oxidative phosphorylation in the maintenance and proliferation of ILC2s, whereas glycolysis is crucial for optimal type 2 cytokine production by ILC2s.

Recent studies suggest that neuronal factors also regulate ILC2 functions in the lung in mouse models of airway inflammation. Although this aspect is still underexplored in humans, ILC2s in mice express the neuropeptide calcitonin gene-related peptide (CGRP; also known as CALCA) and its receptor, which inhibit ILC2 function in vitro[85]. In a mouse model of airway inflammation induced by intranasal administration of IL-33, CGRP receptor deficiency caused worsening of inflammation, indicating that CGRP might have a role in limiting ILC2 responsiveness in the lung. By contrast, IL-25-induced ILC2s in the lung express the neuromedin U receptor (NMUR1) and NMUR1 signalling promotes house-dust mite-induced airway inflammation[86]. Hence, IL-33-induced and IL-25-induced lung ILC2s seem to differ in their responsiveness to neuronal factors. In fact, in helminth infection, CGRP finetunes ILC2 responses induced by IL-33 and neuromedin U to limit IL-13
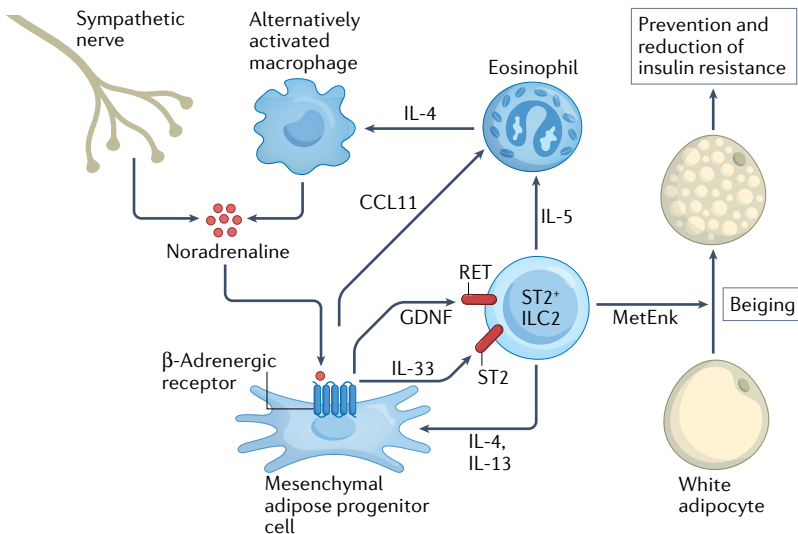

Fig. 3 | **ILC2s are involved in adipose tissue homeostasis.** In mouse adipose tissue, sympathetic nerves and alternatively activated, M2-type macrophages produce noradrenaline that binds β-adrenergic receptors on mesenchymal adipose progenitor cells. This leads to their production of IL-33 and glial cell-derived neurotrophic factor (GDNF), for which the receptors ST2 and RET, respectively, are expressed on adipose tissue type 2 innate lymphoid cells (ILC2s). Activation of adipose tissue ILC2s leads to IL-4 and IL-13 production, which act on mesenchymal adipose cells to promote their production of the eosinophil chemotactic factor CCL11 (also known as eotaxin). Together with ILC2-derived IL-5, this recruits eosinophils to adipose tissue and supports their maintenance. Eosinophils produce IL-4 that supports the differentiation of alternatively activated macrophages, thereby creating a positive-feedback loop for a type 2 environment in the adipose tissue. Adipose tissue ILC2 activation also leads to the production of Met-Enkephalin (MetEnk), which acts on opioid receptors on adipocytes, resulting in a process known as beiging that reduces insulin resistance, a component of the metabolic syndrome.

production while maintaining IL-5 production, thereby controlling the magnitude of the ILC2 response[87]. In a mouse model of ovalbumin-induced airway inflammation, CGRP produced by pulmonary neuroendocrine cells induced IL-5 production by ILC2s and promoted inflammation[88]. Although IL-13 production was not assessed in this study, based on the helminth infection model, CGRP seems to function as a rheostat of lung ILC2 function, which is regulated by an intricate neuroendocrine network of factors with both activating and inhibitory functions. Studies addressing these aspects in human airway inflammation are now eagerly awaited.

ILC2s in skin inflammation

In mice, skin ILC2s have a unique phenotype as compared to those found in lung, adipose tissue and gut, with low levels of expression of ST2 and IL-17RB and high levels of expression of the IL-18 receptor[71]. In healthy skin of mice, ILC2s provide a homeostatic source of IL-13 that, independently of alarmins, contributes to the differentiation of skin CD11b^{low} type 2 conventional dendritic cells. Upon dermal allergen administration, the presence of these dendritic cells underpins a preferential T_H2 cell response, which is not seen following allergen challenge in the lung[89]. Indeed, atopic dermatitis is associated with an accumulation of ILC2s, which enhance allergen-induced type 2 responses, in both mice and humans[90]. However, the downstream and translational consequences of the type 2 response skewing in skin compared with other tissues remain to be explored in more detail. To the best of our knowledge, there is no evidence for a migratory behaviour of skin ILC2s in mice, unlike that reported for gut and lung ILC2s[14,39]. Instead, the data support a model whereby flexible ILC2 responses in the skin are achieved through the plasticity of skin-resident ILC2s without the need for recruitment of ILCs from other tissue sources. IL-23-induced psoriasis-like skin inflammation in mice was shown to be independent of the recruitment of circulating ILCs[91]. Instead, inflammation was mediated by IL-23-driven conversion of homeostatic skin ILC2s into a pathogenic ILC3-like state (BOX 1). These data are supported by a recent single-cell RNA sequencing study of human psoriatic skin, which revealed a spectrum of ILCs with mixed features of ILC2s and ILC3s[92]. By contrast, in humans, psoriasis is associated not only with enrichment of dermal IL-17$^+$IL-22$^+$ ILC3s[25] but also with an increase in the number of circulating ILC3s[93] and skin-homing RORγt$^+$CD117$^+$ ILC2s[25], which suggests that progenitors of ILC3s migrate to psoriatic skin and that mature ILC3s are extruded from psoriatic skin. Further work will determine whether this flux of skin ILCs in humans can be modelled in mice, enabling the study of the mechanisms involved.

ILC2s in microbial infections

One of the first reports of a role of ILC2s in the airways showed that ILC2s contribute to amphiregulin-mediated lung tissue repair following influenza virus infection in an IL-33-dependent manner[5]. There were also early reports of the depletion of ILCs in individuals infected with HIV-1, and it was suggested that such depletion could contribute to the breakdown of gut mucosal barrier function seen in persons living with HIV-1 (REF.[94]). However, in addition to contributing to tissue repair in viral infection, ILC2s have also been implicated in driving viral pathogenesis and exacerbating chronic lung disease. In mice, respiratory syncytial virus (RSV) infection triggers IL-33 production from airway epithelia, which in turn induces ILC2s to produce IL-13 and promotes airway inflammation[95], through effects on both stromal and immune cells, including goblet cell hyperplasia, B cell IgE isotype switching and the polarization of alternatively activated, M2-type macrophages. A recent report identified the uric acid-induced activation of the NLRP3 inflammasome in epithelial cells as being crucial for this process. Inhibition of this pathway in RSV infection leads to a reduction not only of uric acid-induced IL-1β production by myeloid cells but also IL-33 production by epithelial cells and, subsequently, a reduction in the number of ILC2s in the airways of mice[96] (FIG. 4a). Strikingly, a translational study recently revealed the accumulation of ILC2s and the type 2 cytokines IL-33, IL-4 and IL-13 in nasal aspirates of infants with RSV infection with severe disease as compared to moderate disease[97]. These findings provide clinical relevance to the role of ILC2s in driving RSV pathogenesis observed in mice, and suggest that RSV infection of infants might prime for subsequent development of lung diseases later in life[98].

Similarly to RSV infection, rhinovirus infection in mice is also associated with excessive ILC2 activation[99], thereby contributing to asthma exacerbations (FIG. 4b). The translational relevance of these findings was recently confirmed as an increased ratio of ILC2s to ILC1s was found in bronchial biopsy samples of individuals with asthma versus without asthma after rhinovirus infection[100]. Of note, the increased ILC2 to ILC1 ratio in individuals with asthma was associated with greater severity of rhinovirus infection, including reduced lung function and increased respiratory symptoms.

As ILC2s clearly have a role in respiratory virus infections, the recent emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has raised the question of whether ILC2s participate in this disease process (BOX 2; FIG. 4c).

Although there is still little evidence for a role of ILC2s in responding to bacterial infections in humans, recent studies suggest that ILC2s contribute to antibacterial immunity in mice, specifically against the commensal stomach microbiota as well as the pathogen *Helicobacter pylori*[101]. Surprisingly, in contrast to IL-17RB$^+$ 'inflammatory' ILC2s in the small intestine of mice, ILC2s in the stomach are ST2$^+$ and resemble lung ILC2s[14]. IL-5 and IL-13 production by stomach ILC2s depends on the microbiota[101]. In the context of *H. pylori* infection, ILC2s accumulate and produce IL-5, which drives IgA production. Depletion of ILC2s in this model reduced IgA production and induced mucosal inflammation and bleeding, suggesting that ILC2-driven IgA limits tissue damage by coating *H. pylori*. In contrast to mice, there is only a small population of CRTH2$^+$ ILC2s in the adult human intestine and they are absent in the

stomach of most healthy human donors[102]. Given that *H. pylori* causes expansion of stomach ILC2 populations in mice, further studies exploring the potential existence of CRTH2⁻ ILC2s in human stomach and their role in controlling *H. pylori* infection and subsequent *H. pylori*-associated inflammation and cancer are needed.

Conclusions and therapeutic prospects

In contrast to our limited understanding of ILC2s a decade ago, today we know that ILC2s are highly dynamic cells that respond, migrate, establish tissue residency and adapt their effector functions depending on the microenvironment. This flexible behaviour resembles that of T cells and ensures the right response at the right time and place. However, it also means that ILC2s are easily dysregulated to contribute to diseases such as cancer, metabolic disorders, inflammation and infectious diseases. In particular, the recent realization

that IL-4 and IL-13 contribute to epigenetic imprinting of basal stem cells in the nasal epithelium of patients with CRSwNP, with potentially long-lasting effects on type 2 skewing, highlights the therapeutic importance of targeting cells producing such cytokines, including ILC2s[103]. Indeed, ILC2s are a well-recognized component of a network of immune cells that contribute to allergy and asthma and, as such, are targets of multiple biologics currently approved or in advanced clinical trials for adults and, in some cases, adolescents, including those targeting IgE, IL-4, IL-13, IL-5, IL-33 and thymic stromal lymphopoietin[104]. Of note, recent data show effects of the anti-IL-4/anti-IL-13 drug dupilumab in ameliorating uncontrolled moderate-to-severe asthma in 6–11-year-old children[105]. By contrast, the pro-inflammatory functions of ILC2s are beneficial in certain cancers, where ILC2s can be targets for anti-PD1 therapy to improve tumour rejection, at least in mouse models[61]. More recently, the tissue-repair functions
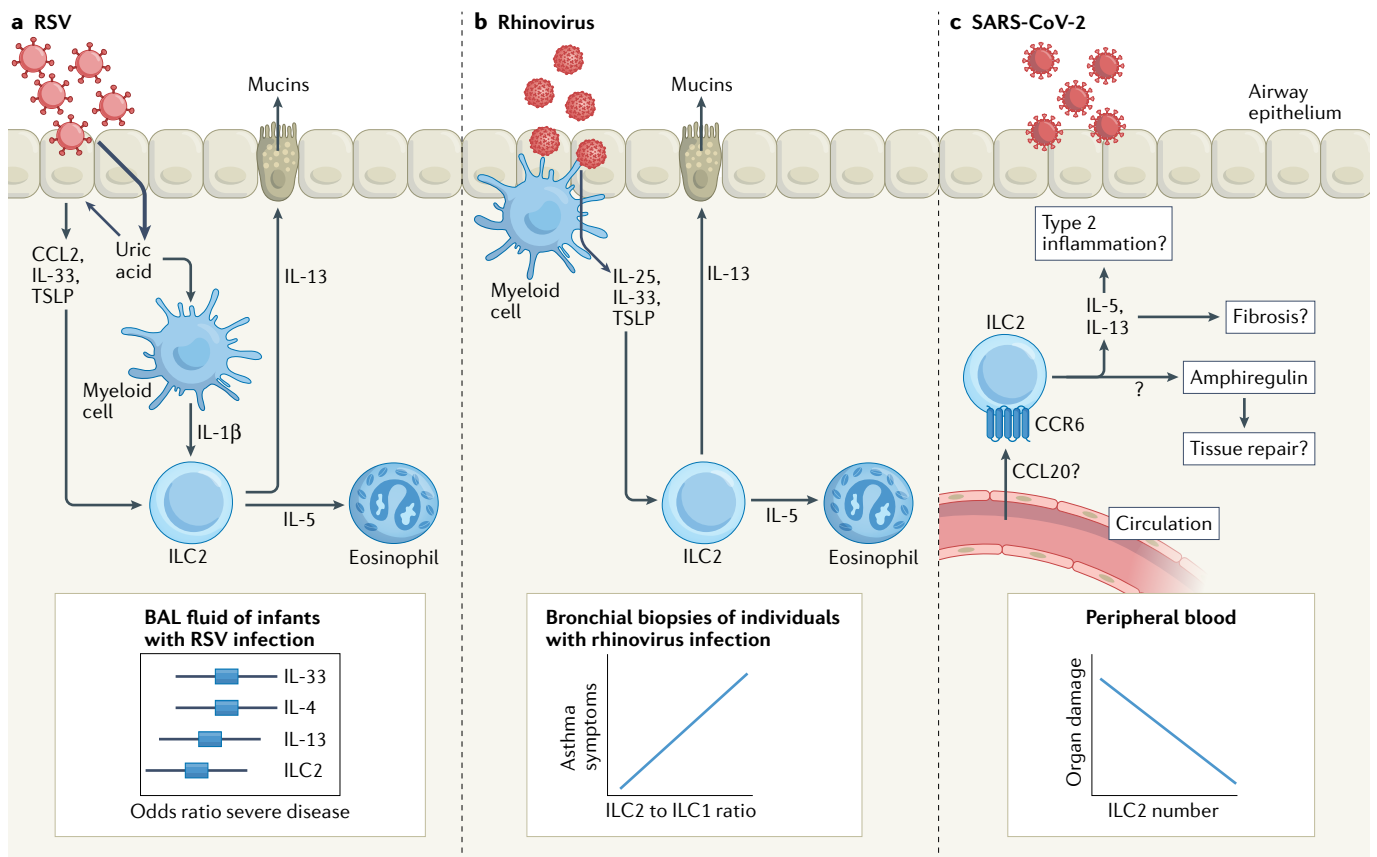

Fig. 4 | **ILC2s are involved in virus-induced exacerbations of airway inflammation. a** | In a mouse model, respiratory syncytial virus (RSV) infection induces activation of type 2 innate lymphoid cells (ILC2s) in the airways via uric acid-mediated production of IL-33, thymic stromal lymphopoietin (TSLP) and CCL2 by airway epithelial cells, as well as IL-1β production by myeloid cells. IL-13 production by ILC2s mediates mucin production as well as other downstream effects associated with asthma such as the IL-5-mediated maintenance of eosinophils. High levels of IL-33, IL-4, IL-13 and ILC2s in bronchoalveolar lavage (BAL) fluid are associated with more severe airway inflammation in infants with RSV infection. **b** | In rhinovirus infection in mice, alarmins such as IL-33, produced by airway epithelial cells and myeloid cells, drive ILC2 activation, leading to IL-5 and IL-13 production for the recruitment

of eosinophils and mucin production, respectively. In experimental rhinovirus infection in humans, the bronchial ILC2 to ILC1 ratio correlates with asthma symptom score. **c** | In severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in humans, numbers of CCR6⁺ ILC2s in the circulation are reduced, which correlates with serum levels of CCL20, indicative of the CCL20–CCR6-dependent recruitment of ILC2s from the circulation to sites of inflammation such as the lungs. Blood ILC2 numbers are inversely correlated with serum markers of organ damage in patients with coronavirus disease 2019 (COVID-19), suggesting a potential detrimental role of ILC2s in inflamed tissues. However, the precise role for ILC2s in the airways, including their production of cytokines, such as amphiregulin, which might be involved in lung tissue repair, in patients with COVID-19 remains unclear.

Box 2 | **Potential role of type 2 innate lymphoid cells in COVID-19**

Although the experimental evidence for a role of type 2 innate lymphoid cells (ILC2s) in coronavirus disease 2019 (COVID-19) is still lacking, two observational studies report depletion of peripheral blood ILCs, including ILC2s, in patients with COVID-19 (REFS[110,111]). Notably, peripheral blood ILC2 frequencies were reduced in severe versus moderate COVID-19, and ILC2 frequencies were negatively correlated with clinical markers of disease severity, including markers of tissue damage[110]. These data support a model for COVID-19 pathology in which ILC2s are recruited from the circulation to contribute to lung pathophysiology (FIG. 4c). In support of that, CCR6^{+} ILC2s were particularly depleted in the peripheral blood of patients with COVID-19, and their frequency was inversely correlated to the serum concentration of the CCR6 ligand CCL20. Indeed, a recent study identified CCR6–CCL20-mediated recruitment of peripheral blood ILC2s to the lung as a driver of excessive collagen production in the airways during cystic fibrosis[112]. The crucial question now is whether ILC2s contribute to tissue repair during COVID-19, as originally described for ILC2s in influenza virus infection[5], and/or drive harmful pathogenic processes such as lung fibrosis, which is a characteristic feature of COVID-19.

of ILC2s have been harnessed for third-party cellular therapy that was well-tolerated in a mouse model of graft-versus-host disease[106], and co-transplanted IL-10-producing ILC2s prevented graft rejection in a mouse model of pancreatic islet transplantation[107]. Collectively, these studies present diverse strategies to interfere with ILC2 function depending on the disease type by reducing or enhancing the pro-inflammatory functions of ILC2s or enhancing the tissue-repair and/or immunosuppressive functions of ILC2s. For such approaches, we need a better understanding of ILC2 diversity across tissues and the factors, including lipids, neurotransmitters, hormones, cytokines and surface ligands, that finetune the kinetics, magnitude and location of ILC2 responses. In particular, we need to better delineate the origin of and relationships between human ILC2 'subsets' to determine if they rather represent states of activation than true subsets with distinct precursors. Furthermore, we need to understand the roles of different ILC2 phenotypes in homeostasis and pathological conditions, such as cancer, obesity, inflammation and infections, to pave the way for the development of even more effective and specific therapies for such diseases.

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