

# Innate lymphoid cells in rheumatoid arthritis as mediators of pathology and resolution

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## Abstract

Innate lymphoid cells (ILCs) are emerging as critical modulators of inflammation in rheumatoid arthritis, contributing to both disease pathology and resolution. Group 3 ILCs (ILC3s) mirror T<sub>H</sub>17 cells in their production of IL-17A and IL-22, promoting fibroblast activation, neutrophil recruitment and synovial inflammatory cascades. By contrast, group 2 ILCs (ILC2s) engage reparative and immunoregulatory pathways via secretion of IL-9, IL-13 and IL-10. Lymphoid tissue inducer (LTi) ILCs contribute to ectopic lymphoid tissue neogenesis and stromal remodelling in early disease. Clinically, alterations in ILC subset composition correlate with disease activity, therapeutic responsiveness and inflammatory burden. Advances in high-dimensional immunophenotyping, spatial transcriptomics and single-cell multi-omics now enable precise mapping of ILC subsets and their effector programmes across peripheral blood and synovial tissue, supporting their use in biomarker discovery and treatment pipelines. Furthermore, modulation of ILCs by targeting upstream cytokines, signalling pathways or the use of microbiota-derived metabolites is a potential therapeutic strategy. Finally, cell-based avenues include IL-10-producing ILC2s (ILC2<sub>10</sub>) and engineered chimeric antigen receptor (CAR)-ILC2s for targeted, tissue-resident immune modulation. Although still in the preclinical stages, these approaches highlight the translational potential of ILCs as biomarkers and therapeutic targets in rheumatoid arthritis.

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## Key points

- Innate lymphoid cells (ILCs) have dual roles in rheumatoid arthritis (RA); ILC3s and ILC1s promote inflammation, whereas ILC2s mediate protection through the production of IL-4, IL-9, IL-10 and IL-13.
- CCR6<sup>+</sup> ILC3s accumulate in the joints in RA and correlate with disease activity; the interaction of these cells with synovial fibroblasts promotes IL-17A-driven inflammation, myeloid skewing and tissue remodelling.
- ILC2s show context-dependent effects in RA, exerting regulatory functions during early inflammation but contributing to pathogenesis via GM-CSF production under specific inflammatory conditions, such as in SKG mice.
- Alterations in ILC subset composition in blood, lymph nodes and synovial tissue could serve as dynamic biomarkers reflecting disease stage, immune activation and treatment response in RA.
- Targeting ILCs via cytokine signals (for example, IL-33), microbial metabolites (such as isoLCA), or pharmacological inhibitors (including JAK inhibition) offers promising therapeutic strategies in combination with conventional DMARDs.
- Preclinical studies support the feasibility of ILC-based cell therapies, including IL-10-producing ILC2s expanded from peripheral blood mononuclear cells or pluripotent stem cells, with the potential to restore immune homeostasis in RA.

## Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of the small joints, permanent joint damage, disability and increased mortality<sup>1</sup>. Nevertheless, no curative treatments currently exist<sup>2</sup>. Achieving sustained remission remains a notable challenge; evidence from randomized controlled trials demonstrates that tapering anti-TNF therapy among patients in durable remission results in disease flares in 65% of individuals within 1 year<sup>3</sup>. These observations imply that underlying immunological imbalances persist, even in patients who are clinically in remission, reflecting a critical gap in understanding of disease triggers and limitations of current therapies in restoring complete immunological homeostasis.

Twin studies show that individuals with an identical twin diagnosed with RA have a -15% risk of developing the disease themselves, indicating a modest but meaningful genetic contribution<sup>4</sup>. However, the rapid rise in the incidence of RA across industrialized regions suggests that environmental factors also have a pivotal role<sup>5</sup>. Epidemiological research has identified key environmental risk factors for RA, including smoking, periodontal disease and exposure to inhaled particulates such as silica and coal dust<sup>6–8</sup>. These risk factors share a common feature: each functions as an inflammatory or toxic insult at mucosal surfaces, particularly within the oral mucosa and respiratory tracts. This pattern supports the concept that mucosal sites could serve as initiation points for autoimmune priming<sup>9</sup>. These surfaces are densely colonized by commensal microbes that are increasingly associated with immune dysfunction and a greater risk of RA in later life<sup>10</sup>. Studies using germ-free mouse models have highlighted the critical

role of specific microbial taxa in driving inflammation; for example, segmented filamentous bacteria promote T<sub>H</sub>17 cell differentiation and can precipitate autoimmune pathology<sup>11</sup>. In K/BxN mice, which develop spontaneous arthritis, germ-free conditions completely abrogate disease, whereas colonization with segmented filamentous bacteria is sufficient to trigger rapid-onset arthritis within days<sup>11,12</sup>. Together, these findings support the concept that microbial exposures represent a second class of immune-priming signals, alongside environmental inflammatory irritants, that shape susceptibility to RA and other autoimmune diseases.

Innate lymphoid cells (ILCs) seed mucosal tissues during early microbial colonization and persist thereafter as long-lived tissue-resident sentinels. By functioning as rapid first responders during inflammatory perturbations, these cells are uniquely poised to influence the long-term sculpting of immune responses<sup>13</sup>. These features collectively position ILCs as prime candidates for involvement in RA pathogenesis. Moreover, these cells are implicated in establishing susceptibility to chronic inflammation in several other inflammatory diseases, including allergic asthma, dermatitis, psoriasis and intestinal inflammation<sup>14</sup>. For example, depletion of short-chain fatty acid-producing commensal bacteria leads to aberrant activation of ILC2s, which in turn drives the production of natural innate IgE antibodies by B1 cells and increases susceptibility to allergic inflammation<sup>15,16</sup>. Similarly, loss of specific bile acid-modifying microbes and enrichment of branched-chain amino acids (such as leucine) results in the expansion of ILC3s and pathogenic T<sub>H</sub>17 responses that enhance susceptibility to hypersensitivity pneumonitis, a T<sub>H</sub>1-driven and T<sub>H</sub>17-driven neutrophilic inflammation<sup>17</sup>.

These findings converge on a broad principle: immune dysregulation arising from disrupted immune sculpting, whether through early microbial perturbation or persistent environmental insult, might represent a shared feature of chronic inflammatory diseases. Building on this framework, we propose that both juvenile and adult-onset RA could be primed much earlier in life than previously appreciated, shaped by exposure-driven changes in the long-term behaviour of ILCs. In this Review, we critically examine the role of ILCs in RA, emphasizing the importance and urgency of elucidating their contributions to rheumatic diseases.

## Innate lymphoid cell biology and subsets

ILCs are a family of lymphocytes that lack antigen-specific receptors but in all other ways resemble polarized T cells. Unlike T cells, however, each ILC subset rapidly integrates epithelial, stromal, neural and microbial cues to coordinate early immune responses and maintain tissue homeostasis. In this section, we describe the major ILC subsets and the functional parallels between these populations and T cells, and then summarize key concepts in ILC development and tissue residency that inform the potential roles of these cells in autoimmune diseases such as RA.

### Innate lymphoid cells as innate homologues of adaptive T cells

ILCs are an emerging family of potent, tissue-resident immune-modulatory cells responsible for homeostasis and the early stages of host defence<sup>13,18</sup>. The ILC family comprises five major groups defined by developmental trajectories and functional characteristics: natural killer (NK) cells, ILC1s, ILC2s, ILC3s and lymphoid tissue inducer (LTi) cells. Although listed as a separate group in this five-subset schema, LTi cells are developmentally related to the broader ILC3 lineage. LTi cells express ROR $\gamma$ t and promote lymphoid

tissue organogenesis; in the absence of these cells, the formation of lymph nodes, Peyer's patches and the lymphoid architecture in the thymus and spleen is severely disrupted<sup>19</sup>. NK cells primarily function as cytotoxic cells and can be viewed as the innate counterpart to cytotoxic CD8<sup>+</sup> T cells. In addition, each T helper cell subset (T<sub>H</sub>1, T<sub>H</sub>2 and T<sub>H</sub>17 cells) corresponds to a functionally analogous ILC population (ILC1, ILC2 and ILC3, respectively) (Table 1).

Unlike T helper cells, which exhibit antigen specificity through the expression of diverse T cell receptor (TCR) repertoires, ILCs lack TCRs and respond rapidly to a variety of environmental factors in an antigen-independent manner<sup>20,21</sup>. Following local insult or infection, tissue epithelial cells and stroma release key 'alarmins', including thymic stromal lymphopoietin (TSLP), IL-33 and IL-25, which activate ILC2s to prime the initial immune response<sup>22–25</sup>. This provides a mechanistic explanation for how the immune system instantly initiates rapid helper responses tailored to the appropriate pathogens long before the development and polarization of antigen-specific T cells in the lymph nodes. In this model, these ILCs serve as tissue-resident first responders that orchestrate the appropriate downstream polarized inflammatory cascade. To fulfil this function, ILCs colonize most mucosal barrier surfaces of the body (such as the lungs, gut and skin) very early in ontogeny<sup>26</sup>.

Given this strategic positioning and involvement in early and sustained responses, ILC dysregulation has been linked to a number of chronic inflammatory diseases, including asthma and atopy, psoriasis, inflammatory bowel disease, fibrosis and cancer<sup>27</sup>. These observations highlight the need to define the mechanisms governing ILC development, fate and function (Box 1), as such knowledge will be essential for future efforts to modulate ILC behaviour therapeutically in systemic autoimmune diseases including RA.

## Developmental lineage and tissue residency

ILC development begins in the fetal liver and continues postnatally in the adult bone marrow<sup>28,29</sup>. Intriguingly, lineage tracing studies have shown that certain ILC subsets, particularly LTi cells, can also arise from the embryonic haemogenic endothelium, rather than exclusively from fetal liver-derived progenitors, suggesting a distinct developmental route for this lineage<sup>30</sup>. This embryonic pathway seems largely

restricted to LTi cells, whereas the development of most ILC subsets during later ontogeny follows the conventional pathway via progenitors in the fetal liver and adult bone marrow. In adult mice, ILCs arise from  $\alpha$ 4 $\beta$ 7-expressing common progenitors known as  $\alpha$ -lymphoid precursors ( $\alpha$ LPs)<sup>28,31,32</sup>. These progenitors progress through a continuum of downstream differentiation stages that ultimately give rise to distinct ILC subsets<sup>33</sup> (Fig. 1). Early innate lymphoid progenitors (EILPs) are defined by expression of TCF1 and the absence of PLZF and these cells retain broad multilineage potential; in clonal differentiation assays, EILPs can generate NK cells as well as ILC1s, ILC2s and ILC3s<sup>32</sup>. Notably, EILPs are transcriptionally heterogeneous and retain the capacity to generate dendritic cells, highlighting a degree of flexibility and imprecision during ILC specification before further lineage commitment<sup>32</sup>.

Progressing beyond this stage, a committed ILC progenitor (ILCP) population emerges, defined by co-expression of TCF1 and PLZF<sup>34</sup>. Adoptive transfer studies have shown that these ILCPs can generate mature, tissue-resident ILCs, including NK cells<sup>31</sup>. However, more recent studies have also revealed the presence of locally maintained ILC progenitors in peripheral tissues, indicating that in situ differentiation also contributes to ILC development and phenotypic heterogeneity<sup>35–37</sup>. Notably, single-cell RNA sequencing (scRNA-seq) of gut ILCs in mice has revealed that, contrary to current dogma, some tissue-resident ILCs display evidence of abortive, neonatal-type TCR rearrangements, suggesting that at least a fraction might arise from neonatal thymic precursors rather than solely from bone marrow progenitors<sup>38–40</sup>. Furthermore, reports of mature ILC 'plasticity' in response to inflammatory cytokines are increasing, suggesting that ILC subset identity might be more flexible than previously thought, with potential for trans-differentiation and alternative cell-fate adoption<sup>41,42</sup>. However, such findings should be interpreted with caution. Apparent 'plasticity' could instead reflect rapid in situ expansion of rare, pre-existing tissue-resident ILC subsets<sup>43–45</sup>, recruitment of ILCs from other sites<sup>46,47</sup> or the differentiation of locally maintained precursor-like cells<sup>36,37,48–50</sup>. Evidence corroborating each of these mechanisms has been reported in various tissues and disease contexts, but the relevance of each process warrants further investigation in autoimmune diseases such as RA.

**Table 1 | Comparative overview of innate lymphoid cell subsets: functions, transcriptional programmes, stimuli and T cell analogues**

ILC subsets	Primary function or context	Key transcription factors	Key activating stimuli	Cytokines and effector molecules produced	Analogous T cell subset
NK cells	Viral immunity, tumour surveillance and chronic inflammation	T-bet and EOMES	IL-12, IL-15, IL-18 and type I interferons	TNF, IFN $\gamma$ , perforin, granzymes and IL-10	CD8 <sup>+</sup> T cells
ILC1	Immunity to viruses and intracellular pathogens, and chronic inflammation	T-bet and low EOMES expression	IL-12, IL-15 and IL-18	TNF, IFN $\gamma$ and granzyme B	CD4 <sup>+</sup> T <sub>H</sub> 1 cells
ILC2	Helminths defence, allergic inflammation, tissue repair and metabolic regulation	GATA3, ROR $\alpha$ , BCL11b and GF11	IL-25, IL-33, TSLP, PGD <sub>2</sub> , NMU and TL1A	IL-4, IL-5, IL-9, IL-13, amphiregulin and IL-10	CD4 <sup>+</sup> T <sub>H</sub> 2 cells
ILC2 <sub>10</sub>	Immunoregulation, tolerance and control of inflammation	GATA3, ID3 and AhR (context-dependent)	TGF $\beta$ , IL-10, IL-27 and retinoic acid	IL-10, TGF and IL-35 (in some cases)	CD4 <sup>+</sup> T <sub>reg</sub> cells
ILC3	Defence against extracellular bacteria and fungi, barrier maintenance and chronic inflammation	ROR $\gamma$ t, and T-bet (in some NCR <sup>+</sup> ILC3)	IL-1 $\beta$ , IL-23, IL-7, TGF $\beta$ and AhR ligands	IL-17A, IL-17F, IL-22, GM-CSF and IFN $\gamma$	CD4 <sup>+</sup> T <sub>H</sub> 17 and T <sub>H</sub> 22 cells
LTi cells	Embryonic and adult lymphoid tissue development	ROR $\gamma$ t and ID2	IL-7, LT $\alpha$ , LT $\beta$ and CXCL13	IL-17A, IL-17F, IL-22, LT $\alpha$ and LT $\beta$	Not applicable

AhR, aryl hydrocarbon receptor; BCL11b, B cell lymphoma/leukaemia 11b; EOMES, eomesodermin; GATA3, GATA binding protein 3; GF11, growth factor independent 1; GM-CSF, granulocyte-macrophage colony-stimulating factor; ILC, innate lymphoid cell; ILC2<sub>10</sub>, IL-10-producing ILC2; LT, lymphotoxin; LTi, lymphoid tissue inducer; NK cell, natural killer cell; NMU, neuromedin U; NCR, natural cytotoxicity receptor; PGD<sub>2</sub>, prostaglandin D<sub>2</sub>; ROR $\alpha$ , retinoic acid receptor-related orphan receptor alpha; ROR $\gamma$ t, retinoic acid receptor-related orphan receptor gamma t; TGF $\beta$ , transforming growth factor beta; T<sub>H</sub>, T helper; TL1A, TNF-like ligand 1A; TSLP, thymic stromal lymphopoietin.

## Box 1 | Genetic tools for dissecting ILC subset-specific functions

Interpretation of the divergent roles of innate lymphoid cells (ILCs) has been hampered by the lack of mouse models that enable selective manipulation of individual ILC subsets. Commonly used transgenic lines, such as *Il7r-Cre*, *Id2-CreERT2* and *Gata3-Cre*, target the entire ILC compartment, for the purpose of lineage-tracing, fate-mapping and deletion of genes of interest<sup>140</sup>, and therefore preclude discrimination of subset-specific contributions. Compounding this issue, models involving pan-haematopoietic deletion of *Rora* influence ILC3 functions by restraining their secretion of IL-17, further complicating the use or targeting of *Rora* in ILC2s<sup>39</sup>.

These challenges have prompted growing recognition of the need for improved animal models with subset-specific reporter systems that enable precise fate mapping and lineage tracing of individual ILC subsets, approaches that will be essential for resolving current controversies and elucidating the physiological role of each subset in health and disease. For example, *Il17rb* (encoding the IL-25 receptor) has been identified as a highly specific marker of ILC2s, irrespective of tissue-specific co-receptor expression programmes<sup>68</sup>. Moreover,

several studies have also taken advantage of *Nmur1-Cre*, which shows largely selective activity in ILC2s<sup>141,142</sup>.

Progress has similarly been made in developing strategies to target ILC3s specifically. One elegant study outlined multiple approaches for specifically targeting ILC3s to disentangle ILC3 function from that of other ILCs and T<sub>H</sub>17 cells<sup>93</sup>. Deletion of a *Rorc*(yt) cis regulatory element located 7 kb downstream of the *Rorc*(yt) transcription start site resulted in mice lacking ILC3s and RORγt<sup>+</sup> dendritic cells while leaving other ILCs and T<sub>H</sub>17 cells unaffected<sup>93</sup>. In parallel, *Serinc2* was identified as a gene with high, selective expression in ILC3s (but not RORγt<sup>+</sup> dendritic cells or other T<sub>H</sub>17 cells), enabling the generation of *Serinc2*-iCre transgenic mice for ILC3-specific fate-mapping and conditional allele deletion<sup>93</sup>.

Existing tools also have limitations. For instance, the current RORγt-GFP knock-in reporter disrupts one *Rorc* allele, resulting in *Rorc* haploinsufficiency and a partial reduction in RORγt<sup>+</sup> cell numbers<sup>143</sup>. Therefore, the generation of the new reporter mouse line targeting *Gm38411* (which faithfully marks RORγt<sup>+</sup> cells without altering *Rorc*) will be a valuable tool for investigating the role of ILC3 in RA<sup>93</sup>.

Human ILC development remains less well defined than that of mice, largely because studies of human embryonic tissues face substantial ethical and practical constraints. In human umbilical cord blood and adult peripheral blood, researchers have described a specific subset of ILCs expressing IL-7R, CD45RA and c-Kit but lacking a mature ILC phenotype<sup>43,51</sup> (Fig. 2). Transcriptomic and chromatin-accessibility analyses indicate that these cells notably overlap with haematopoietic stem cells, while maintaining an ILC profile in a poised state<sup>51</sup>. Both in vitro cloning assays and in vivo transfer experiments have demonstrated that these circulating precursors are multipotent and capable of giving rise to all ILC subsets. Although these cells are also found in the fetal liver, paediatric tonsils and adult lungs, their differentiation potential varies by tissue<sup>51</sup>; clonal analyses reveal that tonsillar precursors retain broad multipotency, whereas fetal liver-derived precursors are predisposed towards the ILC3 lineage and lung-derived precursors are biased towards ILC2s. These findings suggest that local environmental signals shape in situ ILC differentiation and function (Fig. 2). Collectively, these data show that, in both mice and humans, ILC development is not restricted to the bone marrow and can proceed within peripheral tissues<sup>35,52</sup>.

### Innate lymphoid cell precursor metabolism and functional regulation

Metabolic reprogramming is a central regulator of ILC activation, differentiation and effector function. Distinct ILC subsets engage specialized metabolic programmes that integrate nutrient availability, cytokine signals and local tissue cues to shape immune responses<sup>53</sup>. ILC1s rely primarily on glycolysis to support rapid IFNγ production, whereas ILC2s use a flexible combination of fatty acid oxidation and glycolysis to sustain type 2 cytokine output. By contrast, ILC3s depend on oxidative phosphorylation and lipid metabolism to maintain IL-22 secretion and tissue repair<sup>54,55</sup>. Disruption of these metabolic pathways can skew the cytokine balance and prolong inflammatory responses. The availability of specific amino acids, particularly arginine and methionine, functions

as a key rheostat of ILC activation, and mitochondrial STAT3 signalling couples methionine metabolism with type 2 cytokine production<sup>56,57</sup>. Furthermore, microbially induced dysbiosis has been shown to enrich pathways involved in branched-chain amino acid (BCAA) biosynthesis, thereby enhancing type 3 responses in ILC3s<sup>17</sup>. Collectively, these findings highlight metabolism as an important determinant of ILC effector potential.

Evidence also links such metabolic adaptations to autoimmune pathogenesis. In chronic inflammatory settings, nutrient competition, hypoxia and altered redox balance reshape ILC metabolic states, promoting persistent and sustained cytokine production<sup>58</sup>. Although direct evidence of metabolic adaptation in synovial ILCs in RA is currently lacking, studies in other inflamed tissues demonstrate that ILC2s and ILC3s depend on mitochondrial and lipid metabolic programmes to sustain cytokine production (IL-5, IL-13, IL-22) under hypoxic and nutrient-limited conditions<sup>54,55,59</sup>.

The rheumatoid joint is characterized by profound hypoxia and dynamic metabolic reprogramming<sup>60</sup>. In this context, adiponectin, an adipokine substantially upregulated in the inflamed synovium, could further contribute to the metabolically permissive environment that sustains inflammation, and could promote ILC function in RA via AMPK-dependent and lipid-driven signalling pathways<sup>61</sup>. Determining whether similar pathways govern ILC persistence and functional crosstalk with macrophages and fibroblasts in driving chronic inflammation represents an important area for investigation. These tissue-specific metabolic states highlight how ILCs integrate environmental and intrinsic metabolic signals to maintain effector activity in autoimmune disease. Targeting shared metabolic checkpoints, particularly the AMPK–mTOR–STAT3 axis, amino acid transport systems and mitochondrial bioenergetics, is a potential strategy for attenuating ILC-driven pathology while preserving homeostatic immunity. In support of this concept, selective inhibition of mTORC1 was shown to restore immunological balance in streptomycin-induced dysbiosis and attenuate pathological ILC3

responses in mice<sup>17</sup>. Moreover, diagnostic monitoring of ILC metabolic signatures in conjunction with metabolic signalling molecules such as adiponectin might refine disease stratification and improve prediction of therapeutic outcomes in RA.

## Preclinical and clinical evidence of innate lymphoid cells in rheumatoid arthritis

RA can begin many years before overt joint symptoms become apparent, and innate lymphoid cells are emerging as key regulators of tolerance and pathogenesis across this extended preclinical window. Among these populations, ILC2s have been positioned as immune regulatory cells during RA, although their functions seem context dependent and can include both protective cytokine programmes and pathogenic effector outputs. By contrast, ILC3 subsets and type 3 cytokine production, particularly IL-17A-driven inflammation, have been consistently associated with disease severity. ILC3-driven inflammation intersects with fibroblast activation and inflammatory loops implicated in flares. Relatively little, however, is known about specific roles of ILCs in RA.

## Regulatory and inflammatory functions of group 2 innate lymphoid cells

Type 2 immunity, characterized by cytokines such as IL-4, IL-5, IL-9 and IL-13, evolved primarily to promote hypersensitivity reactions and to counter large extracellular parasites, such as helminths, that evade elimination by conventional cytotoxic mechanisms<sup>62,63</sup>. Rather than relying on direct killing, type 2 responses enhance barrier integrity and promote tissue remodelling, most notably through mucus secretion and collagen deposition, to expel or contain these threats. These responses rely heavily on eosinophils, basophils, mast cells and B cells, and are closely linked to IgE-mediated humoral immunity. Interestingly, type 2 immune pathways are also integral to tissue-repair processes, suggesting an evolutionarily conserved role in wound healing<sup>64</sup>.

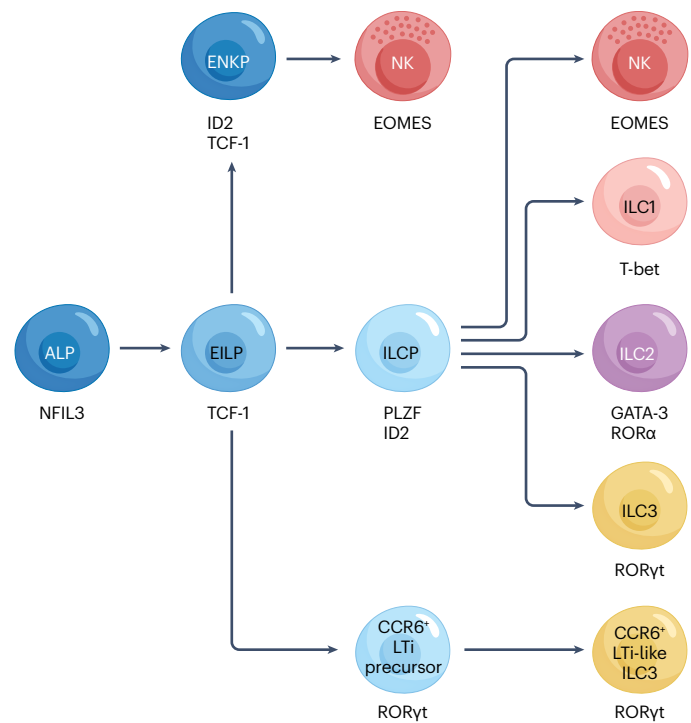
ILC2s, central mediators of type 2 immunity, are present in the blood and synovial tissue of patients with RA and are frequently associated with protective immunoregulation, although abundance and function vary with disease context<sup>65,66</sup>. Notably, several studies report elevated frequencies of circulating ILC2s in patients with RA compared with healthy individuals, with higher levels correlating inversely with disease severity<sup>65,67</sup>. This inverse relationship suggests a potential regulatory function for ILC2s in dampening RA pathology. Supporting this protective role, data from mouse models of arthritis show that expansion of GATA3<sup>+</sup> ILC2s, both in K/BxN serum transfer-induced arthritis and in collagen-induced arthritis, reduces disease severity by increasing production of IL-4 and IL-13 (ref. 67). Furthermore, depletion of ILC2s in GATA-3-Cre  $\times$  *Rora*<sup>fl/fl</sup> mice results in increased numbers of macrophages and exacerbated arthritis, whereas enhancing ILC2 function through adoptive transfer or pre-emptive administration of IL-25 or IL-33 mitigates inflammation and bone erosion<sup>67</sup>. Interestingly, adoptive transfer of ILC2s during the peak of disease activity fails to confer protection in the K/BxN model, highlighting a critical window in early arthritis to mitigate disease risk.

In line with these observations, a complementary study identified IL-9-producing ILC2s as key regulators of inflammation resolution in antigen-induced arthritis<sup>65</sup>. ILC2s were the predominant cellular source of IL-9 within the arthritic joints, and analysis of *IL9*<sup>-/-</sup> mice demonstrated that loss of IL-9-dependent ILC2 activity disrupted immunological homeostasis, resulting in sustained type 3 inflammatory responses mediated by IL-17A-producing T<sub>H</sub>17 cells<sup>65</sup>. Notably,

adoptive transfer of wild type ILC2s into *IL9*<sup>-/-</sup> mice was sufficient to reduce joint swelling in antigen-induced arthritis. However, the study did not selectively deplete ILC2s or specifically target IL-9 within the ILC2 compartment, leaving the requirement for IL-9 production by ILC2s in chronic arthritis resolution unresolved. Interestingly, adoptive transfer of ILC2s into *IL9*<sup>-/-</sup> mice also reduced circulating IL-17A protein levels<sup>65</sup>. In addition, ILC2s are capable of producing IL-10, and thus the contribution of IL-10-producing ILC2s to immune regulation during RA remained undefined<sup>68,69</sup>.

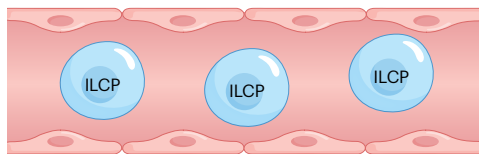
These observations align closely with previously proposed cross-regulatory interactions between ILC2s and type 3 lymphocytes (T<sub>H</sub>17 and ILC3s), first characterized in studies of Crohn's disease-like fibrosis<sup>68</sup>. In earlier work, selective depletion of ILC2s using the *Il17rb*<sup>CreERT2-eGFP</sup>  $\times$  *Rora*<sup>fl/fl</sup> transgenic mouse model led to enhanced accumulation of IL-17A-producing ILC3s and T<sub>H</sub>17 cells, exacerbating chronic fibrotic inflammation. Conversely, depletion of ILC3s and T<sub>H</sub>17 cells reduced fibrotic pathology<sup>68</sup>. Collectively, these findings demonstrate that ILC2s function as regulators that constrain pathogenic type 3 immune activity in the gut<sup>68</sup>.

The relationship between type 2 and type 3 immune responses in RA seems complex (Fig. 3a,c). Elevated IL-25 levels in patients with RA have been shown to promote ILC2 activation and concurrently suppress

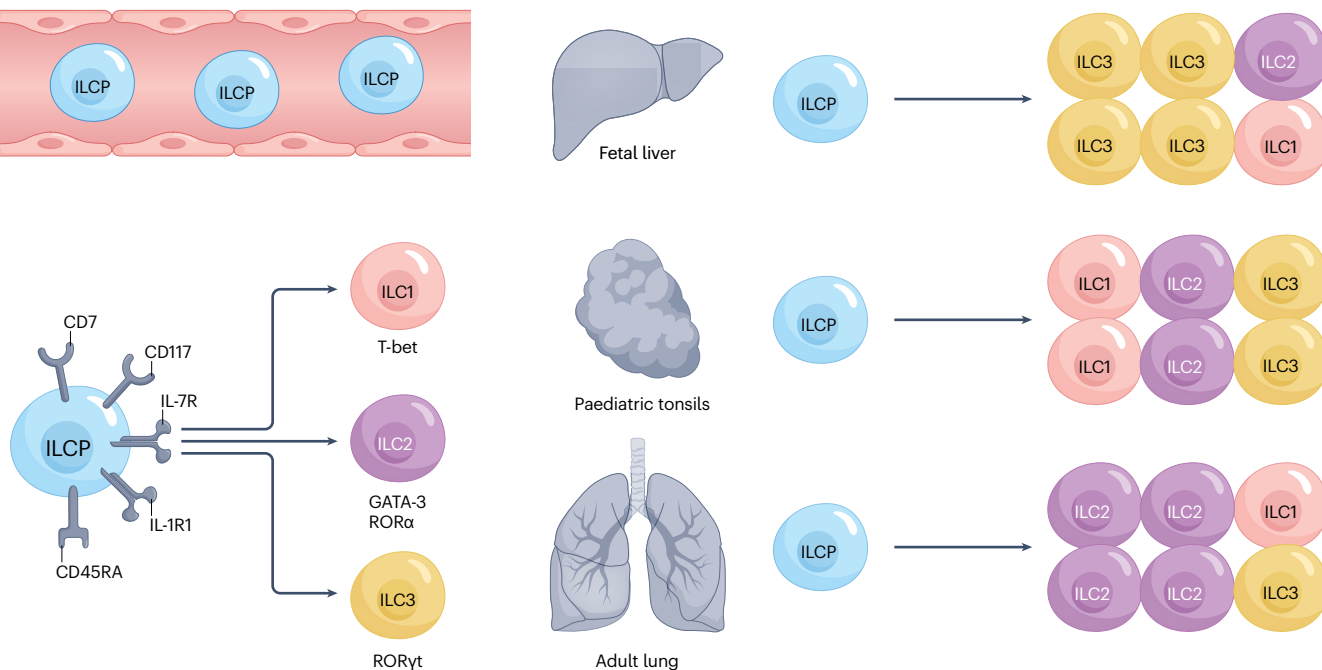


**Fig. 1 | Developmental pathways of bone-marrow-derived innate lymphoid cells in adult mice.** In the adult bone marrow of mice, all lymphoid progenitors (ALPs), which depend on the transcription factor NFIL3, give rise to early innate lymphoid progenitors (EILPs) characterized by expression of TCF1. EILPs retain dendritic cell potential but sequentially differentiate into innate lymphoid cell precursors (ILCPs), which lack this potential. ILCPs, defined by expression of PLZF and ID2, generate the three major ILC lineages, ILC1, ILC2 and ILC3, as well as natural killer (NK) cells. CCR6<sup>+</sup> lymphoid tissue inducer (LTI)-like ILC3s develop from distinct LTI-lineage precursors in the bone marrow. Notably, the majority of NK cells arise from a distinct, recently identified population of early NK progenitors (ENKPs).

## Human cord blood and adult peripheral blood



## Tissue signals drive local ILC differentiation and function



**Fig. 2 | Tissue-specific environmental signals shape local differentiation and function of human innate lymphoid cells.** Human circulating innate lymphoid cell precursors (ILCPs), characterized by the expression of IL-7R, CD45RA and c-Kit, are present in cord blood and adult peripheral blood. These precursors also reside in the fetal liver, paediatric tonsils and adult lungs, but

have a tissue-specific differentiation potential. For example, fetal liver precursors show a preferential commitment towards the ILC3 lineage, whereas lung-derived precursors are biased towards ILC2 differentiation. Together, these patterns suggest that local environmental signals regulate in situ ILC differentiation and functional specialization.

RORγt expression and IL-17A production in CD4<sup>+</sup> T cells derived from peripheral blood mononuclear cells<sup>70,71</sup>. Consistent with these observations, IL-25 administration in collagen-induced arthritis enhances type 2 responses and reduces *IL17A* and *RORC* expression in synovial tissues, resulting in diminished inflammation<sup>70</sup>. However, not all studies align with a protective role for ILC2s. One investigation revealed that GATA-3<sup>+</sup>ST2<sup>+</sup> ILC2s produce GM-CSF within the inflamed joints of arthritic SKG mice, positioning the ILC2 subset GATA-3<sup>+</sup>ST2<sup>+</sup> as an important initiator of autoimmune arthritis in this mouse model<sup>66</sup>. The SKG strain carries a point mutation in *Zap70* that impairs T cell receptor signalling and disrupts thymic selection, predisposing the mice to autoimmune arthritis upon innate immune stimulation<sup>72,73</sup>. This pathogenic function contradicts with previous studies describing immune-regulatory and disease-attenuating functions for ILC2s during the initiation phase of arthritis<sup>65,67</sup>. In line with the functional importance of GM-CSF in this setting, GM-CSF-deficient *Csf2*<sup>-/-</sup> SKG mice exhibit strong resistance to autoimmune arthritis<sup>66,74</sup>. Moreover, adoptive transfer experiments demonstrated that arthritis induction depends specifically on GM-CSF-producing ILC2s rather than GM-CSF-producing CD4 T cells, highlighting a distinct pathogenic facet of ILC2 biology<sup>66</sup>.

This GM-CSF-dependent ILC2 pathway also holds translational relevance, as neutralizing GM-CSF monoclonal antibodies ameliorate established disease across multiple inflammatory arthritis models, including collagen-induced arthritis, zymosan-induced arthritis and K/BxN serum-transfer arthritis<sup>75,76</sup>. Given the early induction of GM-CSF by ILC2s during the course of RA, this pathway could present a unique therapeutic target; indeed, clinical trials investigating

GM-CSF-directed therapies have shown promising results so far<sup>77,78</sup>. However, a critical outstanding question concerns the conditions under which ILC2s adopt regulatory functions (through cytokines such as IL-4, IL-13, IL-9 and IL-10) versus pathogenic functions (mediated by GM-CSF or other unknown cytokines). Future investigations employing selective and temporally controlled deletion of ILC2 subsets will be essential to clarify the therapeutic potential of modulating pathogenic ILC2 responses.

### The pathogenic roles of group 3 innate lymphoid cell subsets

Whereas ILC2s can adopt regulatory or pathogenic functions depending on context, ILC3s are more consistently linked to IL-17-driven inflammatory pathways in RA. Neutralizing IL-17A in the K/BxN serum-transfer arthritis model blocks disease progression, underscoring the pathogenic role of this cytokine<sup>12</sup>. Similarly, IL-17-deficient mice exhibit markedly reduced arthritis severity in collagen-induced arthritis and *Il17a*<sup>-/-</sup> SKG mice are highly resistant to autoimmune arthritis<sup>66,79</sup>. IL-17A production by ILC3s typically depends on STAT3-activating cytokines, such as IL-6 and IL-23 (refs. 80,81). Genetic deletion studies have demonstrated that loss of the IL-23p19 subunit, critical for STAT3 signalling and IL-17A induction, effectively mitigates autoimmune pathology across multiple models, including collagen-induced arthritis, antigen-induced arthritis and experimental autoimmune encephalomyelitis<sup>82-84</sup>. These observations align with the expansion of ILC3 populations reported in the inflamed joints of patients with RA and mice with collagen-induced arthritis<sup>85,86</sup>.

ILC3 subsets, including CCR6<sup>+</sup> LTI-like ILC3s, NCR<sup>+</sup>RORγt<sup>+</sup>T-bet<sup>+</sup> ILC3s and NCR<sup>-</sup> ILC3s, exhibit distinct and sometimes opposing roles

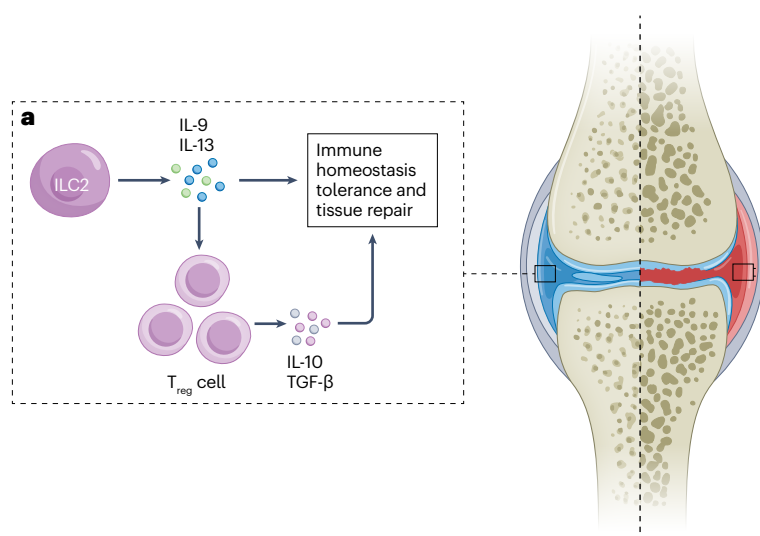
in arthritis pathogenesis<sup>87</sup>. Among these populations, CCR6<sup>+</sup>RORγt<sup>+</sup> LTi-like ILC3s show preferential and robust accumulation in the joints of mice with collagen-induced arthritis<sup>85</sup>. This subset expresses high levels of IL-17A, and increased frequencies of CCR6<sup>+</sup> LTi-like ILC3s in the synovial fluid of patients with RA correlate strongly with disease severity<sup>85</sup>. LTi cells (c-Kit<sup>+</sup>NKp44<sup>-</sup>) support the development and organization of secondary lymphoid tissues through the LTα<sub>1</sub>β<sub>2</sub>-LTβR signalling axis, which induces stromal production of adhesion molecules such as VCAM-1 and ICAM-1 and homeostatic chemokines including CXCL13, CCL19 and CCL21 (ref. 87). In early RA, reduced frequencies of LTi cells in lymph nodes correlate with decreased stromal expression of VCAM-1 and ICAM-1, suggesting that impaired ILC–stromal interactions contribute to the loss of immune tolerance and early inflammatory remodelling<sup>88</sup>. However, as CCR6<sup>+</sup> LTi-like ILC3s have not yet been selectively depleted, neither pharmacologically nor genetically, the extent to which this subset contributes to disease pathogenesis remains unresolved.

By contrast, NOX2-deficient *Ncf1* mice, which are highly sensitive to K/BxN-induced arthritis, exhibit a selective expansion of NCR<sup>+</sup> ILC3 subsets but not CCR6<sup>+</sup> ILC3s or other ILC subsets<sup>89</sup>. NCR<sup>+</sup> ILC3s produce elevated levels of IL-17A within affected joints, and treatment with an IL-1 receptor antagonist selectively reduces the number of NCR<sup>+</sup>

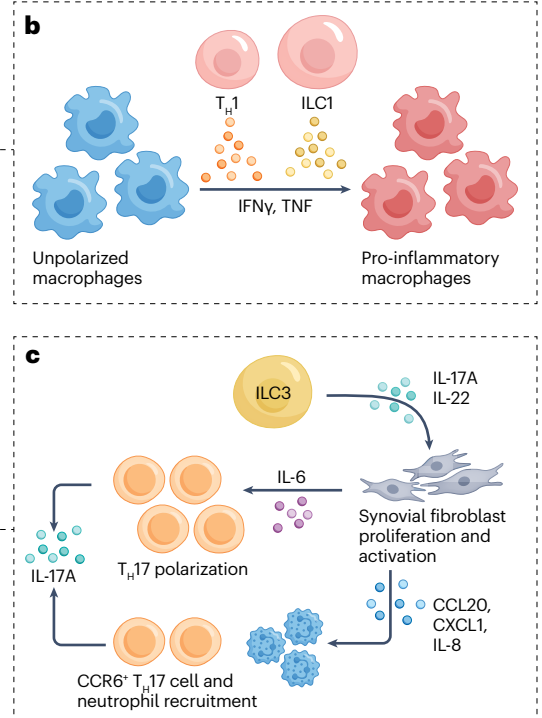
ILC3s, without affecting other ILC subsets, thereby decreasing joint swelling<sup>89</sup>. Human data add further complexity to these observations; some studies report reduced total ILC3 frequencies in the synovial fluid of patients with RA alongside increased ILC1s<sup>90</sup>, whereas others describe increased ILC3 frequencies in the lymph nodes and blood of patients with active RA, suggesting the potential migratory behaviour of these cells<sup>86,88</sup>. Notably, increased frequencies of NCR<sup>+</sup> ILC3s in the lymph nodes of mice with collagen-induced arthritis correlate positively with disease severity<sup>91</sup>. In the same study, NCR<sup>+</sup> ILC3s isolated from mice with collagen-induced arthritis, but not from naive mice, promoted the differentiation of IL-17A-producing CD4<sup>+</sup> T cells when co-cultured under T<sub>H</sub>17 polarizing conditions that included IL-6 and TGF-β<sup>91</sup>. However, the mechanisms by which ILC3s influence T<sub>H</sub>17 cell differentiation in vivo during arthritis and whether this phenomenon extends to other preclinical models of RA remain unknown.

Additional insight comes from a study showing that ILC3s migrate from the circulation to the central nervous system during experimental autoimmune encephalomyelitis<sup>92</sup>. These ILC3s display an inflammatory phenotype characterized by the expression of CCR6, T-bet, IFNγ and MHC class II and, unlike gut-resident ILC3s, express multiple co-stimulatory molecules, including CD80 and CD86, promoting T cell responses in the central nervous system<sup>92</sup>. Genetic deletion of

## Homeostatic joint environment



## Inflamed joint in rheumatoid arthritis



**Fig. 3 | Dual roles of innate lymphoid cells in the pathogenesis and resolution of rheumatoid arthritis. a**, In the healthy or resolving joint, group 2 innate lymphoid cells (ILC2s) help to maintain immune homeostasis by secreting IL-9 and IL-13, promoting regulatory T (T<sub>reg</sub>) cell induction and IL-10 production, limiting inflammation and supporting tissue repair. **b**, In the inflamed joint in rheumatoid arthritis (RA), group 1 innate lymphoid cells (ILC1s) and T helper 1 (T<sub>H</sub>1) cells produce IFNγ and TNF, amplifying type 1 inflammation and promoting myeloid cell activation and macrophage polarization. **c**, Group 3 innate lymphoid cells (ILC3s) exacerbate RA pathogenesis by producing IL-17A and

IL-22, which stimulate synovial fibroblast proliferation and activation. In turn, activated fibroblasts secrete IL-6 to promote T helper 17 (T<sub>H</sub>17) polarization and produce CCL20, CXCL1 and IL-8, recruiting CCR6<sup>+</sup> T<sub>H</sub>17 cells and neutrophils to the joint. Recruited neutrophils adopt a pro-inflammatory phenotype, amplifying joint damage. Reductions in lymphoid tissue inducer (LTi) cells during early RA might reflect disrupted lymphoid tissue organization and stromal remodelling. Overall, the contribution of ILCs to RA reflects a dynamic between pro-inflammatory and homeostatic signals, modulated by cytokine milieu, disease stage and therapeutic intervention.

MHC class II using *Rorc*-Cre mice resulted in reduced frequencies of IFN $\gamma$ <sup>+</sup>IL-17A<sup>+</sup> myelin-specific CD4 T cells in the central nervous system, suggesting a requirement for antigen-presenting ILC3s in sustaining pro-inflammatory T cell responses. However, these findings warrant cautious interpretation, as *Rorc*-Cre-mediated deletion of MHC class II also targets a ROR $\gamma$ t-expressing dendritic-cell population known as Thetis cells<sup>93–95</sup>. These cells have a critical role in the induction of peripheral regulatory T cells in response to dietary antigens and contribute to the establishment of immune tolerance to the gut microbiota<sup>93,96,97</sup>.

Together, these findings highlight functional heterogeneity within the ILC3 compartment in RA and autoimmune disease, suggesting that spatial localization, cytokine profiles and stromal interactions critically influence the contribution of ILC3s to disease progression.

## Innate lymphoid cell–fibroblast interactions

Much like ILCs, synovial fibroblasts have historically been overlooked in the development of targeted therapeutics. Perhaps the most definitive evidence of the role of these cells in disease comes from studies using the SCID mouse model<sup>98</sup>. In these experiments, synovial fibroblasts isolated from patients with established RA were transplanted within a cartilage matrix into immunodeficient SCID mice. Notably, the transplanted fibroblasts continued to invade and degrade the articular cartilage even in the absence of the original human inflammatory milieu<sup>98</sup>. These findings support the concept of epigenetic imprinting, whereby chronic exposure to an inflammatory microenvironment fundamentally establishes a stable, pathogenic fibroblast phenotype that persists independently of continuous external stimuli<sup>98</sup>.

Interestingly, activated fibroblast gene signatures have been detected in peripheral blood shortly before RA flares, highlighting the importance of fibroblast–immune interactions<sup>99</sup>. Both ILC2 and ILC3 subsets interact closely with fibroblasts during chronic inflammation. ILC2s are situated near fibroblasts in adventitial niches<sup>100</sup>, and IL-17A-producing ILC3s directly activate fibroblasts, inducing expression of pro-inflammatory mediators (such as IL-6 and serum amyloid A3 (SAA3)) that sustain pathogenic type 3 responses during chronic fibrosis<sup>68</sup>. Similarly, fibroblast-like synoviocytes isolated from the joints of SKG arthritic mice upregulate *Ccl20* and *Il6* upon exposure to IL-17A, supporting a role for ILC3–fibroblast crosstalk in driving RA pathogenesis<sup>66</sup>. Targeted deletion of pathogenic fibroblast subsets expressing fibroblast activation protein alpha (FAP $\alpha$ ), using the FAP-DTR model, substantially reduces arthritis duration in mice<sup>101</sup>.

Additional mechanistic insight comes from work in *Il23mc*-treated mice (mice treated with IL-23 minicircle DNA for sustained IL-23 overexpression) that also overexpress human TNF, where scRNA-seq analysis of synovial mesenchymal cells has demonstrated that IL-17A inhibition prompts the emergence of a specialized CD200<sup>+</sup> sublining fibroblast population<sup>102</sup>. Unlike the pathogenic CD200<sup>+</sup> IL-6-producing fibroblasts that drive joint destruction, these CD200<sup>+</sup> fibroblasts express *Dkk3* and *Cdh11*, are transcriptionally enriched for pathways that dampen inflammation and are notably increased during the resolution phase of serum-transfer arthritis. Both human and murine ILC2s express high levels of CD200R1, the cognate receptor for fibroblast-derived CD200 (ref. 102). This interaction serves as a critical survival signal whereby CD200<sup>+</sup> fibroblasts maintain the ILC2 phenotype by sustaining high expression levels of CD127 and ST2 while limiting ILC2 apoptosis, thereby establishing a pro-resolving network necessary for restoring tissue homeostasis<sup>102</sup>.

This fibroblast–ILC2 axis provides a compelling mechanistic explanation for the reported discrepancies in ILC2-mediated protection. For example, the inability of adoptively transferred ILC2s to confer protection during the peak of K/BxN serum-induced arthritis probably reflects the absence of pro-resolving CD200<sup>+</sup> fibroblasts at this inflammatory stage and highlights the importance of the activation state within the resident fibroblast compartment<sup>67</sup>. In the hyper-inflammatory environment during peak disease activity, the sublining *Il6*<sup>+</sup> pathogenic fibroblast population might fail to support, or perhaps might even actively suppress, the survival and tissue residency of pro-resolving ILC2s. Consequently, the therapeutic efficacy of ILC2s seems to be temporally constrained by the activation state of resident fibroblasts; thus, an imbalance between ILC subsets and fibroblast-driven inflammatory loops could constitute a fundamental pathogenic mechanism in RA.

RA disease flares are characterized by enhanced neutrophil and inflammatory monocyte responses<sup>99</sup>. IL-17A produced by ILC3s and T<sub>H</sub>17 cells has been shown to directly influence haematopoietic stem and progenitor cells, skewing haematopoiesis towards increased myeloid-cell generation, leading to more neutrophils and inflammatory monocytes during pathological peripheral type 3 responses<sup>17</sup>. Therefore, elevated neutrophils and monocytes during RA flares could reflect amplified IL-17A-driven myelopoiesis in the bone marrow, implicating ILC3-driven responses as critical factors in RA pathogenesis.

## Perinatal origins and pathogenic role of group 1 innate lymphoid cells

Initially identified in the liver as an atypical subset of NK cells, ILC1s provide type 1 immunity against tumours, intracellular microbes and viruses<sup>103,104</sup>. In mice, ILC1s characteristically express NK1.1 and NKp46 but lack the majority of Ly49 inhibitory receptors that recognize MHC class I; instead, these cells sense non-classical MHC class I molecules via NKG2 receptors<sup>105</sup>. ILC1s are activated by cytokines such as IL-7, IL-15 and IL-12, which regulate not only their survival but also their effector functions. Upon activation, ILC1s secrete high levels of IFN $\gamma$  and TNF, thereby amplifying the inflammatory response<sup>105</sup>. A study analysing nephritic mice demonstrated that tissue-resident NKp46<sup>+</sup> ILC1s, rather than NK cells, were the dominant cellular producers of GM-CSF, a functional capacity abolished in *Ncr1*-deficient mice<sup>106</sup>. Notably, GM-CSF blockade in this model reduced epithelial cell injury, and NKp46<sup>+</sup> ILC1s were required for autoimmune organ damage<sup>106</sup>.

In the collagen-induced arthritis model, ILC1 frequencies in the spleen are notably increased 5 weeks after immunization compared with non-arthritic controls, whereas NK cell and total ILC3 frequencies remain unchanged<sup>107</sup>. The mechanistic relevance of this finding remains unclear, especially as accumulating evidence highlights the distinct functional diversity among ILC1s across tissues. Fate-mapping using *Id2*-CreERT2 X R26-YFP mice has shown that uterine ILC1s undergo rapid turnover, whereas liver and splenic ILC1s have markedly slower turnover rates<sup>108</sup>. Furthermore, scRNA-seq in the same study showed that ILC1s emerge during embryogenesis and expand perinatally, whereas NK cells originate and mature much later, from the post-natal period into adulthood<sup>108</sup>. This developmental timeline aligns with our hypothesis that both juvenile and adult-onset RA might be primed much earlier in life than previously recognized, raising the possibility that perinatally derived ILC1s constitute an underappreciated contributor to pathogenesis. Within the inflamed RA joint, IFN $\gamma$  and TNF produced by ILC1s could amplify type 1 inflammatory pathways and favour classical (M1-like) macrophage polarization, a mechanism closely associated with RA synovitis<sup>107,109</sup> (Fig. 3b). Such a role could

involve the transcription factor Hobit, a regulator of tissue-residency programmes in lymphocytes, including the perinatal emergence of cytotoxic ILCs<sup>110,111</sup>.

Future research utilizing temporally controlled deletion strategies will be necessary to define the specific window during which ILCs influence RA pathogenesis. For example, in a liver metastasis model using *Ncr1*-Cre XR26-DTR mice, early depletion of ILCs increased the metastatic load, whereas deletion in later stages was less effective<sup>112</sup>. Therefore, the temporal regulation of ILCs in RA warrants rigorous investigation, as the contribution of these cells might be stage-specific and crucial for the early phase of disease initiation.

## Therapeutic and diagnostic implications of innate lymphoid cells

As important early responders within the inflamed synovium, ILCs are increasingly recognized for their potential translational relevance in RA. Dynamic regulation by cytokines and stromal cues, together with the capacity to both mirror and influence inflammatory trajectories, positions distinct ILC subsets as promising biomarkers of disease activity, targets for immunomodulatory intervention and candidates for emerging cellular therapies.

### Innate lymphoid cells as biomarkers for disease activity and immune dynamics

Accumulating evidence indicates that ILCs can serve as tissue-resident and circulating biomarkers, with shifts in ILC abundance and activation state mirroring RA disease activity, cytokine gradients and stromal remodelling. Disease-specific expansion of CCR6<sup>+</sup> ILC3s has been reported in both the peripheral blood and synovial fluid<sup>85</sup>. In a translational study integrating analysis of patient samples with experimental validation, circulating ILC3 frequencies correlated positively with the abundance of T<sub>H</sub>1 and T<sub>H</sub>17 cell subsets in the peripheral blood, as well as with clinical disease activity scores<sup>91</sup>, supporting the role of ILC3s as amplifiers or reflectors of local inflammation. Complementary findings from lymph node biopsies in early RA have revealed a redistribution of ILC subsets, characterized by marked reductions in LT<sub>i</sub> cells and increases in ILC1 and ILC3 populations relative to both at-risk individuals and healthy individuals<sup>88</sup>. Again, these shifts were often paralleled by elevated expression of VCAM-1 and ICAM-1 in the lymph-node endothelium, suggesting a potential bidirectional interaction between ILCs and stromal scaffolding during disease initiation.

Within the synovial microenvironment, CCR6<sup>+</sup> ILC3s are selectively enriched in RA compared with osteoarthritis<sup>85</sup>. The abundance of this population correlates closely with CCL20 concentrations, a chemokine critical for T<sub>H</sub>17 cell recruitment, indicating a shared chemotactic axis<sup>85</sup>. This axis supports the concept that CCR6<sup>+</sup> ILC3s not only reflect T<sub>H</sub>17 pathway activation, but might also reinforce this axis through the production of IL-17 and IL-22 (ref. 85). These findings support the hypothesis that CCR6<sup>+</sup> ILC3s not only reflect activation of the T<sub>H</sub>17 axis but could also actively contribute to this axis via IL-17 and IL-22 secretion.

Conversely, ILC2s seem to exhibit an anti-inflammatory profile. In comparative analyses of patients with active RA versus patients with stable disease, those with stable disease displayed higher peripheral ILC2 frequencies; by contrast, ILC1 levels correlated positively with disease activity<sup>107</sup>. Notably, ILC2 proportions also correlated inversely with Disease Activity Score in 28 joints (DAS28), consistent with an association between ILC2 abundance and disease quiescence. ILC2-derived IL-13, which is present in synovial fluid and tissue from patients with

arthritis, further supports this regulatory phenotype, as ex vivo and in vitro studies show that IL-13 suppresses pro-inflammatory cytokine production and modulates synovial immune activation<sup>113,114</sup>.

Comparative studies in psoriatic arthritis and ankylosing spondylitis further underscore the utility of ILC profiling for disease stratification. IL-17A-producing NKp44<sup>+</sup>CCR6<sup>+</sup> ILCs, largely absent in RA, are abundant in psoriatic arthritis synovial fluid and show an inverse correlation with clinical disease activity<sup>90</sup>. In ankylosing spondylitis, IL-17A-producing and IL-22-producing ILC3s are expanded in the gut, synovial tissue and bone marrow. This expansion seems to be driven in part by synovial myeloid cells expressing CX3CR1 and IL-23 (refs. 115,116).

Together, these studies provide a compelling rationale for incorporating ILC subset profiling into biomarker discovery frameworks, offering a dynamic readout of immunological perturbations that could enable longitudinal monitoring of disease progression and prediction of therapeutic outcomes. Unlike conventional serological markers such as rheumatoid factor or anti-citrullinated protein antibodies, ILCs provide temporal and spatial resolution of immune activity, reside in both tissue and circulatory niches and could reflect dynamic shifts in inflammatory networks. The integration of ILC profiling into the RA biomarker landscape is becoming increasingly feasible owing to advances in high-resolution immunophenotyping and proteomic technologies. Techniques such as spectral flow cytometry and antibody-dependent proximity-ligation proteomics enable multiplexed, deep immunophenotyping of ILC subsets and their effector cytokines and chemokines (for example, IL-13, IL-22 and GM-CSF). These approaches could be leveraged in future studies to comprehensively profile ILCs in both peripheral blood and synovial fluid, facilitating integration into RA biomarker frameworks<sup>117,118</sup>.

Single-cell multi-omics provide additional opportunities to interrogate ILC heterogeneity and functional plasticity. Spatial transcriptomics platforms (for example, Visium and Stereo-seq) have already been applied to map ILCs in various healthy and diseased tissues<sup>119–123</sup> and could be used to localize cytokine-producing ILCs within inflamed synovial niches and define context-dependent interactions with stromal and immune cells. In parallel, AI-based tools such as CellPhenoX support the identification of disease-relevant immune phenotypes across multimodal datasets, enabling predictive modelling of ILC-driven inflammation<sup>124</sup>. Collectively, these advances provide a multidimensional framework for tracking ILC dynamics that might enhance biomarker development in RA<sup>125</sup> (Box 2).

Nonetheless, translating ILC profiling into clinically actionable biomarkers will require further standardization of phenotyping protocols across platforms, as well as integration with longitudinal clinical and multi-omics datasets to validate utility across disease stages, clinical variables and treatment contexts. Alterations in circulating ILC subsets might not fully capture the frequency, phenotype or functional state of ILCs within synovial tissue. Given the compartmentalized nature of ILC responses, peripheral blood analyses should therefore be interpreted cautiously and ideally complemented by synovial profiling to delineate tissue-resident dynamics from systemic immune changes.

### Immunomodulatory targeting of innate lymphoid cells in rheumatoid arthritis

ILCs have emerged not only as biomarkers but also as promising therapeutic targets in RA. Rapid responsiveness to local cues, marked functional plasticity and tissue-specific distribution position these populations

## Box 2 | Therapeutic and diagnostic implications of innate lymphoid cells in rheumatoid arthritis

### Innate lymphoid cells as biomarkers of disease activity and immune state

- Quantification of innate lymphoid cell (ILC) subsets in peripheral blood and synovial fluid
- Identification of disease-associated profiles (for example, ILC3 enrichment or ILC2 depletion)
- Correlation with clinical indices (such as Disease Activity Score in 28 joints (DAS28), C-reactive protein concentration and erythrocyte sedimentation rate)
- Integration with multi-omics approaches (for example, single-cell RNA sequencing and proteomics) to delineate ILC-driven inflammatory pathways

### Immune stratification and patient segmentation

- Definition of ILC-based endotypes (for example, ILC3 and T<sub>H</sub>17-dominant versus ILC2-associated profiles)
- Identification of predictive biomarkers of therapeutic response (for example, changes in PD1<sup>+</sup> ILC3 cells during JAK inhibitor therapy)
- Integration with cytokine profiles (for example, IL-18 and IL-23) to distinguish JAK-dependent from JAK-independent inflammation

### Therapeutic modulation of innate lymphoid cells

- Conventional synthetic DMARDs and biologic DMARDs:
  - Methotrexate

- TNF inhibitors\*
- GM-CSF inhibitors
- Targeted synthetic DMARDs
  - JAK inhibitors (such as tofacitinib and baricitinib)
  - PI3K $\delta$  inhibitors (for example, seletalisib)
- Cytokine and metabolic modulation
  - Recombinant cytokines or cytokine blockade
  - Microbial metabolites (such as isoLCA that modulate ROR $\gamma$ <sup>+</sup> ILC3s)

### Emerging innate lymphoid cell-directed therapeutic strategies

- Selective targeting of pathogenic ILC subsets (for example, the ILC3-T<sub>H</sub>17 axis)
- Enhancement of regulatory ILC2 functions (for example, IL-13-mediated anti-inflammatory activity)
- Combination approaches that integrate ILC modulation with existing DMARDs

### Experimental innate lymphoid cell-based cellular therapies

- Generation of ILC2-like cells from induced pluripotent stem cells
- Expansion of peripheral blood mononuclear cell-derived ILC2 populations

\*As part of a combination therapy with conventional DMARDs.

as ideal candidates for immunomodulatory interventions aimed at restoring balance within chronically disrupted immune networks.

Efforts to therapeutically modulate the ILC landscape have focused on promoting regulatory subsets while dampening inflammatory populations. Administration of IL-33 expands IL-10-producing ILC2 populations and has demonstrated protective effects in multiple inflammatory disease models<sup>126,127</sup>. Complementary approaches leverage microbiota-derived metabolites such as short-chain fatty acids, which restrain ILC2 effector functions and pathological type 2 immune skewing, or secondary bile acid metabolites such as isoLCA, an inverse agonist of ROR $\gamma$  that inhibits ROR $\gamma$ <sup>+</sup> ILC3s and thereby limits IL-17A-driven inflammation during pathological peripheral type 3 responses<sup>15–17,68</sup>. Collectively, these examples illustrate the therapeutic potential of targeting upstream signals to reprogramme ILC activity.

Another promising strategy involves disrupting pro-inflammatory effector functions, such as GM-CSF secretion by ILC2s. This cytokine promotes the differentiation of inflammatory monocytes into dendritic cells, exacerbating synovial inflammation. The IL-33–ILC2–GM-CSF axis is a critical driver of this process<sup>45,66</sup>. Therapeutic agents that target IL-33 or GM-CSF signalling, including otilimab and mavrilimumab, are currently under clinical investigation and could offer a route to dampen ILC-driven inflammation in RA. Overall, these approaches highlight a growing therapeutic toolbox capable of rebalancing ILC subsets, promoting regulatory ILC2 responses while attenuating pathogenic ILC1 and ILC3 populations (Box 2).

Existing DMARDs can also modulate ILC activity. For example, clinical data indicate that the JAK inhibitor baricitinib reduces circulating

PD1<sup>+</sup> ILC3 frequencies, and these reductions are accompanied by improvements in inflammatory markers, including C-reactive protein, erythrocyte sedimentation rate, swollen joint count and DAS28 (ref. 128). Notably, shifts in ILC3 subsets, characterized by decreased PD1<sup>+</sup> ILC3s and increased CTLA-4<sup>+</sup> ILC3s, correlate with clinical response, suggesting that these populations reflect JAK-dependent inflammatory activity rather than simply serving as baseline predictors of therapeutic responsiveness.

Similarly, patients with RA receiving the JAK inhibitor tofacitinib exhibited marked reductions in circulating ILC1 frequencies and IFN $\gamma$  production after 3 months, whereas anti-TNF therapy did not yield similar changes<sup>129</sup>. Mechanistically, JAK–STAT signalling is known to regulate ILC development and function, providing a rationale for why JAK inhibition might impact ILC networks<sup>130</sup>. Other small molecule inhibitors such as the selective PI3K $\delta$  inhibitor seletalisib suppress IL-17A and IL-17F production by innate-like lymphocytes, including ILC3s, suggesting that drugs designed to modulate adaptive immunity can also influence innate lymphoid circuits<sup>128</sup>.

Together, these data suggest that DMARDs not only suppress adaptive inflammation but could also modulate ILC-driven circuits, thereby offering an opportunity to combine ILC-directed therapies with standard treatments to enhance efficacy and restore balance in RA immune networks.

ILC profiles also hold the potential to guide treatment decisions in RA, particularly in the context of therapeutic resistance. For instance, baseline ILC1, ILC2 and ILC3 numbers have been shown to correlate with ultrasound-detected synovitis and predict methotrexate

responsiveness in a cohort of patients with RA or spondyloarthritis<sup>131</sup>. In patients undergoing JAK inhibitor therapy, a subset of patients with persistently elevated systemic IL-18 exhibited reduced responsiveness to JAK inhibition, consistent with IL-18-driven inflammation operating through JAK-independent pathways<sup>119</sup>. Together, these findings highlight the potential for immune stratification based on ILC and cytokine profiles to refine therapeutic decision-making. Although the contribution of ILC2 modulation to RA pathogenesis remains uncertain, aligning therapeutic strategies with underlying immune phenotypes, including ILC signatures, offers a route towards more effective, individualized treatment regimens<sup>132</sup> (Box 2).

Together, these findings underscore the therapeutic relevance of ILCs in RA and support a multidimensional strategy that includes immune profiling, cytokine modulation, metabolite intervention and targeted pharmacological inhibition. Strategically targeting ILC subsets might not only mitigate inflammation but also help to restore immune homeostasis, paving the way for more precise and durable treatment outcomes.

## Emerging innate lymphoid cell-based cellular therapies for rheumatoid arthritis

At the forefront of immunotherapy innovation are cellular strategies that harness the regulatory potential of ILCs, particularly ILC2s. Among the most promising are autologous ILC2-based approaches, in which IL-10-producing ILC2s are expanded ex vivo from peripheral blood mononuclear cells and reinfused to restore immune homeostasis. Although these strategies have not yet been tested in RA, related preclinical studies provide compelling proof of concept. In a mouse model of islet transplantation, IL-10-producing human ILC2s improved graft function and prevented allograft rejection<sup>133</sup>. In a separate mouse model of xenogeneic graft-versus-host disease, the same cell type limited disease by suppressing pathogenic human T cell responses in vivo<sup>134</sup>. Despite differences between islet transplantation and graft-versus-host disease, the shared mechanism of action highlights the broad immunoregulatory potential of IL-10-competent ILC2s. Given the parallels in effector T cell dysregulation and tissue-specific inflammation in RA, these findings support the feasibility of adapting ILC2-based cellular therapy to suppress synovial immune activation and promote tissue repair in autoimmune arthritis (Box 2).

These ILC-based strategies conceptually parallel advances in chimeric antigen receptor (CAR)-T<sub>reg</sub> cell therapies, in which regulatory T cells are engineered to recognize synovial autoantigens and suppress local inflammation. For example, preclinical studies of CAR-T<sub>reg</sub> cells directed against antigens such as citrullinated vimentin and type II collagen have shown that these cells can dampen T<sub>H</sub>17 responses and joint damage in mouse models of arthritis<sup>135,136</sup>. However, regulatory T cells in RA can exhibit context-dependent plasticity, acquiring T<sub>H</sub>17-like features and losing suppressive function within the synovial milieu under the influence of IL-6 and IL-23, which might limit their therapeutic stability in chronic inflammation<sup>137</sup>. By contrast, the innate characteristics of ILCs, such as their rapid effector function, TCR-independent activity and lower risk of inflammatory reprogramming, might provide a more stable platform than CAR-T<sub>reg</sub> cell approaches for achieving tissue-localized immune regulation in autoimmune arthritis.

Advancing this concept, induced pluripotent stem cell (iPSC)-derived ILC-like cells engineered with CARs could, in principle, be adapted to target citrullinated vimentin, a post-translational neoantigen enriched in the synovial extracellular matrix of patients with RA<sup>138</sup>. Foundational studies have shown that iPSCs can be differentiated into

ILC-like cells and further modified to express CARs, establishing a platform capable of generating scalable, antigen-specific regulatory ILC populations<sup>139</sup>. In an RA setting, such CAR-ILC<sub>reg</sub> cells could be directed to sites of joint inflammation, where these cells would be expected to release suppressive cytokines (such as IL-10 and IL-13) and promote local immune regulation in an antigen-restricted, tissue-resident manner.

Although CAR-ILC therapies remain untested in RA or other autoimmune conditions, the concept represents a promising translational avenue. Future work should prioritize rigorous preclinical assessment in relevant inflammatory models to evaluate safety, phenotypic stability and therapeutic potential.

## Conclusions

ILCs have emerged as context-dependent regulators in RA pathogenesis, capable of both sustaining and resolving inflammation. Pathogenic roles are primarily attributed to ILC1s and ILC3s, which produce pro-inflammatory cytokines such as IFN $\gamma$  and IL-17, thereby exacerbating synovial inflammation. By contrast, ILC2s, particularly those producing IL-10 or IL-13, are increasingly implicated in tissue protection and restoration of immune homeostasis.

Emerging evidence suggests that modulating the balance of ILC subsets could offer therapeutic benefit in RA by tipping immune responses towards tolerance and resolution of inflammation. ILCs could also serve as valuable biomarkers in peripheral blood or synovial fluid, contributing to disease stratification and the monitoring of therapeutic responses. Advances in multi-omics technologies, such as single-cell RNA sequencing and proteomics, are beginning to elucidate subset-specific roles and uncover novel therapeutic targets. Innovative strategies, including the expansion of autologous IL-10-producing ILC2s, the development of iPSC-derived ILCs and the engineering of CAR-expressing ILCs directed against synovial autoantigens, hold considerable promise for next-generation cell therapies. Combining ILC-directed interventions with established DMARDs, such as methotrexate or JAK inhibitors, might further enhance therapeutic efficacy while mitigating systemic toxicity. The incorporation of ILC-targeted strategies into personalized medicine paradigms has the potential to reshape RA treatment; however, successful clinical translation will require a deeper mechanistic insight and rigorous validation in human trials.

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## Author contributions

All authors contributed substantially to discussion of the content and viewed and/or edited the manuscript before submission. K.M.M., I.-C.K. and A.K.K. wrote the article.

## Competing interests

The authors declare no competing interests.

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