ILC3s as central regulators of mucosal homeostasis and disease pathogenesis (Review)

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2Abstract. Type 3 innate lymphoid cells (ILC3s) constitute key components of mucosal innate immunity and serve key roles in maintaining mucosal barrier homeostasis and regulating inflammatory responses. The present review summarizes the biological characteristics and regulatory mechanisms of ILC3s, while discussing their interactions with the gut microbiota and pathological functions in mucosa-associated disorders. Derived from bone marrow-resident common lymphoid progenitors, ILC3s differentiate under the transcriptional control of retinoid-related orphan receptor γ-t into distinct functional subsets, including natural cytotoxicity receptor (NCR)$^+$ ILC3s, NCR$^-$ ILC3s and lymphoid tissue inducer cells. ILC3s maintain epithelial barrier integrity, enhance antimicrobial defense and support lymphoid tissue development through the production of effector molecules such as IL-22, IL-17 and granulocyte-macrophage colony-stimulating factor. These subsets can undergo phenotypic conversion in response to microenvironmental signals. ILC3 activity is tightly regulated by transcription factors, metabolic pathways, neuroimmune interactions and the circadian clock system. In addition, ILC3s establish bidirectional interactions with the gut microbiota: Microbial metabolites regulate ILC3 activity, whereas ILC3s influence microbial composition through IL-22-dependent antimicrobial peptide production and IgA responses. Depending on subset composition, local cytokine networks and tissue microenvironment, ILC3s may exert either pathogenic or protective effects in a number of diseases. Future investigations should aim to further elucidate the molecular mechanisms underlying ILC3 subset plasticity, tissue-specific interaction networks and clinically translatable strategies for targeted intervention. Building upon these findings, the present review proposes a spatiotemporal-quantitative framework and three regulatory axes that may account for disease-specific variations in ILC3 responses, providing a basis for understanding distinct ILC3 functions and developing targeted therapeutic strategies. Systematic investigation of the regulatory principles governing ILC3 biology will not only deepen the understanding of innate immune homeostasis but also provide potential targets and strategies for precision immunotherapy in diseases such as inflammatory bowel disease and colorectal cancer.

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Contents

1. Introduction

Innate lymphoid cells (ILCs) represent a subset of innate immune cells derived from common lymphoid progenitors

(CLPs) in the bone marrow. Morphologically, they resemble adaptive lymphocytes; however, they lack specific antigen recognition receptors generated through antigen receptor gene rearrangement. Their surfaces are generally enriched in the IL-7 receptor α-chain (CD127/IL-7Rα), identifying them as key mediators of innate immune responses in mucosal tissues (1).

Based on transcription factor expression and cytokine profiles, ILCs are classified into three groups. Type 1 ILCs (ILC1s) are regulated by T-box expressed in T cells (T-bet). Upon stimulation with IL-12, IL-15 and IL-18, they secrete T helper (Th)-1-like cytokines, including IFN-γ (2). Through IFN-γ production, ILC1s mediate type 1 immune responses and contribute to host defense against viral and intracellular bacterial infections at the initial site of invasion (3). Type 2 ILCs (ILC2s) function as early effectors of type 2 immune responses. They are primarily regulated by retinoid-related orphan receptor (ROR)-α and GATA binding protein 3 (GATA3) and activated by IL-25 and thymic stromal lymphopoietin. ILC2s produce Th2-like cytokines, including IL-5 and IL-13, as well as amphiregulin, a member of the EGF family. They participate in defense against helminth infection and tissue repair. ILC2s are widely distributed in tissues including the fetal intestine, skin, adipose tissue, lungs and intestinal submucosa (4-6). Type 3 ILCs (ILC3s) are characterized by RORγt expression and share phenotypic similarities with Th17 cells. Based on surface marker expression, ILC3s are classified into natural killer (NK)-p46$^+$ ILC3s and NKp46$^-$ ILC3s. They produce effector cytokines, including IL-22, IL-17, granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-γ and TNF-α, as well as the growth factor heparin-binding EGF-like growth factor (HB-EGF) (7,8). ILC3s express RORγt, CD44 and C-C motif chemokine receptor (CCR)-6 and produce IL-17 rather than IL-13, distinguishing them from ILC2s (9). Their activation is primarily driven by IL-1β and IL-23 produced by myeloid cells, which enhance effector molecule production (10). ILC3s are enriched in the intestinal mucosa, skin, lung and mesenteric lymph nodes. Within the intestine, ILC3s sense microbial signals and participate in tissue homeostasis. On the one hand, they secrete IL-22 to preserve the integrity of the intestinal epithelial barrier; on the other hand, intestinal MHC-II-expressing ILC3s restrict CD4$^+$ T-cell responses against commensal bacteria via MHC-II molecules (11).

Recently, Wang *et al* (12) identified a novel ILC subset termed regulatory ILCs (ILCregs). A population of IL-10-producing innate cells predominantly localized in the gut expresses a number of ILC markers, including CD25, IL-2R, stem cell antigen-1 and CD90. Unlike CD4$^+$ regulatory T cells (Tregs), these cells do not express CD4 or FoxP3, the latter being the defining marker of Tregs. ILCregs originate from common helper ILC progenitors (CHILPs) rather than ILC precursors (ILCPs). They exhibit high expression levels of inhibitor of DNA binding 3 (Id3) and Sox4 but lack numerous ILC-associated transcription factors, including nuclear factor, IL-3 regulated (NFIL3), ROR, GATA3 and aryl hydrocarbon receptor (AHR). Through IL-10 and TGF-β production, ILCregs alleviate intestinal inflammation (12,13) (Fig. 1). Functionally, ILCregs specifically suppress excessive activation of ILC1s and ILC3s through IL-10 secretion, thereby reducing the production of proinflammatory cytokines IFN-γ and IL-17A and limiting innate immune-mediated inflammatory damage in the gut. This regulatory pathway operates independently of Tregs and suppresses pathogenic ILC3 activation while preserving IL-22-mediated epithelial barrier protection, representing a negative feedback mechanism for maintaining mucosal homeostasis (12). Furthermore, Wang *et al* (14), demonstrated, through single-cell transcriptomic analysis, that TGF-β signaling within the colorectal cancer microenvironment can induce transdifferentiation of ILC3s into ILCregs. Following differentiation, ILCregs secrete a large amount of IL-10, establishing an immunosuppressive microenvironment that promotes tumor immune evasion and disease progression. This ILC3-to-ILCreg transdifferentiation mechanism represents a potential target for precision tumor immunotherapy.

Overall, as important regulators of mucosal immunity, ILC3s have attracted increasing attention due to their diverse subsets (3,11), regulatory networks (11,15,16) and interactions with the microbiota, influencing both tissue homeostasis and disease development (3,11,15,16). However, the mechanisms by which these regulatory signals integrate to determine disease-specific ILC3 responses remain incompletely understood. Therefore, the present review summarizes the developmental characteristics, regulatory mechanisms, microbiota interactions and disease-associated functions of ILC3s, with a particular emphasis on the molecular mechanisms underlying their functional outcomes across tissues and disease stages.

2. Biological characteristics and functional subsets of ILC3s

ILC3s are characterized by hierarchical lineage differentiation and functional heterogeneity among subsets. Their development is regulated by transcription factors, cytokines and tissue-derived signals. Through functional specialization, distinct ILC3 subsets contribute to mucosal immune homeostasis and host defense (Fig. 1).

Development and differentiation pathways and key regulatory nodes of ILC3. ILC3 development is an ordered process governed by hierarchical transcriptional regulation, cytokine signaling and the tissue microenvironment. Compared with other ILC subsets, ILC3s exhibit distinct lineage bifurcation during development. From a hematopoietic perspective, CLPs, under the regulation of NFIL3 and inhibitor of DNA binding 2 (ID2), first diverge from the adaptive lymphocyte lineage and differentiate into CHILPs. CHILPs express high levels of ID2 and IL-7R and are restricted to differentiation into ILC1, ILC2 and ILC3 subsets, having lost the potential to generate T cells, B cells or NK cells (17). Following the CHILP stage, further differentiation generates ILCPs, which express the transcription factor promyelocytic leukemia zinc finger (PLZF) and the surface molecule programmed cell death protein 1. ILCPs give rise to ILC1, ILC2 and NCR$^+$ ILC3 subsets, but cannot generate lymphoid-tissue-inducer (LTi)-like ILC3s (17,18). LTi-like ILC3s are derived from a distinct LTi progenitor (LTiP). LTiP and ILCP represent two separate branches that diverge from a common early

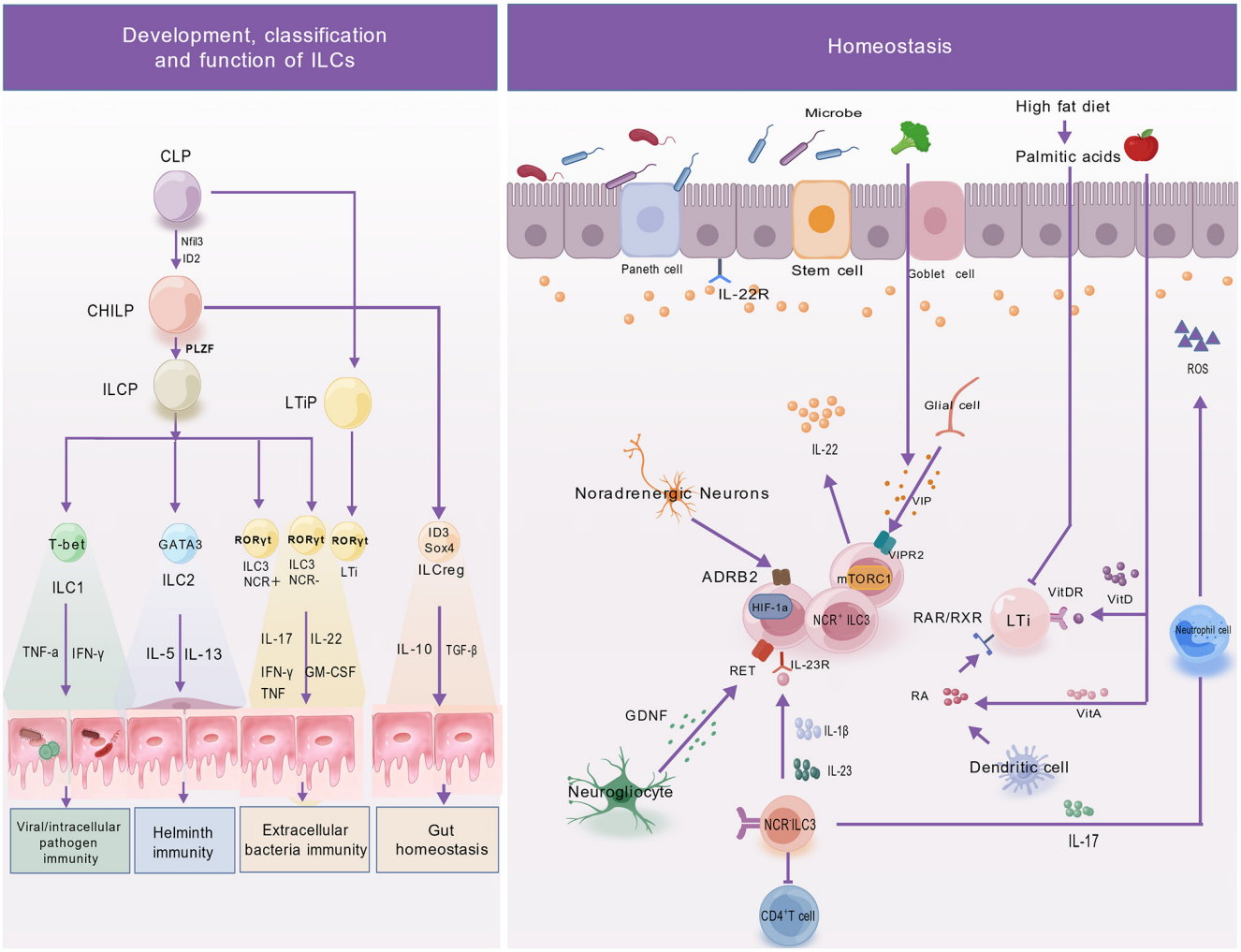

Figure 1. Schematic overview of ILC3 development, differentiation and homeostatic regulation. Left panel (development, classification and function of ILCs): ILCs originate from bone marrow-resident CLPs, which differentiate into CHILPs under the control of NFIL3 and ID2. CHILPs further give rise to ILC1, ILC2, ILC3 and ILCreg subsets through either the LTiP pathway or the ILCP route. ILC3s are further subdivided into NCR$^+$ and NCR$^-$ subsets, with RORγt serving as the master lineage-defining transcription factor. Right panel (homeostatic regulation): Functions of NCR$^+$ ILC3s and LTi cells are coordinately regulated by metabolic, neuro-immune and immune cytokine signals. At the metabolic level, RA acts through RAR/RXR and VitD through VitDR, to regulate LTi cells, while palmitic acid derived from a high-fat diet participates in ILC3 homeostasis. At the neuro-immune level, three pathways, GDNF-RET, VIP-VIPR2 and sympathetic ADRB2, cooperatively regulate IL-22 secretion by ILC3s. In addition, dendritic cell-derived IL-23 and IL-1β activate ILC3s through IL-23R, thereby maintaining intestinal epithelial homeostasis. ILC, innate lymphoid cell; CLP, common lymphoid progenitor; CHILP, common helper-like ILC progenitor; ILCreg, regulatory ILC; LTi, lymphoid tissue inducer; LTiP, LTi progenitor; ILCP, ILC precursor; ROS, reactive oxygen species; RA, retinoic acid; RAR, RA receptor; RXR, retinoid X receptor; VitA, vitamin A; VitD, vitamin D; VIPR2, VIP receptor 2; VitDR, VitD receptor; NFIL3, nuclear factor, IL-3 regulated; ID, inhibitor of DNA binding; PLZF, promyelocytic leukemia zinc finger; T-bet, T-box expressed in T cells; GATA3, GATA binding protein 3; NCR, natural cytotoxicity receptor; RORγt, retinoid-related orphan receptor γ-t; GM-CSF, granulocyte-macrophage colony-stimulating factor; GDNF, glial cell-derived neurotrophic factor; VIP, vasoactive intestinal peptide; HIF-1α, hypoxia-inducible factor 1-α; RET, receptor tyrosine kinase; ADRB2, β_2-adrenergic receptor.

progenitor before PLZF expression is initiated (17,18). This progressive commitment to the ILC lineage is also regulated by a number of transcription factors, including GATA3, thymocyte selection-associated high mobility group box (TOX), T cell factor-1 and NFIL3, although their contributions vary among developmental stages (19-23). Subsequent studies have demonstrated that LTi-like ILC3s originate from a distinct progenitor population downstream of CHILPs with the phenotype ID2$^+$α4β7$^+$-C-X-C chemokine receptor type (CXCR)-5$^+$. This progenitor population is separated from the ILCP lineage before PLZF acquisition, thereby establishing a developmental pathway distinct from that of other ILC subsets (18,24-27). Accordingly, LTi-like ILC3s develop through a pathway different from other ILC family members, including NCR$^+$ ILC3s. This developmental divergence likely contributes to the transcriptional and functional differences among ILC3 subsets reported in previous studies (28-30), including distinct cytokine-production profiles, divergent surface-marker signatures and variable ILC3-to-ILC1 plasticity. Accumulating evidence has further indicated that RORγt (encoded by RORC) directs ILC3 differentiation from ILCPs (31).

Subclassification and functional heterogeneity of ILC3s

Differentiation of NCR$^+$ ILC3s and NCR$^-$ ILC3s. In both mice and humans, ILC3s can be broadly divided into two major subsets, NCR$^+$ and NCR$^-$, based on the expression of NCRs, including NKp46 and NKp44 (32). Human NCR$^+$ ILC3s are characterized by high NKp44 expression and low NKp46

expression, account for ~70% of intestinal ILCs and predominantly secrete IL-22. By contrast, NCR$^-$ ILC3s comprise ~15% of intestinal ILCs and primarily produce IL-17 (33,34). In mice, it has been shown that NCR$^+$ ILC3s are defined by NKp46 expression, whereas NCR$^-$ ILC3s lack CD117 expression. This represents a species-specific difference given that human NCR$^-$ ILC3s express CD117 (35). NCR$^-$ ILC3s can be generated *in vitro* following IL-1β and IL-23 stimulation through Notch2-dependent signaling and T-bet upregulation (7,36-40). IL-17, produced by NCR$^-$ ILC3s, stimulates epithelial and endothelial cells to release chemokines such as CXCL8 (41), thereby promoting neutrophil recruitment and supporting epithelial barrier function through production of reactive oxygen species (ROS) and α-defensin (3,42). Following acute intestinal injury, IL-17 can regulate tight junction proteins in an IL-23-independent manner and cooperate with early protective IL-17 derived from γδ T cells to maintain intestinal mucosal integrity. However, in chronic inflammatory settings, such as recurrent DSS-induced colitis or established IBD, ILC3-derived IL-17 primarily contributes to disease progression (42,43).

Functional characteristics of LTi/LTi-like cells. LTi cells were the first identified subset within the ILC3 family and are characterized by their distinct developmental origin and functional properties (25,44). During embryogenesis, LTi cells arise from the fetal liver and promote the formation of secondary lymphoid tissues, including lymph nodes and Peyer's patches, through responses to TNF-α and lymphotoxin-β signaling. This process establishes the structural foundation for subsequent adaptive immune responses, including T-cell activation, B-cell homing to follicles and antibody production (44-48). After birth, LTi cells continue to develop from bone marrow progenitor cells. Despite their capacity to induce lymphoid tissue formation in adulthood remaining incompletely defined, they contribute to gastrointestinal pathogen defense through IL-17A and IL-22 production and participate in the formation of cryptopatches and isolated lymphoid follicles (15,45,46,49).

With regard to surface markers, murine LTi cells express CD117 (c-kit), CD45, CCR6, CD4 and CD127, whereas human LTi cells share lineage homology with murine LTi cells but lack CD4 expression. LTi cells can be distinguished from other ILC3 subsets by the expression of the chemokine receptor CCR6 (15,49,50). CCR6$^+$ LTi cells represent the predominant ILC3 population in lymphoid organs and can internalize antigens and present them to CD4$^+$ T cells, thereby inducing T cell-dependent antibody production (51). In response to IL-1β, LTi and LTi-like cells in lymphoid organs express CD80 and CD86 and produce IL-2, TNF-α and IFN-γ, leading to T-cell activation (52). Functionally, ILC3s respond to IL-1β and IL-23. Specifically, IL-23 stimulation induces IL-17 production mainly in LTi cells and NCR$^-$ ILC3s, whereas both NCR$^+$ and NCR$^-$ ILC3s retain the ability to produce IFN-γ (7,49).

3. Multidimensional regulatory mechanisms of ILC3s

Functional activities of ILC3s are regulated by an interconnected network involving transcriptional, metabolic, neuroimmune and circadian clock mechanisms. These regulatory pathways collectively maintain ILC3 homeostasis and effector functions, whereas disruption of this network contributes to mucosal immune imbalance and disease development (Fig. 1).

Transcriptional regulatory networks

ROR. ROR, as a transcription factor family primarily composed of RORγt and RORα, regulates ILC3 lineage development, functional maintenance and phenotypic stability. Their coordinated actions shape the biological characteristics of ILC3s. RORγt, encoded by the RORC gene, is a 495-amino-acid transcription factor key in the specification of ILC3s and LTi cells. Deletion of RORγt in mice results has been shown to result in complete failure of ILC3 development, demonstrating its important role in establishing the ILC3 lineage (3,53,54). In mature ILC3s, however, RORγt is not necessarily required for cell survival. Instead, it primarily regulates cytokine production, including the expression of effector molecules such as IL-17A and IL-22. RORγt is also expressed by LTi cells and can be further induced by IL-23, thereby enhancing ILC3 activity (54-56). In mature ILC3s, survival does not strictly depend on continuous expression of RORγt or RORα (57). However, simultaneous deletion of RORγt and RORα markedly reduces the expression of metabolic regulators such as arginase-1. Consequently, ILC3 identity is disrupted, leading to the transdifferentiation of RORγt$^-$RORα$^-$T-bet$^+$NCR$^+$ ILC3s into ILC1s (57).

In an IL-23-induced innate colitis model, RORγt-expressing ILCs have been shown to accumulate in the inflamed intestine. Conversely, RORγt-deficient mice exhibited markedly reduced intestinal inflammation, as evidenced by lower histological scores, diminished inflammatory cell infiltration, and impaired IL-17 and IL-22 production. These findings establish the pathogenic contribution of RORγt to IL-23-driven innate intestinal inflammation (16). Given its involvement in both ILC3s and Th17 cells, RORγt has emerged as a potential therapeutic target for intestinal inflammation. Studies have demonstrated that transient pharmacological RORγt inhibition in pathogen-infection or neonatal inflammatory mouse models can selectively dampen pathogenic Th17-cell-derived responses while preserving the innate protective functions of ILC3s, representing a promising targeted therapeutic concept (58,59).

T-bet. T-bet suppresses transcription of the RORC gene, thereby reducing RORγt expression (60). Previous studies have shown that ex-ILC3s, a transitional population representing ILC3-to-ILC1 conversion, exhibit increased T-bet expression (17,36,57). This finding indicates that the balance between RORγt and T-bet is key in maintaining an equilibrium between ILC3 and ILC1 subsets. Fiancette *et al* (57) reported that ILC3s with dual deletion of T-bet and RORγt (T-bet$^{-/-}$RORγt$^{-/-}$) failed to undergo ILC3-to-ILC1 conversion and instead generated a distinct ILC population with undefined functions. In addition, these cells were unable to produce IL-22 following IL-23 stimulation. Collectively, these findings indicate that T-bet, in addition to RORγt, is required for ILC3-to-ILC1 conversion. Similarly, Stehle *et al* (61) demonstrated in a mouse model that T-bet deficiency restored lymphoid tissue organogenesis defects caused by RORγt deficiency. Intestinal barrier repair in this context was mediated not by ILC3s but by ILCPs, which lack both T-bet and RORγt and promote repair through IL-22 secretion (61). Therefore, low-level T-bet expression in ILC3s may contribute to maintaining ILC subset balance and immune homeostasis. Recent studies have further identified an upstream mechanism regulating T-bet

expression. Huang *et al* (62) demonstrated that the intestinal lipid metabolite 12R-hydroxyeicosatetraenoic acid functions as an endogenous ligand for the nuclear receptor Nur77. Nur77 signaling subsequently increases T-bet expression, promoting the differentiation of NKp46$^-$ ILC3s into NKp46$^+$ ILC3s and enhancing IFN-γ secretion. Nur77-deficient mice exhibit reduced ILC3 numbers, impaired differentiation of the NKp46$^+$ subset and increased susceptibility to *Salmonella typhimurium* infection. Mechanistically, this process depends on inosine monophosphate dehydrogenase 1, a downstream target gene regulated by Nur77 (62). These findings indicate an association between metabolic signals and T-bet-mediated ILC3 subset fate determination, revealing the role of the 'metabolite-nuclear receptor-T-bet' axis in intestinal immune development.

GATA3. GATA3 has long been recognized as a key transcriptional regulator of Th2 cell and ILC2 development and function (23). However, subsequent studies have demonstrated that GATA3 is also required for ILC3 development (20,63). Precursor cells lacking GATA3 fail to differentiate into ILC3s, whereas wild-type cells undergo normal development, indicating that GATA3 acts as a cell-intrinsic regulator of ILC3 lineage establishment (19). Within ILC3s, GATA3 promotes cell survival and expansion through binding to the RORC and IL-17R gene loci, thereby enhancing the expression of RORγt and CD127 (54). In addition, GATA3 regulates IL-22 expression while having limited effects on IL-17A production, suggesting selective regulation of ILC3 effector functions (54). In infection models, GATA3-deficient chimeric mice exhibit reduced intestinal IL-22 expression, decreased production of the antimicrobial peptide regenerating islet-derived protein 3-γ (RegIIIγ) and systemic pathogen dissemination, demonstrating how GATA3 contributes towards ILC3-mediated innate immune defense (19).

mTOR. mTOR is a serine/threonine kinase that integrates intracellular and extracellular signals through two distinct complexes, mTORC1 and mTORC2, thereby regulating cell proliferation, metabolism and immune response (64). Recent studies have begun to reveal the regulatory functions of the mTOR pathway in ILC3 biology.

At the functional level, mTORC1 is required for ILC3-mediated anti-infective immunity. ILC3s rely on mTORC1-dependent activation of hypoxia-inducible factor 1-α (HIF-1α), which drives metabolic reprogramming, enhances glycolysis, maintains RORγt expression and promotes cell proliferation and production of the type 3 cytokines IL-22 and IL-17A (65). Under homeostatic conditions, both mTORC1 and mTORC2 contribute to maintaining ILC3 stability in the small intestine. Deletion of regulatory protein associated with mTOR (Rptor), a key component of mTORC1, markedly reduces the numbers of both NCR$^+$ and NCR$^-$ ILC3 subsets in the small intestine, consistent with observations reported by Di Luccia *et al* (65). Similarly, deletion of rapamycin-insensitive companion of mTOR, a component of mTORC2, decreases intestinal ILC3 levels, although this effect is less pronounced compared with that caused by mTORC1 deficiency (64). However, additional studies have indicated that mTORC2 is not indispensable for basal ILC3 homeostasis (64,66). Selective mTORC2 deletion does not notably affect ILC3 numbers, subset distribution or cytokine production, whereas enhanced mTORC2 activity can compensate for impaired mTORC1 function and provide protective effects (66). mTORC1 and mTORC2 also exhibit reciprocal regulation. In IL-23-stimulated ILC3s, both complexes become activated. Conversely, inhibition of mTORC1, such as through Rptor deletion or rapamycin treatment, further increases mTORC2 activity (66).

Metabolic signaling regulatory networks

Regulation of ILC3s by vitamin metabolites. Retinoic acid (RA), a metabolite of vitamin A, is required for fetal LTi cell development and lymphoid tissue formation (67). During embryogenesis, maternally derived RA binds directly to the RORC gene locus through RA receptor (RAR) and retinoid X receptor (RXR), thereby increasing RORγt expression. This process promotes the differentiation of ID2$^+$RORγt$^+$CD4$^-$ LTi cells into ID2$^+$RORγt$^+$CD4$^+$ LTi cells and facilitates the formation of secondary lymphoid organs (SLOs) (26,67). Blocking RA signaling has been shown to reduce the number of ID2$^+$RORγt$^+$CD4$^-$ LTi cells and decrease SLO density, whereas RA stimulation has been shown to expand the ID2$^+$RORγt$^+$CD4$^+$ LTi population (26). Administration of the RA signaling inhibitor BMS493 to pregnant mice has been shown to reduce fetal LTi cell numbers and impair SLO development in the small intestine (67). RA also contributes to maintaining ILC3 populations in adulthood. Vitamin A deficiency or RAR inhibition reduces intestinal ILC3 numbers, IL-22 secretion and the frequency of lymphoid follicle formation in the intestine (68,69). In addition to supporting ILC3 maintenance, RA regulates the balance among ILC subsets. In vitamin A-deficient mice, ILC3 numbers and their signature cytokines IL-22 and IL-17 are reduced, whereas ILC2 numbers and associated cytokines, including IL-4, IL-5 and IL-13, are increased. These findings suggest that vitamin A contributes to maintaining the balance between ILC2 and ILC3 subsets (68).

In addition to vitamin A, vitamin D also regulates ILC3 function. Intestinal ILC3s exhibit high expression of the vitamin D receptor (VDR). ILC3-specific deletion of VDR primarily affects the expansion of the LTi-like subset, resulting in reduced proliferation and impaired IL-22 production, ultimately decreasing host resistance to infection (70). Furthermore, a vitamin D-deficient diet markedly reduces the proportion of ILC3s in the small intestine and colon of mice, thereby increasing susceptibility to infection (71).

Regulation of ILC3s by lipid metabolites. Short-term consumption of a high-fat diet (HFD) enriched in saturated long-chain fatty acids markedly suppresses IL-22 production by murine ILC3s within 48 h. This impairment compromises intestinal barrier integrity, as indicated by reduced expression of antimicrobial peptides (including RegIII), mucin (including Muc2) and tight junction proteins (such as occludin), together with increased epithelial permeability. Consequently, the intestine becomes more susceptible to inflammation and injury (72). Intermittent fasting induces IL-22 release by ILC3s and enhances their interactions with dendritic cells and macrophages. These effects promote the browning of subcutaneous white adipose tissue in obese mice and reveal a potential mechanism underlying metabolic protection (73).

The molecular mechanisms underlying fatty acid-mediated regulation of ILC3 function involve two complementary pathways. First, saturated fatty acids such as palmitic acid can induce expression of diacylglycerol O-acyltransferase 1, an enzyme involved in triglyceride synthesis, in ILC3s. However, this response paradoxically leads to defective lipid droplet formation, disrupting the balance between lipid storage capacity and metabolic homeostasis. Second, saturated fatty acids induce mitochondrial hyperpolarization, ROS accumulation and impaired oxidative phosphorylation. Enhanced fatty acid oxidation further promotes metabolic stress in ILC3s, leading to reduced IL-22 expression and decreased RORγt stability. By contrast, unsaturated fatty acids such as oleic acid promote the formation of structurally stable lipid droplets and preserve mitochondrial homeostasis, thereby supporting sustained IL-22 secretion (72). Intestinal ILC3s, particularly the $CD4^+$ LTi subset, sense oxysterol signals produced by intestinal stromal cells through expression of G-protein-coupled receptor (GPR)-183 (74,75). This chemotactic signal directs ILC3 localization within cryptopatches and isolated lymphoid follicles, contributing to the formation of local lymphoid tissues (74). Experimental studies have shown that GPR183 knockout disrupts this process, reducing ILC3 accumulation in cryptopatches and isolated lymphoid follicles while increasing their numbers in mesenteric lymph nodes. These findings further support the role of the GPR183 signaling axis in tissue-specific ILC3 localization (74,75).

In addition to these metabolites, prostaglandin E2, a lipid-derived mediator, regulates ILC3 functions through its receptors EP4 and EP2. Activation of these pathways promotes IL-22 and HB-EGF secretion, respectively, thereby contributing to mucosal repair and inflammatory regulation (76,77).

Neuro-immune regulation

Regulation of ILC3s by glial cells. In response to signals from the intestinal microenvironment, glial cells release glial cell-derived neurotrophic factor (GDNF) through a myeloid differentiation primary response 88 (MyD88)-dependent mechanism. GDNF binds to receptor tyrosine kinase (RET) expressed on ILC3s and activates the STAT3 and p38 MAPK/ERK-AKT signaling pathways, resulting in IL-22 production. This neuroimmune signaling axis contributes to intestinal protection and maintenance of mucosal homeostasis (78). Systemic RET deletion in mice impairs Peyer's patch development and reduces intestinal $IL\text{-}22^+$ ILC3 numbers. Conversely, ILC3-specific conditional deletion of RET aggravates dextran sulfate sodium (DSS)-induced colitis and *Citrobacter rodentium* infection in rodents, whereas gain-of-function RET mutations protect against DSS-induced intestinal injury (78,79).

Regulation of ILC3s by neural signals. During intestinal injury repair, a number of neural signals contribute to an immune regulatory network through their effects on ILC3s. The sympathetic nervous system regulates ILC3 function through norepinephrine signaling. Norepinephrine directly promotes IL-22 production by ILC3s through the β_2-adrenergic receptor (ADRB2) expressed on their surface, thereby enhancing intestinal epithelial regeneration (80). In this experimental model, chemical sympathectomy or ADRB2 blockade reduces intestinal crypt proliferation and decreases expression of the stem cell marker leucine-rich repeat-containing G protein-coupled receptor 5 (Lgr5). In addition, single-cell RNA sequencing has revealed the reduced expression of IL-22 downstream target genes, including C-type regenerating islet derived-3 (Reg3)-b and Reg3g, in intestinal epithelial cells following denervation. Neutralization of IL-22 blocks the regenerative effects induced by noradrenergic nerves, whereas exogenous IL-22-Fc restores repair defects caused by denervation. These findings indicate that IL-22 functions as the major effector molecule within the sympathetic neuroimmune pathway (80).

The parasympathetic nervous system, particularly the vagus nerve, also regulates ILC3 activity. In addition to RET expression, ILC3s express a number of cholinergic receptors, including Chrm1, Chrm2, Chrm4 and Chrm5. Vagus nerve-derived acetylcholine (ACh) activates the protectin conjugates in tissue regeneration 1 (PCTR1) biosynthetic pathway in ILC3s (81). Vagotomy reduces peritoneal ILC3 numbers and impairs clearance of *Escherichia coli* infection. Conversely, administration of ACh-preactivated ILC3s restores antimicrobial defense and improves tissue-repair defects caused by vagotomy (81). These findings identify vagal cholinergic signaling as another pathway involved in ILC3 regulation. Collectively, these studies reveal numerous neuroimmune regulatory mechanisms involving ILC3s, including the 'sympathetic-ILC3-L-22' and 'vagus-ILC3-PCTR1' pathways and suggest potential therapeutic targets for intestinal injury repair and inflammatory bowel disease (IBD). Recent studies have further identified a third neural regulatory mechanism mediated by enteric GABAergic neurons. Liu *et al* (82) demonstrated that GABA released from enteric GABAergic neurons suppresses ILC3 proliferation and IL-17A production through γ-amino-butyric acid type B receptor 1/2 (GABBR1/2) receptors expressed on ILC3s. Mechanistically, GABA signaling reduces expression of the liver-enriched inhibitory protein isoform of CCAAT/enhancer-binding protein β in ILC3s, thereby relieving transcriptional repression of the insulin like growth factor binding protein 7 (IGFBP7) gene. IGFBP7 subsequently regulates ILC3 activation through an autocrine negative feedback loop mediated by insulin-like growth factor 1 (IGF)-1R (82). Conditional deletion of GABBR1 or depletion of GABAergic neurons enhances IL-17A-mediated intestinal inflammation. In addition, inhibition of this pathway is positively associated with disease severity in patients with IBD (82). The present study establishes the enteric GABAergic neuron-ILC3 axis as an additional neuroimmune regulatory pathway, expanding the understanding of how neural signals contribute to intestinal immune homeostasis.

Circadian clock systems integrate neuro-environmental signals to regulate rhythmic ILC3 function. Circadian clock systems in ILC3s integrate environmental cues to coordinate rhythmic cellular functions and maintain intestinal immune homeostasis. Current evidence has identified three major regulatory pathways. First, light signals, acting as primary zeitgebers, are transmitted through the central clock located in the hypothalamic suprachiasmatic nucleus and synchronize clock gene expression in ILC3s. Experimental studies have shown that changes in photoperiod can reverse the rhythmic expression pattern of the period circadian regulator 1 gene in ILC3s (83,84). Second, feeding signals regulate ILC3

rhythmic activity through vasoactive intestinal peptide (VIP)-ergic neurons. These neurons release VIP, which modulates rhythmic IL-22 secretion through the VIPR2 receptor expressed on ILC3s. Exogenous VIP enhances IL-22 production by ILC3s, whereas VIPR2$^{-/-}$ mice exhibit reduced ILC3-derived IL-22 secretion and aggravated inflammatory responses during DSS-induced colitis (84,85). Third, the gut microbiota regulates rhythmic ILC3 function through microbial metabolites. Antibiotic treatment has been shown to markedly reduce the rhythmicity of IL-22 production, indicating that the microbiota is required for maintaining normal circadian ILC3 activity (86).

Collectively, light, feeding and microbial signals coordinate ILC3 circadian regulation through distinct pathways, allowing immune functions to adapt to environmental changes and supporting intestinal mucosal homeostasis. In a complementary study, Bhattarai *et al* (87) further elucidated the mechanisms associating circadian regulation with ILC3 lineage plasticity. This study demonstrated that circadian clock proteins reverse (REV)-ERBα/β maintain an accessible chromatin state at the RORC locus through epigenetic regulation, thereby preserving canonical ILC3 identity (87). Simultaneous deletion of REV-ERBα and REV-ERBβ reverses the repression of the transcription factor NFIL3. NFIL3 subsequently binds a cis-regulatory element ~2 kb upstream of the RORC gene, suppresses RORγt transcription and activates a T-bet-dominant differentiation program. This transcriptional switch promotes transdifferentiation of NKp46^{+} ILC3s into ILC1s, accompanied by reduced IL-22 production and increased IFN-γ secretion, ultimately impairing host defense against *Citrobacter rodentium* infection (87). Furthermore, loss of REV-ERBα/β reduces surface major histocompatibility complex (MHC)-II expression on CCR6^{+} ILC3s, suggesting that circadian regulation influences not only cytokine production but also immunomodulatory functions of ILC3s, including antigen presentation (87).

4. Interactions between ILC3s and the microbiota

Gut microbiota and ILC3s establish a dynamic bidirectional association that contributes to mucosal homeostasis. The microbiota regulates ILC3 development and function through direct and indirect mechanisms, whereas ILC3s influence microbial composition and colonization by regulating epithelial barrier integrity and IgA production. Disruption of this interaction is associated with the development and progression of diseases including IBD and tumors (Fig. 2).

Direct regulation of ILC3s by the microbiota. Microbial metabolites regulate ILC3 function through numerous signaling pathways. Microbiota-derived tryptophan metabolites act as ligands for the AHR. By directly activating AHR in ILC3s, these metabolites promote IL-22 transcription and secretion, thereby enhancing epithelial repair and antimicrobial defense (39,88-90). Studies using human ILC3s have shown that co-stimulation with AHR agonists and IL-1β induces IL-22 production, whereas AHR antagonists promote the generation of IFN-γ-expressing ex-ILC3s. These findings support a conserved role for AHR in maintaining ILC3 function (91). Beyond the AHR pathway, microbiota-derived short-chain fatty acids (SCFAs) regulate ILC3 activity through specific G protein-coupled receptors. Acetate (C2) primarily signals through free fatty acid receptor 2 (FFAR2; GPR43), which regulates the CCR6^{+} ILC3 subset localized in colonic cryptopatches and isolated lymphoid follicles (92). Mechanistically, acetate promotes CCR6^{+} ILC3 proliferation through FFAR2-mediated activation of the Akt, STAT3 and mTOR pathways (92). In addition, acetate increases IL-1β receptor expression on ILC3s, thereby enhancing their capacity for IL-22 production (92). Consistent with these findings, conditional deletion of FFAR2 impairs CCR6^{+} ILC3 proliferation and IL-22 production, resulting in reduced antimicrobial defense and tissue repair capacity (92). By contrast, propionate (C3) preferentially enhances IL-22 production by ILC3s through FFAR3 (GPR41) signaling (92). Butyrate (C4) promotes IL-22 production by RORγt^{+} ILCs through the GPR41 pathway (93). However, butyrate can also act through GPR109a expressed by dendritic cells to indirectly suppress IL-17 and IL-22 production by ILC3s under IL-25 stimulation (94,95).

In addition, gut microbiota-derived cyclic dinucleotides can be directly sensed by ILC3s through the stimulator of interferon genes (STING) pathway (96). Under homeostatic conditions, STING activation induces CCR7 expression in ILC3s and promotes their migration to lymph nodes. This process facilitates microbiota-specific Treg differentiation, which in turn establishes immune tolerance by suppressing pathogenic effector T cell responses against commensal bacteria (96). Microbial signals also regulate ILC3 function through additional receptor pathways. Upon sensing microbiota-derived signals, toll-like receptor 2 induces IL-2 production by ILC3s. IL-2 is mainly consumed by local Tregs expressing high levels of CD25 and promotes IL-22 expression through an autocrine mechanism, thereby selectively maintaining Treg homeostasis in the small intestine (97,98). Collectively, the gut microbiota regulates ILC3 function through diverse molecular mechanisms, including AHR-mediated sensing of tryptophan metabolites, GPCR-mediated recognition of short-chain fatty acids, STING-mediated detection of cyclic dinucleotides and TLR2-mediated responses to microbial components. However, further studies are required to define the specific microbial signals that activate, suppress or fine-tune ILC3 activity.

Indirect regulation of ILC3s by the microbiota through immune cell mediation. Mononuclear phagocyte systems, particularly CX3C motif chemokine receptor 1 (CX3CR1)$^{+}$ macrophages and CD14^{-} dendritic cells, function as a central hubs for sensing and transmitting microbiota-derived signals, thereby regulating ILC3 activation. Upon sensing microbiota-derived cues through the MyD88 and nucleotide-binding oligomerization domain-containing protein 2 (NOD2) pathways, CX3CR1^{+} macrophages specifically produce IL-1β, which directly activates ILC3s (98,99). Activated ILC3s subsequently secrete granulocyte-macrophage colony-stimulating factor (GM-CSF, also known as colony-stimulating factor 2 or CSF2). GM-CSF, in turn, induces IL-10 secretion by dendritic cells and promotes Treg differentiation, thereby indicating an association between early ILC3-mediated innate immune responses and subsequent adaptive immune tolerance mechanisms (99,100). In addition, microbial stimulation

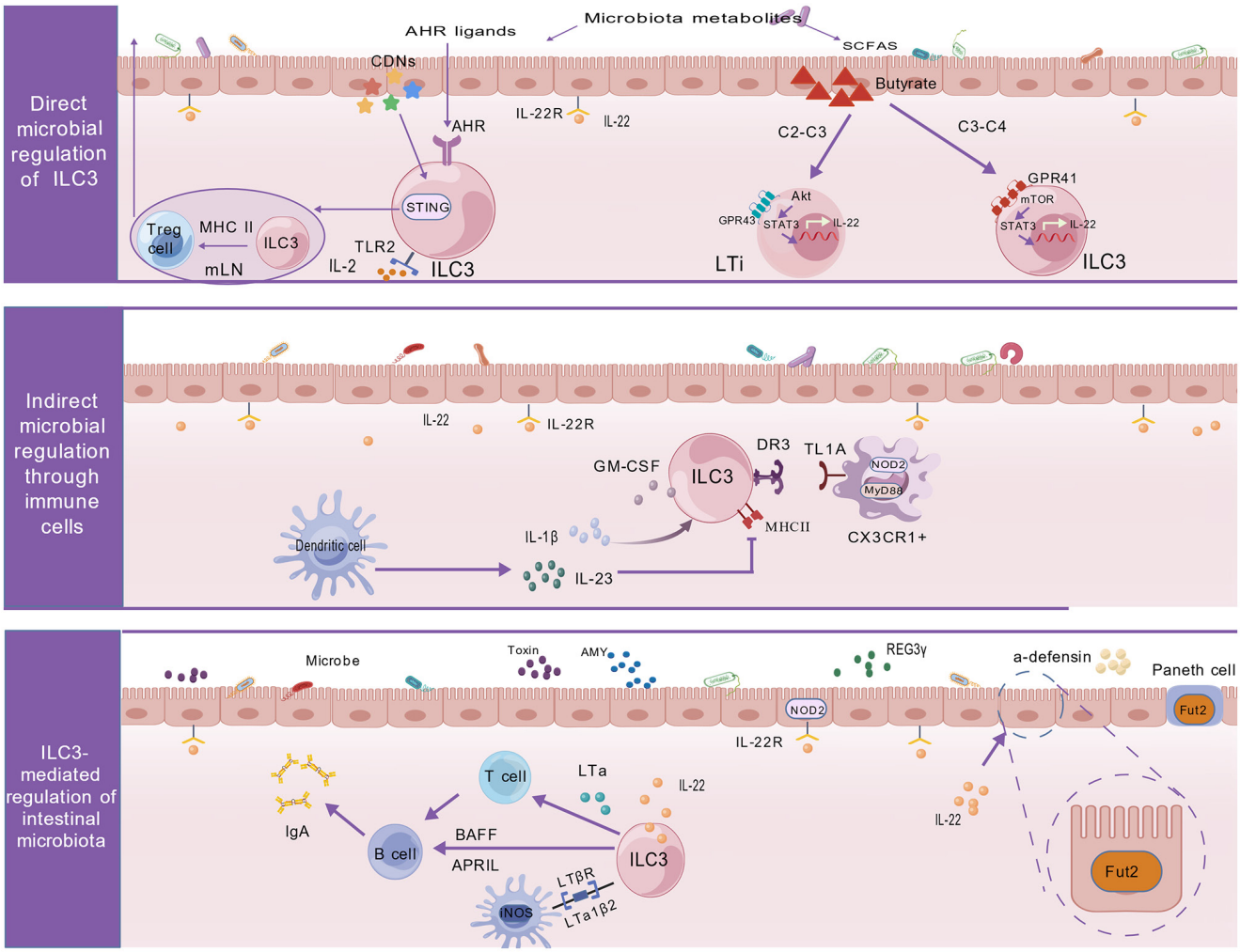

Figure 2. Schematic representation of the bidirectional regulatory network between ILC3s and the gut microbiota. Upper panel (direct microbial regulation of ILC3): Microbiota-derived tryptophan metabolites activate the AHR pathway in ILC3s to promote IL-22 production. Gut microbial SCFAs act through distinct receptors: Acetate and propionate signal through GPR43 (FFAR2) on LTi cells, while propionate and butyrate bind to GPR41 (FFAR3) on ILC3s; collectively, these signals activate the STAT3 pathway to drive IL-22 secretion. In addition, microbial cyclic dinucleotides activate STING signaling in ILC3s, promoting their migration to mesenteric lymph nodes, where they cooperate with IL-2 and MHC-II to induce Treg cell differentiation. Middle panel (indirect microbial regulation through immune cells): CX3CR1$^+$ dendritic cells recognize intestinal microbial signals and secrete IL-1β and IL-23, which act on ILC3s. ILC3s express DR3 and the NOD2/MyD88 complex on their surface, enabling them to respond to TL1A and intracellular microbial signals. Furthermore, dendritic cell-derived IL-23 dynamically modulates MHC class II expression and the antigen-presenting capacity of ILC3s. Lower panel (ILC3-mediated regulation of intestinal microbiota): ILC3-derived IL-22 acts on intestinal epithelial cells to induce the production of antimicrobial peptides (RegIIIβ/γ), Fut2-dependent epithelial fucosylation and abundant mucin secretion, thereby establishing physical and chemical barriers that restrict bacterial invasion. ILC3s also secrete LTα and membrane-bound LTβ to facilitate T cell-dependent IgA responses, while simultaneously producing BAFF and APRIL to directly promote T cell-independent IgA production by B cells. Through mucosal IgA, ILC3s reshape the colonization structure of the gut microbiota. ILC, innate lymphoid cell; AHR, aryl hydrocarbon receptor; SCFA, short-chain fatty acid; GPR, G-protein-coupled receptor; FFAR, free fatty acid receptor; LTi, lymphoid tissue inducer; STING, stimulator of interferon genes; MHC, major histocompatibility complex; Treg, T regulatory cell; CX3CR, CX3C motif chemokine receptor 1; DR3, death receptor 3; NOD2, nucleotide-binding oligomerization domain-containing protein 2; MyD88, myeloid differentiation primary response 88; TL1A, TNF-like ligand 1A; Fut2, fucosyltransferase 2; BAFF, B cell-activating factor; APRIL, A proliferation-inducing ligand; TLR, toll-like receptor; REG3γ, C-type regenerating islet derived-3-γ; RegIII, regenerating islet-derived protein 3; mLN, mesenteric lymph nodes; GM-CSF, granulocyte-macrophage colony-stimulating factor; LT, lymphotoxin. CDNs, cyclic dinucleotides.

induces CX3CR1$^+$ macrophages to release TNF-like ligand 1A (TL1A). Upon binding to death receptor 3, which is expressed on the surface of human ILC3s, TL1A not only promotes ILC3 proliferation but also enhances IL-22 production in the presence of synergistic cytokine stimulation (101,102). Collectively, microbiota-induced production of signaling molecules, including IL-1β and TL1A, by mononuclear phagocytes activates ILC3s and regulates their secretion of cytokines such as GM-CSF and IL-22, thereby establishing a regulatory axis that coordinates immune regulation throughout the gastrointestinal tract (98,99).

Under conditions of intestinal homeostasis, the microbiota also influences the antigen-presenting function of ILC3s by modulating mononuclear phagocyte responses. Specifically, microbiota stimulation induces mononuclear phagocytes, including dendritic cells and macrophages, to secrete IL-23. As a regulatory signal, IL-23 reversibly suppresses the expression of MHC class II molecules on the surface of ILC3s, thereby reducing their capacity to present antigens to CD4$^+$ T cells within the intestinal mucosa (103). This reversibility indicates that ILC3 antigen-presenting function is dynamically regulated: Enhanced IL-23 signaling suppresses MHC II

expression, whereas reduced IL-23 signaling or alterations in the intestinal microenvironment restore antigen-presenting capacity (103). This regulatory mechanism highlights the dynamic role of ILC3s in maintaining intestinal immune homeostasis, allowing tolerance toward commensal microbes while preserving the capacity to mount immune responses against pathogenic infections (103).

Regulatory role of ILC3s in the microbiota. ILC3s exert multifaceted regulatory effects in maintaining gut microbiota homeostasis. These functions are primarily mediated through IL-22 secretion, which reinforces epithelial barrier integrity, shapes the microbial colonization environment and regulates the production of antimicrobial effector molecules. IL-22 initiates signaling by binding to the heterodimeric IL-22R1/IL-10R2 receptor complex expressed on intestinal epithelial cells. Under homeostatic conditions, IL-22 signaling induces the production of antimicrobial peptides, including RegIIIβ, RegIIIγ and S100A/B, thereby limiting excessive epithelial invasion by commensal bacteria. In addition, IL-22 promotes epithelial expression and fucosylation of fucosyltransferase 2 (Fut2), thereby enhancing intestinal resistance and tolerance to pathogenic bacteria. Fut2-positive Paneth cells further strengthen antimicrobial defense through secretion of α-defensins (104-108). IL-22 also promotes NOD2 expression, with NOD2 signaling stimulates mucin and antimicrobial peptide secretion while promoting expansion of commensal bacteria through N-glycosylation. These commensal bacteria compete with *Clostridium difficile* for dietary niches, thereby contributing to gut microbiota stability (109,110). IL-22 contributes to prevention of bacterial infection, attenuation of intestinal inflammation and tissue repair during conditions such as hepatitis and colitis (111). IL-22 deficiency compromises barrier integrity, resulting in bacterial translocation and subsequent systemic inflammation (112). Loss of ILC3 function is frequently accompanied by alterations in microbial composition, including expansion of segmented filamentous bacteria and *Clostridiales*, together with reduced abundance of beneficial bacteria such as *Lactobacillus* spp. These findings suggest that ILC3s restrict the expansion of potentially pathogenic bacteria and contribute to maintenance of microbial homeostasis (113-115). In addition to IL-22-mediated regulation, ILC3s indirectly shape the microbial ecosystem through modulation of mucosal immune responses. ILC3s regulate IgA production by influencing germinal center B cell responses and antigen presentation to follicular helper T cells. Mechanistically, ILC3-derived LTα promotes T-cell homing to the intestine, thereby supporting T cell-dependent IgA induction. In addition, ILC3s upregulate inducible nitric oxide synthase expression through membrane-bound lymphotoxin-β (LTβ) interactions with dendritic cells, promoting IgA generation (115,116). Furthermore, ILC3s directly support B cell survival and IgA secretion through production of B cell-activating factor (BAFF) and A proliferation-inducing ligand (APRIL) (117). As a key effector molecule of mucosal immunity, IgA influences microbiota composition through immune exclusion and regulation of bacterial colonization (118). Therefore, by regulating IgA responses, ILC3s indirectly contribute to the maintenance of intestinal microecological homeostasis.

5. Role of ILC3s in diseases

Role of ILC3 in intestinal diseases

Role in IBD. IBD comprises a group of disorders characterized by chronic intestinal inflammation, primarily including ulcerative colitis (UC) and Crohn's disease (CD). Increasing evidence has indicated that ILC3 dysfunction represents an important mechanism contributing to the pathogenesis of these conditions (119,120) (Fig. 3). In inflamed intestinal tissues from patients with IBD, the frequency of ILC3s is markedly reduced, whereas IFN-γ-secreting ILC1s are notably increased. These changes suggest that conversion of ILC3s into ILC1s may contribute to disease progression (120,121). This conversion process is tightly regulated by the local cytokine environment, consisting primarily of IL-12, IL-23, IL-1β and IL-18, which are elevated in the inflamed intestinal mucosa. *In vitro* experiments and analyses of clinical tissue specimens have demonstrated that IL-12 produced by $CD14^+$ dendritic cells induces IL-22-secreting $ROR\gamma t^+NKp44^+$ ILC3s to convert into IFN-γ^+ ILC1s. This phenotypic shift increases the proportion of ILC1s while reducing ILC3 numbers in the intestines of patients with CD, thereby promoting chronic intestinal inflammation (15,35). Conversely, in the presence of IL-23, IL-1β and RA produced by $CD14^-$ dendritic cells, $CD127^+$ ILC1s can revert to IL-22^+ ILC3s. This was demonstrated by single-cell cloning experiments showing that individual $CD127^+$ ILC1 gave rise to progeny containing both ILC1 and ILC3 phenotypes, and by adoptive-transfer experiments in which ex-$ROR\gamma t^+$ ILC3 (cells that had lost RORγt and become ILC1-like) re-expressed RORγt after being transferred into $Rag2^{-/-}Il2rg^{-/-}$ mice (34). Clinical specimen analyses have further revealed increased expression of ILC3 activation markers, including NKp44 and CD56, in peripheral blood from patients with CD and UC. At the same time, human leukocyte antigen-DR isotype expression on ILC1s and ILC2s is also elevated, supporting the contribution of ILC lineage imbalance to IBD pathogenesis (122). The GPR183 pathway is closely associated with IBD. Animal studies have shown that colonic inflammation increases levels of its ligand 7α,25-hydroxycholesterol, thereby activating GPR183 signaling. This activation promotes abnormal migration of ILC3s toward inflammatory sites, disrupting their local distribution and resulting in excessive IL-22 production (74,123). In addition, the IL-23/IL-17 axis serges an important role in IBD pathogenesis. Animal studies have further demonstrated that IL-23 activates intestinal NCR^- ILC3s and LTi cells, inducing robust IL-17 secretion and promoting intestinal inflammation (16,64). Consistently, IL-23 levels are elevated in the intestines of patients with IBD, indicating the relevance of this pathway in human disease (122). IL-17 promotes tissue injury by inducing epithelial and endothelial cells to produce chemokines, which recruit neutrophils into the intestinal mucosa. These recruited neutrophils subsequently release ROS and proteases, further contributing to inflammation (42). In addition, IL-17 reduces tight junction protein expression, thereby impairing epithelial barrier integrity (43). One mechanism underlying the therapeutic efficacy of clinically approved IL-23 monoclonal antibodies, such as ustekinumab, is the inhibition of IL-17 production by ILC3s and Th17 cells (124). Similarly, animal studies have further demonstrated that IL-23 blockade

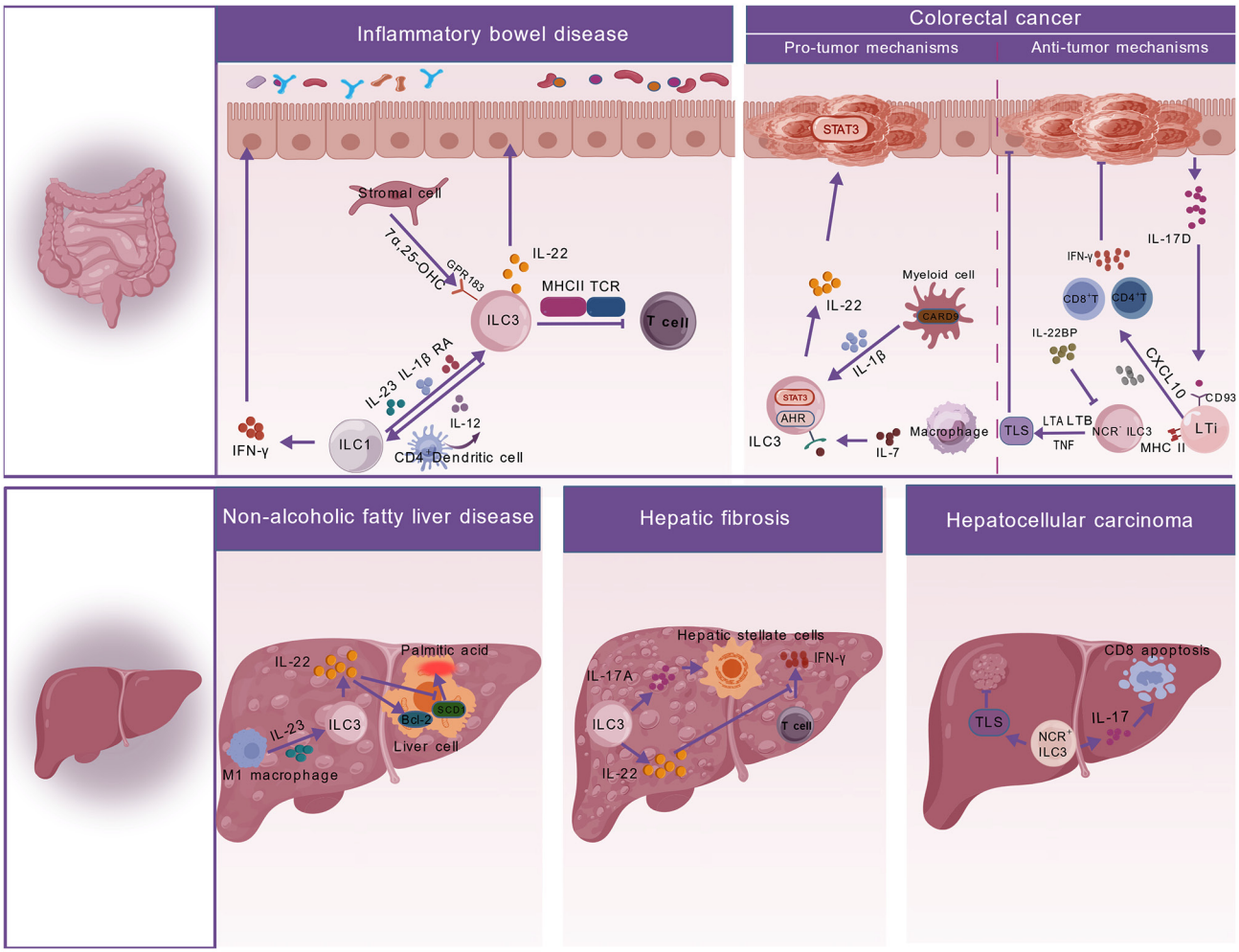

Figure 3. Mechanistic roles of ILC3s in intestinal and liver diseases. Inflammatory bowel disease: 7α,25-OHC binds to GPR183 on ILC3s, mediating aberrant migration of ILC3s to inflammatory intestinal lesions. Dendritic cell-derived IL-12 induces ILC3-to-ILC1 phenotype conversion and the resulting ILC1s produce large amounts of IFN-γ, which exacerbates epithelial damage and chronic intestinal inflammation. Colorectal cancer: Pro-tumor mechanisms encompass macrophage-derived IL-7 acting on ILC3s, activating intracellular STAT3 and AhR signaling, which promotes large IL-22 secretion by ILC3s and mediates pro-tumorigenic effects. Antitumor mechanisms encompass: i) LTi cells expressing MHC class II molecules and directly presenting antigens to activate $CD4^+$ and $CD8^+$ antitumor T cells; ii) NCR^+ ILC3s secreting LTA, LTB and TNF to induce the formation of TLS within tumor lesions and; iii) ILC3s secreting IL-22BP to antagonize pro-tumorigenic IL-22, while $CD4^+$/$CD8^+$ T cells secrete IFN-γ, synergistically exerting antitumor immunity. Non-alcoholic fatty liver disease: A high-fat diet induces hepatic M1 macrophage activation and IL-23 secretion whereby IL-23 activates hepatic ILC3s to secrete IL-22. IL-22 upregulates the anti-apoptotic protein Bcl-2 in hepatocytes and suppresses SCD1 expression, thereby alleviating hepatic lipid injury and exerting hepatoprotective effects. Hepatic fibrosis: ILC3-derived IL-17A and IL-22 directly activate hepatic stellate cells to promote collagen deposition. IL-22 also suppresses IFN-γ production by T cells, indirectly exacerbating fibrosis. Hepatocellular carcinoma: NCR^+ ILC3s are present in hepatic tumor lesions and participate in the formation of intratumoral TLS. The tumor microenvironment can induce $CD8^+$ T cell apoptosis, thereby weakening antitumor immune responses. ILC, innate lymphoid cell; AHR, aryl hydrocarbon receptor; GPR, G-protein-coupled receptor; MHC, major histocompatibility complex; TLS, tertiary lymphoid structures; 7α,25-OHC, 7α,25-hydroxycholesterol; NCR, natural cytotoxicity receptor; LT, lymphotoxin; SCD1, stearoyl-CoA desaturase; IL-22BP, IL-22 binding protein; RA, retinoic acid; CXCL, chemokine (C-X-C motif) ligand; CARD9, caspase recruitment domain-containing protein 9; TCR, T cell receptor.

reduces IL-17 secretion by ILC3s and attenuates intestinal inflammation (16). In children with IBD, MHC-II expression on ILC3s has been reported to be notably reduced. Given that $MHC\text{-}II^+$ ILC3s contribute to $CD4^+$ T-cell apoptosis and maintenance of immune tolerance, restoration or modulation of this pathway may represent a potential therapeutic strategy (125).

Role in colorectal cancer (CRC). In CRC, ILC3s exhibit both pro-tumorigenic and anti-tumorigenic activities, which are influenced by subset composition, local cytokine networks and the gut microbiota (Fig. 3). Regarding their pro-tumorigenic functions, studies using mouse models of colitis-associated cancer have shown that ILC3s promote epithelial cell proliferation through IL-22-mediated activation of the STAT3 signaling pathway, thereby contributing to CRC initiation and maintenance (126,127). Further studies using genetically deficient mouse models demonstrated that this process is regulated by a myeloid cell-derived caspase recruitment domain family member 9-IL-1β signaling axis (128). In addition, mouse studies have shown that IL-17 produced by the NCR^- ILC3 subset following IL-23 stimulation promotes the development of duodenal adenomas (126,129). An additional study combining mouse fecal microbiota transplantation experiments with *in vitro* coculture systems demonstrated that macrophage-derived IL-7 enhances STAT3 and AHR expression in ILC3s, thereby increasing IL-22 production and promoting intestinal tumorigenesis (130). In addition, analyses of human CRC tissue specimens have revealed reduced expression of IL-22 binding protein (IL-22BP), an endogenous

inhibitor of IL-22, in tumor tissues. Loss of IL-22BP results in dysregulated IL-22 signaling and accelerates inflammation-associated tumor progression, an effect further validated in mouse models (127,131).

Conversely, ILC3s also exert protective antitumor functions. Mouse models of colitis-associated cancer have demonstrated that epithelial cell-derived IL-17D binds to CD93 expressed on the surface of ILC3s and regulates IL-22 secretion. This pathway subsequently affects antimicrobial peptide expression and gut microbiota composition, thereby suppressing tumorigenesis (132). Studies using genetically deficient mouse models and human CRC tissue specimens have further shown that $CCR6^+$ ILC3s expressing MHC-II molecules and displaying an LTi-like phenotype promote type 1 immune responses, enhance antitumor immunity and improve responses to immunotherapy through interactions with T cells (133,134). In murine tumor models, cisplatin induces tumor cells to produce C-C motif chemokine ligand (CCL)-20, while also elevating intratumoral IL-1β levels derived from myeloid and tumor compartments (135,136). These signals activate ILC3s to release chemokine (C-X-C motif) ligand (CXCL)-10, which recruits $CD4^+$ and $CD8^+$ T cells. Consequently, immunologically 'cold' tumors, which are characterized by sparse T cell infiltration, low mutational burden and resistance to immune checkpoint blockade, are converted into 'hot' tumors that exhibit abundant T cell infiltration, a proinflammatory microenvironment and enhanced sensitivity to immunotherapy. This conversion toward an inflamed tumor microenvironment substantially improves therapeutic responses to immune checkpoint inhibitors (135).

Tertiary lymphoid structures (TLS) exhibit functional heterogeneity in inflammatory and tumor contexts. In DSS-induced colitis models, TLS formation is associated with inflammatory progression. In tissues from patients with UC, TLS are increased in frequency and are often associated with extra-intestinal inflammation (137). However, cohort studies in patients with CRC have demonstrated that TLS serve as independent prognostic markers associated with favorable outcomes. Mechanistic studies have shown that mature $NKp44^+$ ILC3s express TLS-associated genes, including lymphotoxin (LT)-A, LTB and TNF, thereby contributing to the formation of protective TLS. Conversely, expression of these genes is markedly reduced in advanced CRC tissues, accompanied by a decline in ILC3 populations (138,139).

Role of ILC3s in liver diseases

Role in non-alcoholic fatty liver disease (NAFLD). In HFD-induced mouse models of NAFLD/non-alcoholic steatohepatitis (NASH), ILC3s exert hepatoprotective effects (Fig. 3). Studies have demonstrated that HFD promotes the accumulation of hepatic M1 macrophages, which subsequently produce IL-23 and stimulate ILC3 expansion and activation (140). Activated ILC3s secrete IL-22, which inhibits PA-induced apoptosis in primary hepatocytes and upregulates anti-apoptotic genes, including Bcl-2 (140). IL-22 treatment reduces intracellular palmitate levels in hepatocytes and suppresses expression of stearoyl-CoA desaturase-1 indicating its involvement in regulating lipid synthesis and accumulation (140). In NAFLD, M1 macrophage-derived IL-23 induces ILC3s to produce IL-22. This pathway exerts anti-inflammatory and anti-apoptotic effects, regulates lipid metabolism, reduces HFD-induced hepatotoxicity and delays progression toward NASH and liver fibrosis (140).

Role in liver fibrosis. Increasing evidence has indicated that ILC3s also participate in the progression of numerous liver diseases, particularly liver fibrosis (Fig. 3). Clinical studies have shown that, in patients with chronic hepatitis B virus-associated liver fibrosis, IL-17A- and IL-22-producing ILC3 subsets are highly active during fibrotic progression. These findings suggest that both cytokines may contribute to profibrotic responses and are positively associated with disease severity (141). Mechanistic studies have revealed that ILC3s regulate liver fibrosis through a number of pathways. *In vitro* coculture experiments have demonstrated that IL-17A and IL-22 secreted by ILC3s directly act on hepatic stellate cells (HSCs), promoting their activation, proliferation and collagen production. In a coculture system involving ILC3s and the HSC cell line LX-2, ILC3s were shown to notably increase the expression of fibrosis-associated genes, including collagen type I α 2 chain, α-SMA and TGF-β1, in LX-2 cells. These effects were specifically inhibited by neutralizing antibodies against IL-17A or IL-22 (141). In addition, cellular studies have shown that ILC3-derived IL-22 can suppress production of the antifibrotic cytokine IFN-γ by immune cells, including T cells, thereby indirectly promoting fibrotic progression (141). This regulatory pattern, involving both direct enhancement of HSC activation and indirect inhibition of antifibrotic immune responses, highlights the complex role of ILC3s within the hepatic immune microenvironment.

Mouse models have further supported the profibrotic functions of ILC3s. In liver fibrosis models, ILC3 numbers and $IL\text{-}17A^+IL\text{-}22^+$ ILC3 subsets are markedly increased in both the liver and spleen. In recombination-activating $gene\text{-}1^{-/-}$ mice lacking T and B cells, depletion of ILCs reduces fibrosis severity, whereas adoptive transfer of ILC3s accelerates fibrotic progression (141). The functions of ILC3s in the liver vary according to disease stage. In acute liver injury models, ILC3-mediated hepatoprotection is primarily associated with IL-22 secretion (142). By contrast, chronic viral hepatitis and liver fibrosis models are characterized by predominantly pro-inflammatory and profibrotic effects of ILC3s (143). This functional duality is likely associated with ILC3 subset heterogeneity, local cytokine environments and interactions with other immune cells.

Role in hepatocellular carcinoma (HCC). During the initiation and progression of HCC, the IL-23/IL-17 axis represents a major inflammatory pathway involved in tumor development (Fig. 3). Studies using mouse models of HCC have shown that elevated IL-23 levels within the tumor microenvironment expand the NCR^- ILC3 subset and promote its differentiation into IL-17-high cells, thereby accelerating HCC progression (144). IL-17 recruits myeloid-derived suppressor cells and enhances their immunosuppressive activity, resulting in impaired $CD8^+$ T cell-mediated antitumor immunity. This mechanism has been validated in a number of HCC models, including subcutaneous, orthotopic and chemically induced models (145).

In addition, *in vitro* coculture experiments have demonstrated that NCR^- ILC3s can directly induce $CD8^+$ T-cell apoptosis and inhibit their proliferation through

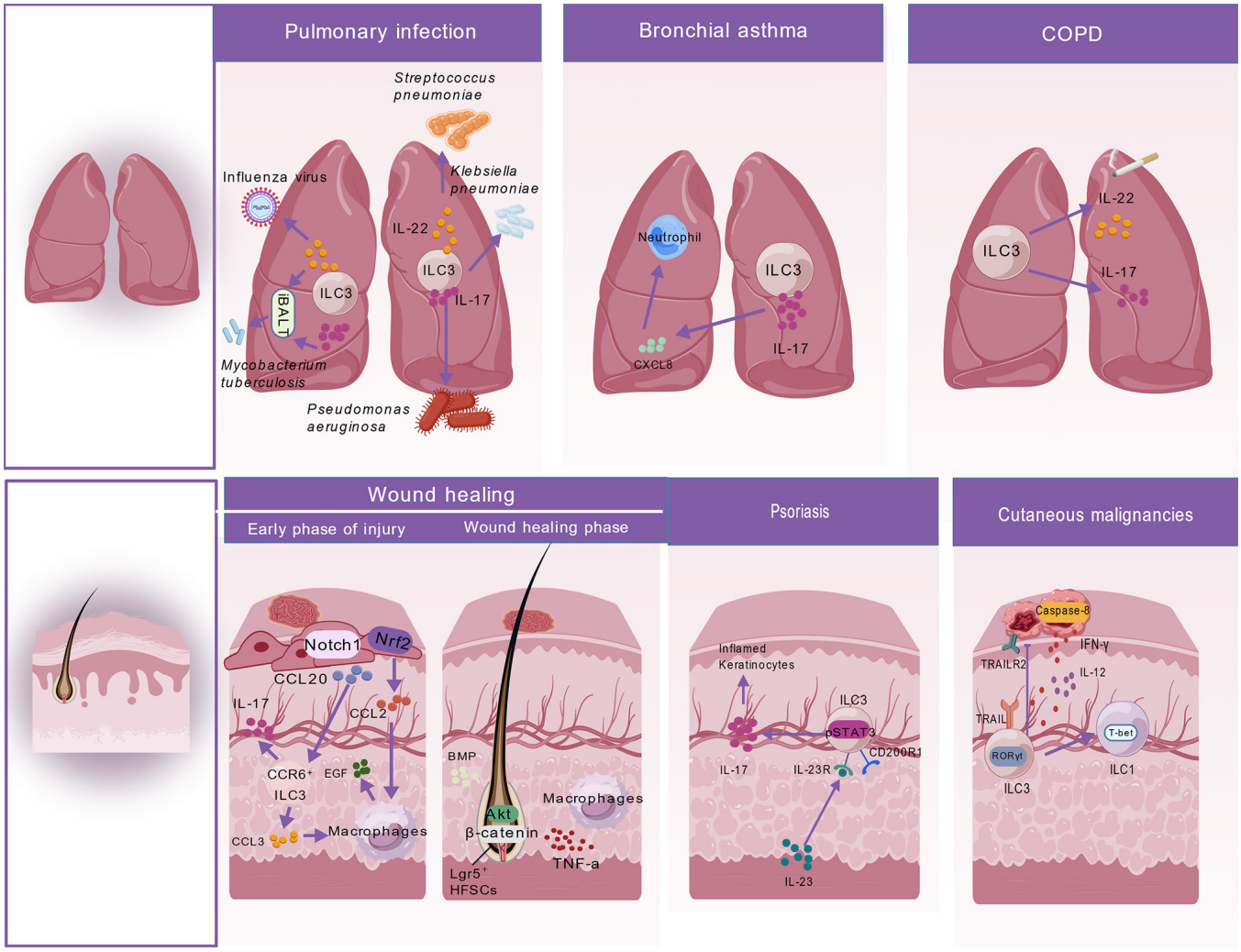

Figure 4. Mechanistic roles of ILC3s in pulmonary and skin diseases. Pulmonary infection: Infection with *Streptococcus pneumoniae*, *Klebsiella pneumoniae* or *Pseudomonas aeruginosa* stimulates pulmonary ILC3s to secrete IL-17, which mediates neutrophil recruitment to clear pathogens. During *Mycobacterium tuberculosis* infection, ILC3s participate in local immune responses by secreting IL-23, IL-17 and IL-22 and contribute to the formation of iBALT in the airways. Influenza virus stimulates ILC3s to produce IL-22, which maintains airway epithelial integrity. Bronchial asthma: Airway ILC3s secrete IL-17, which induces CXCL8 release, recruits neutrophils into the airways and mediates airway inflammation. COPD: ILC3s secrete IL-17, which sustains chronic pulmonary inflammation and mediates alveolar tissue damage. Wound healing: Early phase of injury: Notch1 signaling in skin cells upregulates CCL20, recruiting CCR6$^+$ ILC3s to the wound site. These CCR6$^+$ ILC3s secrete CCL3 and IL-17F to promote macrophage infiltration into the wound. Wound healing phase: Macrophages secrete TNF-α, which, together with BMP and Akt/β-catenin signaling, activates Lgr5$^+$ hair follicle stem cells, thereby participating in skin wound healing. Psoriasis: Within the lesional microenvironment, IL-23 binds to IL-23R on ILC3s, activating the CD200R1-pSTAT3 signaling pathway, which enhances ILC3 function and induces robust IL-17 secretion, continuously amplifying the inflammatory response of skin keratinocytes. Cutaneous malignancies: IL-12 in the tumor microenvironment drives the plastic conversion of RORγt$^+$ ILC3s into T-bet$^+$ ILC1s. Upon activation by inflammatory cytokines, RORγt$^+$ ILC3s persistently express TRAIL, which binds to TRAILR2 on tumor cells to initiate caspase-8-dependent apoptosis. Meanwhile, non-converted activated ILC3s directly secrete IFN-γ and the differentiated T-bet$^+$ ILC1s also produce large amounts of IFN-γ, jointly mediating antitumor immune responses. TRAIL, TNF-related apoptosis-inducing ligand; TRAILR2, TRAIL receptor 2; Lgr5, leucine-rich repeat-containing G protein-coupled receptor 5; BMP, bone morphogenetic protein; T-bet, T-box expressed in T cells; RORγt$^+$, retinoid-related orphan receptor; pSTAT3, phosphorylated STAT3; CCR, C-C motif chemokine receptor; CCL, C-C motif chemokine ligand; ILC, innate lymphoid cell; iBALT, inducible bronchus-associated lymphoid tissue; CXCL, chemokine (C-X-C motif) ligand; COPD, chronic obstructive pulmonary disease.

cell-contact-dependent mechanisms. This effect further contributes to the establishment of an immunosuppressive tumor microenvironment (144). However, the effects of ILC3s on tumor immunity are not uniform across different contexts. Analyses of clinical specimens from patients with non-small cell lung cancer have shown that the NCR$^+$ ILC3 subset is associated with TLS formation and early-stage tumors, suggesting its potential contribution to antitumor immunity (146). These findings indicate that ILC3 functions in HCC and other tumor settings are influenced by cytokine environments, tumor stage, tissue origin and subset composition.

Role of ILC3s in pulmonary diseases. In the lung, ILC3s contribute to both host defense and inflammatory pathology across numerous infectious and chronic diseases (16,39) (Fig. 4). Despite ILC2s being numerically predominant in lung tissue, ILC3s serve important roles in early anti-infective immunity, tissue repair and inflammatory regulation through rapid secretion of effector cytokines, including IL-17, IL-22 and GM-CSF, in response to inflammatory signals such as IL-1β and IL-23 (147,148). This function is particularly relevant during the neonatal period, when IGF1-mediated expansion and maturation of ILC3 precursors are required for establishing early pulmonary defense capacity (149).

The contribution of ILC3s is especially evident during bacterial pneumonia. In a mouse model of *Klebsiella pneumoniae* infection, ILC3s were identified as the key source of early IL-17 and depletion of ILC3s resulted in impaired bacterial clearance (150). Similarly, in a mouse model of *Streptococcus pneumoniae* infection, IL-22 production was shown to be dependent on ILC3s and exogenous flagellin treatment enhanced ILC3 function and improved host survival (147). In *Pseudomonas aeruginosa* pulmonary infection models, ~90% of early IL-17 production was derived from ILC3s, further supporting their role in bacterial control (151).

ILC3s also contribute to protective immunity during tuberculosis infection. Mouse studies have demonstrated that ILC3s participate in granuloma formation and maintenance and promote the development of inducible bronchus-associated lymphoid tissue through the IL-23-IL-17/IL-22 axis, thereby enhancing local immune responses (152,153). Human genetic studies further support this function: Individuals carrying RORC mutations that impair IL-17 signaling are more susceptible to severe mycobacterial infections (154). During influenza virus infection, ILC3s exhibit context-dependent functions. Studies in murine models have demonstrated that excessive or premature IL-17 production drives robust neutrophil recruitment. Recruited neutrophils exhibit elevated myeloperoxidase activity, triggering oxidative-mediated lipid peroxidation and consequent lung tissue injury (155,156). Conversely, IL-22 produced by ILC3s preserves epithelial integrity and promotes tissue repair, providing protective effects during infection (157). ILC3s also participate in chronic inflammatory airway diseases, including asthma. Studies using obese mouse models and preliminary clinical evidence have shown that patients with asthma, particularly those with severe or obesity-associated asthma, exhibit increased numbers of IL-17$^+$ ILC3s, which is associated with airway hyperresponsiveness (158,159).

In vitro experiments using human primary bronchial epithelial cells, together with clinical association studies, suggest that this phenotype may be mediated by IL-17-induced production of neutrophil-attracting chemokines, including CXCL8 (41). However, a recent study has reported that NCR$^+$ ILC3 frequencies are notably reduced in the lungs of patients with severe asthma compared with healthy controls (160). These findings suggest functional differences among ILC3 subsets during asthma pathogenesis. In chronic obstructive pulmonary disease, the smoking-induced inflammatory microenvironment is associated with increased levels of IL-17 and associated cytokines, suggesting that ILC3s may also contribute to disease development (161).

Role of ILC3s in skin diseases

Skin cancer. ILC3s are implicated in melanoma immunosurveillance (Fig. 4). *In vivo* studies have indicated that, in the presence of IL-12, NKp46$^+$ ILC3s exert antitumor activity against B16 melanoma cells by initiating inflammatory cascades and increasing adhesion molecule expression. These effects remodel the tumor microvasculature, suppress tumor growth and are dependent on IL-12R and RORγt signaling (162). *In vitro* studies have further demonstrated that human ILC3s isolated and purified from peripheral blood of healthy donors or noncancerous liver tissue can directly destroy the melanoma cell line SK-Mel-37. This cytotoxic activity involves TNF-related apoptosis-inducing ligand (TRAIL) binding to TRAIL receptor 2, which activates caspase-8 in target cells and promotes IFN-γ secretion, ultimately inducing tumor apoptosis (163). However, in murine models, TRAIL expression has been primarily associated with NK cells and ILC1s and its surface expression depends on NKp46 (NCR1) (164,165). Notably, NKp46$^+$ ILC3s can undergo phenotypic conversion into ILC1s, including pre-ILC3 cells, accompanied by reduced RORγt expression and increased T-bet and Notch signaling (36,166). Therefore, further studies are required to determine whether human ILC3s maintain lineage stability during *in vitro* culture or acquire TRAIL expression through differentiation toward ILC1-like states. Clarifying this issue will help define the precise mechanisms by which human ILC3s contribute to antitumor immunity.

Psoriasis. Psoriasis is a chronic inflammatory skin disease predominantly associated with Th17 responses (167) (Fig. 4). In psoriasis, both ILC1 and ILC3 populations are increased, whereas expansion of ILC2s is relatively limited (168). Notably, IL-17- and IL-22-producing NCR$^+$ ILC3s are markedly increased in both peripheral blood and lesional skin from affected patients (169). These NCR$^+$ ILC3s express cutaneous lymphocyte-associated antigen and their abundance in non-lesional skin is already higher compared with that in healthy controls, suggesting that they may contribute to disease initiation and early pathogenesis (170). Psoriatic inflammation driven by Th17 and ILC3 responses can be attenuated by biologic therapies targeting IL-23 (124). Mechanistic studies have shown that ILC3s within psoriatic lesions express CD200R1. In mouse models, CD200R1 signaling enhances IL-23-induced IL-17 production by promoting STAT3 phosphorylation, while IL-23 itself induces CD200R1 expression on ILC3s, establishing a positive regulatory loop (171). Clinical specimen analyses have further revealed increased CXCL16 expression in monocytes and skin cells from patients with psoriasis, together with elevated expression of CXCR6, the receptor for CXCL16, on ILC3s. These findings suggest that the CXCL16-CXCR6 axis may promote recruitment of proinflammatory ILC3s into skin tissues, thereby exacerbating psoriatic inflammation (172).

Role of ILC3s in wound healing and hair follicle neogenesis. Following skin injury, epidermal keratinocytes activate numerous signaling pathways that coordinate immune cell recruitment and tissue regeneration (Fig. 4). Animal studies have shown that, during the early phase of injury, Notch1 activation induces the expression of chemokines such as CCL20, thereby recruiting CCR6$^+$ ILC3s to the dermis surrounding the wound (173). These recruited ILC3s promote early macrophage infiltration through CCL3 secretion and participate in local inflammatory regulation through IL-17F production (173). Meanwhile, mouse models have demonstrated that injury-induced nuclear factor erythroid 2-related factor 2 (Nrf2) activation directly promotes CCL2 transcription, thereby recruiting F4/80$^+$ macrophages to the wound site (174). Following CCL2 stimulation, these macrophages produce EGF, which promotes keratinocyte proliferation through a feedback loop and accelerates re-epithelialization (174). During the remodeling phase of wound repair, ~7-12 days after injury, microenvironmental changes such as

reduced bone morphogenetic protein signaling induce phenotypic transition of macrophages. Infiltrating CX3CR1$^{lo/med}$ CCR2^{+} cells gradually differentiate into CX3CR1^{hi}CCR2^{+} macrophages, which subsequently accumulate around hair follicles. Using a dual-reporter lineage-tracing system, Rahmani *et al* (175) demonstrated that this macrophage subset expresses high levels of TNF-α and TGF-β1. Consistent with this, the functional requirement of macrophage-derived TNF-α in wound-induced hair follicle regeneration has been further supported by an independent study (176). Macrophage-derived TNF-α activates Akt/β-catenin signaling, which directly stimulates Lgr5^{+} hair follicle stem cells and initiates wound-induced hair follicle neogenesis, thereby promoting hair follicle cycling and post-injury regeneration (176).

By contrast, TGF-β1 maintains local macrophage survival and chemotaxis through CX3CR1 signaling, indirectly supporting tissue regeneration (175). Consistent with the critical role of CX3CR1 in skin wound healing (177,178), Rahmani *et al* (175) demonstrated that CX3CR1 deficiency markedly reduces the CX3CR1^{hi} macrophage population and decreases local TGF-β1 expression, resulting in complete loss of hair follicle regeneration. Collectively, skin wound repair is a continuous process initiated by epidermal signals, including Notch1 and Nrf2 activation and sequentially mediated by innate immune cells such as ILC3s and macrophages. The coordinated actions of ILC3-derived CCL3 and keratinocyte-derived CCL2 facilitate timely macrophage recruitment, whereas phenotypic transition of CX3CR1^{+} macrophages and their secretion of TNF-α and TGF-β1 associate inflammatory resolution with tissue regeneration.

Conclusions and future prospects. ILC3s have emerged as an important research focus in innate immunity, particularly due to their subset diversity and interactions with the microenvironment. The present review summarizes the developmental and differentiation pathways of ILC3s, their regulatory networks and the mechanisms underlying their bidirectional interactions with the gut microbiota. In addition, the present review highlights the functional heterogeneity of ILC3s in diseases affecting the gut, liver, lung and skin, emphasizing their roles in both immune homeostasis and disease progression. These findings provide a theoretical basis and translational perspective for precise immune intervention in mucosa-associated diseases (Tables I and II).

Based on an integrated synthesis of the regulatory mechanisms governing ILC3 functions across different disease contexts, the present review proposes, to the best of our knowledge, for the first time, a systematic classification of three universal molecular switches that determine the functional outcomes of ILC3s. Collectively, current evidence supports the existence of three interconnected regulatory nodes. The first node is the T-bet/RORγt transcriptional antagonism axis. High RORγt expression maintains ILC3 lineage identity and promotes IL-17/IL-22 production, whereas increased T-bet expression directly suppresses RORC promoter activity and drives the conversion of CD127^{+} ILC3s toward an ILC1-like phenotype. Through reciprocal inhibition, these two transcription factors establish a molecular switch controlling ILC3 fate determination. In IBD, persistent IL-12 stimulation increases T-bet expression, promoting phenotypic conversion of NCR^{+} ILC3s and thereby exacerbating intestinal inflammation (15,34). The second node is the IL-12/IL-23 signaling balance axis. IL-12 preferentially activates STAT4 phosphorylation, leading to T-bet induction and promoting ILC1-like proinflammatory or antitumor functions. By contrast, IL-23 favors STAT3 activation, stabilizes RORγt expression and maintains ILC3 lineage characteristics associated with inflammatory or tumor-promoting effects (16). This balance axis is supported by evidence across a number of diseases (144,145,162,165).

The third node is the IL-22/IL-22BP axis, in which the relative balance between IL-22 and IL-22BP determines the net biological effects of IL-22 signaling. In CRC, lymphotoxin LTα1β2 suppresses IL-22BP expression in dendritic cells through NF-κB signaling, allowing for sustained IL-22 activity. Persistent IL-22 signaling subsequently activates epithelial STAT3, promoting abnormal proliferation and tumorigenesis. In CRC, IL-22BP expression is reduced in dendritic cells, partly due to diminished LTα1β2 signaling, thereby unleashing sustained IL-22 activity. Persistent IL-22 signaling subsequently activates epithelial STAT3, driving uncontrolled hyperproliferation of pre-neoplastic and neoplastic intestinal epithelial cells and promoting tumorigenesis (127,131). These three molecular switches function within a hierarchical and interconnected regulatory network. The IL-12/IL-23 balance regulates the strength of T-bet/RORγt antagonism through differential STAT activation. This transcriptional equilibrium subsequently influences IL-22 production and alters the IL-22/IL-22BP balance. Meanwhile, upstream environmental signals, including gut microbial metabolites, RA, neural signals and circadian rhythms, can reset these regulatory states by reshaping cellular metabolism or modulating cytokine production, ultimately determining ILC3 functional outcomes during infection, chronic inflammation and tumor development.

Based on the aforementioned three-tier molecular regulatory network, the present review proposes three experimentally testable hypotheses. First, with regard to the T-bet/RORγt transcriptional antagonism axis, it may be hypothesized that persistent IL-12 stimulation within the IBD microenvironment drives NCR^{+} ILC3-to-ILC1 conversion through the STAT4/T-bet pathway. The present review further predicts that ILC3-specific T-bet deletion will prevent this conversion and attenuate DSS-induced intestinal inflammation. This hypothesis can be evaluated using ILC3-specific gene-targeted mice combined with flow cytometric analysis of intestinal lymphocytes and histopathological assessment. Second, regarding the IL-12/IL-23 balance axis, it may be hypothesized that an IL-23-dominant microenvironment in HCC promotes expansion of pro-tumorigenic NCR^{-} ILC3s. The present review predicts that low-dose recombinant IL-12 treatment will restore this imbalance by reducing the intratumoral NCR^{-}/NCR^{+} ILC3 ratio, enhancing CD8^{+} T-cell infiltration and suppressing tumor growth. This hypothesis can be tested using orthotopic HCC mouse models combined with immune phenotyping by flow cytometry. Third, with regard to the IL-22/IL-22BP balance axis, it may be hypothesized that reduced IL-22BP expression in the CRC microenvironment increases free IL-22 availability, thereby promoting STAT3-dependent epithelial proliferation. The present study predicts that restoration of

Table I. Functional heterogeneity of ILC3s in intestinal and liver diseases: Mechanistic evidence and translational potential.

Disease type	Key ILC3 subsets	Protective mechanisms	Pathogenic/pro-inflammatory (or pro-tumorigenic) mechanisms	Key evidence (models/clinical) and translational risks
IBD	NCR^+ ILC3, NCR^- ILC3/LTi and $MHC\text{-}II^+$ ILC3	$MHC\text{-}II^+$ ILC3 maintain intestinal immune tolerance by inducing $CD4^+$ T-cell apoptosis; their numbers are markedly reduced in children with IBD	ii) IL-12 drives NCR^+ ILC3 conversion into ILC1s, leading to increased IFN-γ production and disruption of the epithelial barrier; NCR^- ILC3/LTis secrete IL-17, which recruits neutrophils and downregulates tight junction proteins; and iii) GPR183 senses 7α,25-OHC, guiding aberrant ILC3 accumulation at inflammatory sites	Models: ILC3 deficiency exacerbates pathology in DSS colitis; adoptive transfer alleviates it; GPR183-deficient mice show reduced colonic inflammation. Clinical: In patients with IBD, intestinal NCR^+ ILC3 are decreased, while ILC1 and IL-23 levels are elevated; peripheral ILC3 activation markers (NKp44/CD56) are also increased. Translational strategies: Anti-IL-23 monoclonal antibodies; RORγt inhibitors; GPR183 antagonists. Risks: Long-term immunosuppression may increase infection risk; acute-phase IL-17 blockade may compromise barrier protection.
CRC	NCR^- ILC3 (pro-tumor), $MHC\text{-}II^+$ $CCR6^+$ ILC3 (anti-tumor) and $NKp44^+$ ILC3 (anti-tumor)	i) Epithelial IL-17D binds CD93 on ILC3s, regulating IL-22 secretion to inhibit tumorigenesis; ii) $MHC\text{-}II^+$ ILC3 activate T cells, promoting type 1 anti-tumor immunity and improving immunotherapy responses and; iii) $NKp44^+$ ILC3s promote TLS formation, which is positively associated with favorable prognosis	i) ILC3-derived IL-22 activates STAT3, promoting epithelial cell proliferation; ii) IL-22BP expression is reduced in tumor tissues, leading to dysregulated IL-22 signaling; iii) NCR^- ILC3 secrete IL-17, promoting duodenal adenoma development; iv) macrophage-derived IL-7 enhances STAT3 and AhR expression in ILC3s, increasing IL-22 production; and v) in advanced CRC, the number of $NKp44^+$ ILC3s is decreased and expression of TLS-associated genes (LTA, LTB and TNF) is downregulated, resulting in impaired TLS formation and loss of anti-tumor immune surveillance	Models: Anti-IL-22 antibody inhibits tumors in the AOM/DSS model; IL-22BP-deficient mice show increased tumor burden; MHC-II knockout impairs anti-tumor immunity. Clinical: Low IL-22BP levels in CRC tissues correlate with poor prognosis; high TLS density is associated with good prognosis; $NKp44^+$ILC3 are reduced in advanced CRC. Translational strategies: IL-22-Fc combined with immune checkpoint inhibitors; induction of TLS formation (LTβR agonists/chemokine inducers); IL-17D-CD93 agonists Risks: IL-22-Fc. requires strict control of timing and administration site to avoid pro-fibrotic and pro-tumor effects; TLS induction may trigger autoimmunity; the IL-17D-CD93 axis is mainly validated in animal models, with limited human evidence and unclear off-target effects.
NAFLD	Gut-derived ILC3	IL-22 upregulates the anti-apoptotic gene Bcl-2 in hepatocytes, inhibiting palmitate-induced apoptosis; it also suppresses SCD1 expression, thereby regulating lipid metabolism	Predominantly protective in this disease; pathogenic role is limited	Models: ILC3-deficient mice show exacerbated liver injury in the high-fat diet induced NASH model. Clinical evidence: Direct human evidence is currently lacking. Translational strategies: Target the IL-23/IL-22 axis to enhance ILC3-derived IL-22 secretion. Risks: Chronic IL-22 activation may promote fibrosis, requiring

Table I. Continued.

Disease type	Key ILC3 subsets	Protective mechanisms	Pathogenic/pro-inflammatory (or pro-tumorigenic) mechanisms	Key evidence (models/clinical) and translational risks
				differentiation between acute and chronic phases.
Liver fibrosis	IL-17A$^+$ IL-22$^+$ ILC3	Limited evidence	i) ILC3-derived IL-17A and IL-22 directly activate hepatic stellate cells, promoting collagen deposition and; ii) IL-22 suppresses IFN-γ production by T cells, indirectly exacerbating fibrosis	Models: In the CCl_4-induced fibrosis model, hepatic ILC3 numbers associate positively with fibrosis severity; adoptive transfer of ILC3 exacerbates fibrosis in RAG-deficient mice; neutralizing antibodies against IL-17A or IL-22 reduce collagen deposition. Clinical: Peripheral blood ILC3 levels are positively associated with fibrosis severity in patients with chronic hepatitis B. Translational strategies: Anti-IL-17A/IL-22 neutralizing antibodies. Risks: Complete blockade of IL-22 may abrogate its hepatoprotective functions.
HCC	NCR$^-$ ILC3 (pro-tumor) and NCR$^+$ ILC3 (potential anti-tumor subset)	Limited evidence	i) IL-23 expands the NCR$^-$ ILC3 subset and induces high IL-17 expression; ii) IL-17 recruits myeloid-derived suppressor cells and enhances their immunosuppressive activity, thereby weakening CD8$^+$ T-cell-mediated anti-tumor immunity and; iii) NCR$^-$ILC3 directly inhibit CD8$^+$ T-cell proliferation and induce their apoptosis through cell-contact-dependent mechanisms	Models: IL-23 treatment expands NCR$^-$ ILC3 and promotes tumor growth in orthotopic xenograft models; IL-17-deficient mice show reduced tumor growth and MDSC infiltration; co-culture experiments demonstrate that NCR$^-$ ILC3 directly suppress CD8$^+$ T cells. Clinical: NCR$^+$ ILC3 are associated with TLS in non-small cell lung cancer; HCC-associated data are still pending. Translational strategies: Anti-IL-23/anti-IL-17 antibodies; induction of NCR$^-$ILC3-to-ILC1 conversion. Risks: IL-17 blockade may compromise ant-iinfective immunity.

Table systematically summarizing the core ILC3 subsets, protective mechanisms and pathogenic, pro-inflammatory and pro-tumorigenic mechanisms across five key intestinal and liver diseases: IBD, CRC, NAFLD, liver fibrosis and HCC. It also compiles preclinical animal model data and clinical evidence from patient samples, as well as the translational risks of corresponding therapeutic strategies. The term 'model' refers to experimental data from animal studies, whereas 'clinical' denotes results obtained from patient-derived biospecimens. The 'translational risks' column lists the primary safety hazards of candidate therapies, including increased infection susceptibility and profibrotic and pro-tumor side effects. IBD, inflammatory bowel disease; CRC, colorectal cancer; NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma; ILC, innate lymphoid cell; NCR, natural cytotoxicity receptor; LTi, lymphoid tissue inducer; MHC, major histocompatibility complex; GPR, G-protein-coupled receptor; 7α,25-OHC, 7α,25-hydroxycholesterol; DSS, dextran sulfate sodium; NK, natural killer; ROR, retinoid-related orphan receptor; CCR, C-C motif chemokine receptor; IL-22BP, IL-22 binding protein; AOM, azoxymethane; TLS, Tertiary lymphoid structures; AhR, aryl hydrocarbon receptor; LT, lymphotoxin; NASH, non-alcoholic steatohepatitis; SCD1, stearoyl-CoA desaturase; CCl_4, carbon tetrachloride; RAG, recombination-activating gene.

IL-22BP through adeno-associated virus-mediated delivery to colonic tissues will reduce tumor burden while preserving antimicrobial defense. This hypothesis can be evaluated using the azoxymethane (AOM)/DSS CRC model together with phosphorylated STAT3 detection and tumor burden assessment (127,131).

The biological functions of ILC3s are largely determined by the dynamic balance between two key cytokine pathways,

Table II. Functional heterogeneity of ILC3s in pulmonary and skin diseases: Mechanistic evidence and translational potential.

Disease type	Key ILC3 subsets	Protective mechanisms	Pathogenic/pro-inflammatory mechanisms	Key evidence (models/clinical) and translational risks
Pulmonary infection	NCR$^+$ ILC3	i) IL-22 maintains airway epithelial integrity and promotes tissue repair; ii) IL-17 recruits neutrophils to clear extracellular bacteria (for example, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) and; iii) the IL-23-IL-17/ IL-22 axis promotes iBALT formation, enhancing local anti-tuberculosis immunity.	During influenza virus infection, excessive or premature IL-17 expression can lead to neutrophil over-infiltration and immunopathological lung tissue damage	Models: ILC3s are the predominant early source of IL-17 in the *K. pneumoniae* model; their depletion impairs bacterial clearance; in *Streptococcus pneumoniae* models, pulmonary ILC3s mediate protection through IL-22 and flagellin enhances ILC3 function; RORC-deficient mice exhibit impaired iBALT formation and increased susceptibility to tuberculosis. Clinical: Patients with RORC mutations have defective IL-17 signaling and are more susceptible to mycobacterial infections. Translational strategies: Flagellin-mediated ILC3 activation; IL-22-Fc to enhance antimicrobial defense; targeting IL-23 to promote iBALT formation. Risks: Upregulation of IL-17 may cause immunopathological tissue injury.
Asthma	IL-17$^+$ ILC3 (pro-inflam matory) and NCR$^+$ ILC3 (protective)	NCR$^+$ ILC3 serve a potential protective role in maintaining airway homeostasis; their frequency is reduced in the lungs of patients with severe asthma.	IL-17$^+$ ILC3 secrete IL-17, which induces epithelial production of the neutrophil chemoattractant CXCL8, recruiting neutrophils and exacerbating airway hyperresponsiveness and inflammation	Models: IL-17$^+$ ILC3s are increased in obese asthmatic mice and IL-17 neutralization alleviates airway hyperresponsiveness; IL-23 treatment expands IL17$^+$ ILC3 and aggravates inflammation. Clinical: NCR$^+$ ILC3s are decreased, whereas IL-17$^+$ILC3s are increased in patients with severe asthma. Translational strategies: Anti-IL-23 to suppress IL-17$^+$ ILC3s; enhancement of NCR$^+$ILC3 function. Risks: Subset-specific targeting techniques are not yet mature.
Skin cancer (melanoma)	NKp46$^+$ ILC3 (pre-ILC3)	i) In the presence of IL-12, NKp46$^+$ ILC3 initiate an inflammatory cascade, upregulate adhesion molecules, remodel tumor microvasculature and suppress tumor growth in an IL-12R- and RORγt-dependent manner; ii) NKp46$^+$ ILC3 can convert	Limited evidence	Models: Adoptive transfer of NKp46$^+$ LTi cells in the presence of IL-12 inhibits tumor growth in B16 melanoma grafts. Clinical: Human ILC3s derived from peripheral blood of healthy donors or non-cancerous liver tissue directly kill melanoma cell lines *in vitro*. Translational strategies: Combine with IL-12 to activate NKp46$^+$ ILC3; induce TRAIL expression by modulating T-bet/ Notch signaling; expand and maintain human ILC3 lineage stability *in vitro*.

Table II. Continued.

Disease type	Key ILC3 subsets	Protective mechanisms	Pathogenic/pro-inflammatory mechanisms	Key evidence (models/clinical) and translational risks
		into ILC1s (with downregulation of RORγt and upregulation of T-bet/ Notch), potentially acquiring TRAIL expression and; iii) human ILC3s induce melanoma cell apoptosis through TRAIL-TRAILR2 binding, activating caspase-8 and promoting IFN-γ secretion		Risks: Human ILC3s may convert to ILC1s during *in vitro* culture, altering their function; IL-12 combination therapy may cause systemic inflammation.
Psoriasis	NCR^+ ILC3	NCR^+ILC3s predominantly serve a pathogenic role in this disease	i) IL-23 stimulates NCR^+ ILC3s to secrete IL-17/IL-22, amplifying skin inflammation; ii) CD200R1 signaling enhances pSTAT3, promoting IL-23-driven IL-17 production and; iii) the CXCL16-CXCR6 axis mediates migration of pro-inflammatory ILCs into the skin	Models: CD200R1-knockout mice exhibit reduced IL-17 production by ILC3s and attenuated skin lesions; CD200R1 agonists exacerbate lesions. Clinical: NCR^+ ILC3 are notably increased in peripheral blood and lesional skin and produce IL-17/IL-22. Translational strategies: Anti-IL-23 monoclonal antibodies; anti-CD200R1 blocking antibodies; CXCL16-CXCR6 axis inhibitors. Risks: Long-term blockade of the IL-23/IL-17 pathway may increase susceptibility to infections.
Skin wound healing	$CCR6^+$ ILC3	i) Early after injury, Notch1 activation upregulates CCL20, recruiting $CCR6^+$ ILC3 to the dermis surrounding the wound; ii) ILC3s secrete CCL3 to promote early macrophage infiltration and IL-17F participates in local inflammatory regulation and; iii) under CCL2 stimulation, macrophages produce EGF, promoting keratinocyte proliferation and re-epithelialization	Uncontrolled inflammatory responses during this process may lead to pathological scar formation	Models: Notch1 activation upregulates CCL20, driving $CCR6^+$ILC3 recruitment; Nrf2 activation upregulates CCL2, driving macrophage recruitment. Clinical: Clinical sample data are limited, with the majority of evidence derived from animal models. Translational strategies: Enhance ILC3 recruitment (CCL20/Notch1 agonists); combine with macrophage modulation (for example, Ccl2/Nrf2 signaling modulation); promote phenotypic transition of $CX3CR1^+$ macrophages. Risks: Excessive inflammation may lead to scar formation.

Table systematically summarizing disease-specific key ILC3 subsets, their protective and pro-inflammatory/pathogenic mechanisms across five pulmonary and cutaneous disorders: Pulmonary infection, asthma, melanoma, psoriasis and skin wound healing. It further integrates preclinical animal model data, human clinical specimen evidence, as well as corresponding therapeutic strategies and translational risks. The translational risk section lists major safety drawbacks, such as tissue inflammatory injury, ILC3 phenotypic conversion and increased infection susceptibility induced by pathway blockade. ILC, innate lymphoid cell; NCR, natural cytotoxicity receptor; iBALT, inducible bronchus-associated lymphoid tissue ROR, RAR-related orphan receptor; NK, natural killer; LTi, lymphoid tissue inducer; IL-12R, IL-12 receptor; ROR, retinoid-related orphan receptor; T-bet, T-box expressed in T cells; TRAIL, TNF-related apoptosis-inducing ligand; pSTAT3, phosphorylated STAT3; CXCL, chemokine (C-X-C motif) ligand; CXCR, C-X-C chemokine receptor type; CCR, C-C motif chemokine receptor; CCL, C-C motif chemokine ligand; Nrf2, nuclear factor erythroid 2-related factor 2; CX3CR1, C-X3-C motif chemokine receptor 1.

namely IL-17 and IL-22. Therefore, ILC3-mediated disease outcomes are not determined solely by ILC3 abundance, but rather by the balance between IL-17 and IL-22 production, the nature of upstream stimuli and the local immune microenvironment. Based on the integrated analysis of pathological features and multilayer regulatory networks across diseases, the present review proposes a 'spatiotemporal-quantitative' three-dimensional framework to interpret the context-dependent functional outcomes of ILC3s. This framework describes the dynamic transition between protective and pathogenic states through three dimensions. The first dimension is the disease phase. During acute injury, ILC3s primarily contribute to barrier defense through IL-22 production. However, prolonged stimulation reshapes ILC3 plasticity and promotes conversion toward ILC1-like or ILCreg states, with persistent IL-17/IL-22 signaling contributing to pathological progression. The second dimension is the tissue microenvironment. Organ-specific signals, including gut microbial metabolites, hepatic lipid signals, cutaneous neuropeptides, local chemokines and circadian rhythms, differentially regulate ILC3 recruitment, activation and functional polarization. The third dimension is signal dosage. Effector molecules such as IL-17 and IL-22 exhibit concentration-dependent effects: Physiological levels support antimicrobial defense and epithelial repair, whereas sustained excessive activation promotes inflammation, excessive epithelial proliferation and tumor progression. Collectively, these findings indicate that ILC3s do not possess an intrinsically fixed pro-inflammatory or anti-inflammatory identity. Instead, their functional state may represent an integrated outcome determined by multidimensional environmental signals. This three-dimensional framework integrates previously fragmented findings from IBD, solid tumors, metabolic liver diseases and infectious immunity into a unified conceptual model. It provides one perspective for understanding the context-dependent functions of ILC3s and establishes a theoretical foundation for developing subset-specific therapeutic strategies.

Based on the three-dimensional analytical framework, the present study further proposes an integrative quantitative hypothesis whereby the IL-17/IL-22 secretion ratio of ILC3s may serve as a quantitative indicator of their functional polarity. Specifically, it may be hypothesized that during acute infection or tissue injury, the IL-22/IL-17 ratio increases and is positively associated with epithelial repair and pathogen clearance, whereas IL-22 neutralization delays tissue repair. Conversely, during chronic inflammation and tumor progression, the IL-17/IL-22 ratio gradually increases and is associated with IBD histopathological severity and CRC tumor burden. IL-23 blockade is predicted to reduce this ratio and alleviate tissue damage. This hypothesis can be evaluated through time-course analyses using DSS-induced colitis, AOM/DSS CRC and *Streptococcus pneumoniae* infection models. ILC3s isolated from tissues at acute and chronic stages can be analyzed by intracellular cytokine staining and flow cytometry. Intervention groups involving ILC3 depletion, IL-22 neutralization and IL-23 blockade should be included to establish causal associations between cytokine ratios and pathological outcomes.

The regulation of ILC3 plasticity is not mediated by isolated signaling pathways, but rather by the integration of multilayered signals through three key molecular hubs: mTOR, STAT3 and AHR. The mTOR complex functions as a metabolic-transcriptional regulatory hub. It senses extracellular metabolic signals, including microbiota-derived SCFA signals through FFAR2 (92), as well as intracellular changes in amino acid availability and energy status. Through the mTORC1/HIF-1α pathway, mTOR signaling stabilizes RORγt expression, promotes glycolysis and regulates mitochondrial ROS production, thereby supporting ILC3 lineage stability and effector functions (65). When mTORC1 activity is impaired, mTORC2 can undergo compensatory activation, partially restoring ILC3 numbers and preserving intestinal antimicrobial defense (66). STAT3 represents a common downstream signaling component of neural, microbial and inflammatory pathways. Enteric glial cells release GDNF, which activates RET and induces STAT3 phosphorylation through the p38 MAPK/ERK-Akt pathway (78). In parallel, sympathetic nerve-derived norepinephrine activates ADRB2 and enhances STAT3 activity, with both neural pathways promoting IL-22 transcription (81). In addition, IL-23-mediated inflammatory stimulation can directly activate STAT3 and further enhance IL-22 responses (16). AHR functions as a direct sensor of microbiota-derived tryptophan metabolites. Binding of indole derivatives to AHR initiates IL-22 transcriptional programs (88,89), while AHR activity can also be modulated by intracellular metabolic and inflammatory signals such as IL-1β (91). Collectively, mTOR, STAT3 and AHR form an interconnected regulatory network that integrates microbial, neural, metabolic and inflammatory signals to determine ILC3 lineage identity and effector output.

Despite mouse models having provided important insights into ILC3 biology, notable phenotypic and functional differences exist between human and murine ILC3s. Human NCR^+ ILC3s are defined primarily by NKp44 expression, whereas murine NCR^+ ILC3s are characterized by NKp46 expression (33-35) In addition, human NCR^- ILC3s express CD117, whereas murine NCR^- ILC3s lack this marker (35). Furthermore, TRAIL is predominantly expressed by NK cells and ILC1s in mice, whereas human ILC3s can directly express TRAIL and mediate antitumor effects (163-165). These interspecies differences represent a key challenge in translating basic ILC3 research into clinical applications. Therefore, clinical development of ILC3-targeting strategies requires precise characterization of human ILC3 subsets using integrated single-cell multi-omics approaches and primary patient-derived samples. In addition, humanized mouse models and organoid-ILC3 coculture systems should be prioritized to improve recapitulation of human physiology and facilitate clinically relevant translational studies.

In addition to classical proinflammatory ILC3s, the discovery of ILCregs has expanded the understanding of mucosal immune regulation. These two populations form a complementary regulatory system in the gut: ILCregs suppress excessive activation of ILC1s and ILC3s through IL-10 while preserving protective IL-22 secretion by ILC3s, thereby contributing to the resolution of intestinal inflammation (12). This regulatory pathway functions independently of Treg cells and represents a specialized tolerance mechanism within innate immunity. However, in the tumor microenvironment, TGF-β can alter this balance. Current evidence

Table III. Summary of completed and ongoing clinical trials targeting ILC3-associated signaling pathways.

Target/drug Class	Drug name	Mechanism of action	Indication	Clinical trial phase	Key endpoints and findings	Development status
Anti-IL-23	Risankizumab	Anti-IL-23 p19 monoclonal antibody; selectively blocks IL-23 pathway	Moderate-to-severe Crohn's disease	Phase III (SEQUENCE)	Incidence of SAE was 10.3 vs. 17.4% for ustekinumab; serious infection rates were 3.1 vs. 4.2%, respectively	Completed
Anti-IL-23	Ustekinumab	Anti-IL-12/IL-23 p40 monoclonal antibody; dual blockade of IL-12/IL-23 pathways	Moderate-to-severe Crohn's disease	Phase III (SEQUENCE)	SAE rate 17.4%; serious infection rate 4.2%; served as active comparator against risankizumab	Completed
RORγt inhibitor	BI 730357	Oral small-molecule RORγt transcriptional inhibitor; blocks IL-17-driven pro-inflammatory pathway	Moderate-to-severe plaque psoriasis with inadequate response to TNF inhibitors	Phase II dose-ranging trial	PASI75 response rate at week 12 was only 30% at the 200 mg dose, with no additional efficacy at higher doses (plateau effect); overall drug-associated AEs ≤15.8%; nonclinical toxicology identified potential human carcinogenicity risk	Phase II main trial completed; long-term extension and full development discontinued
GPR183 antagonist	Compound 33	Selective small-molecule GPR183 antagonist; blocks ILC3 intestinal chemotactic infiltration	DSS-induced experimental colitis in mice	Preclinical only	Dose-dependent inhibition of aberrant ILC3 intestinal recruitment and colonic inflammation; weak hERG inhibition with high target selectivity and low potential cardiotoxicity	Preclinical candidate; no human trials initiated
IL-22-Fc fusion protein	Efmarodocokin alfa	IL-22 fusion protein; exogenously supplies protective IL-22 and upregulates mucosal repair markers	Moderate-to-severe ulcerative colitis with prior standard-of-care failure	Phase II (YELLOWSTONE)	Clinical remission rates at week 8 were 12, 9 and 12% for the 30, 60 and 90 μg/kg dose groups, respectively, vs. 9% for placebo; no significant	Phase II terminated; no further clinical development

Table III. Continued.

Target/drug Class	Drug name	Mechanism of action	Indication	Clinical trial phase	Key endpoints and findings	Development status
					difference in endoscopic healing; trial terminated early for futility	

Table summarizing monoclonal antibodies, small-molecule inhibitors and cytokine fusion proteins targeting the core regulatory axes of ILC3s (IL-23, RORγt, GPR183 and IL-22). It records the mechanism of action of each candidate drug and covers human clinical indications including Crohn's disease, plaque psoriasis and ulcerative colitis, as well as the preclinical DSS-induced experimental colitis model. Trials are classified as preclinical animal studies, Phase II and Phase III human clinical trials, with key efficacy endpoints, safety profiles and final development outcomes (completed, discontinued or preclinical candidate) listed together. DSS, dextran sulfate sodium; AE, adverse event; SAE, severe AE; ILC, innate lymphoid cell; ROR, retinoid-related orphan receptor; hERG, human Ether-à-go-go-related gene; GPR, G-protein-coupled receptor; PASI, Psoriasis Area and Severity Index.

indicates that ILC3s can transdifferentiate into ILCregs, which subsequently produce high levels of IL-10, establish an immunosuppressive microenvironment and promote tumor immune evasion (14). These findings suggest that ILCreg functions are strongly influenced by the surrounding microenvironment, with protective roles during inflammatory responses but tumor-promoting effects in malignant settings. Therefore, classification of ILC3s and ILCregs as simply proinflammatory or anti-inflammatory populations does not fully reflect their biological plasticity. Further investigation is required to identify the upstream signals controlling the balance between these populations and to develop strategies for targeted intervention. However, the majority of current evidence is derived from mouse models and the lineage characteristics, differentiation mechanisms and functional roles of human ILCregs in inflammation and cancer remain to be systematically defined. Future studies should aim to integrate humanized mouse models, organoid systems and clinical samples to investigate cross-species conservation and microenvironment-driven transdifferentiation mechanisms.

From the perspective of current translational strategies, three key therapeutic approaches can be considered. The first involves upstream signaling inhibitors that target key regulators of ILC3 activation and lineage plasticity, including IL-23 and RORγt. Anti-IL-23 monoclonal antibodies inhibit inflammatory pathways associated with excessive ILC3 activation and have demonstrated improved efficacy compared with conventional anti-TNF monoclonal antibodies in IBDs such as CD (179). In the phase III SEQUENCE head-to-head trial in patients with moderate-to-severe Crohn's disease refractory to anti-TNF therapy, the p19-specific anti-IL-23 monoclonal antibody risankizumab demonstrated superiority in endoscopic remission compared with ustekinumab (which targets the shared p40 subunit of IL-12/IL-23), with rates of 31.8 vs. 16.2% ($P<0.001$). Safety profiles were acceptable, with comparable serious infection rates (3.1 vs. 4.2%) and lower serious adverse events with risankizumab (10.3 vs. 17.4%) (179). These clinical findings support the therapeutic potential of selective IL-23-p19 inhibition, a pathway central to ILC3-driven intestinal immunopathology (179). A Bayesian network meta-analysis of 22 randomized controlled trials further demonstrated that risankizumab exhibited the lowest overall risks of adverse events, serious adverse events and serious infections during the induction phase among evaluated biologic agents for IBD (180). Notably, this safety advantage was observed only during induction therapy and not reproduced in the maintenance-phase comparisons. This meta-analytic evidence is mechanistically relevant to the present review, as risankizumab selectively targets the IL-23 p19 subunit, a key upstream cytokine that drives ILC3-mediated intestinal immunopathology. Thus, these findings complement the head-to-head SEQUENCE trial by providing aggregated population-level evidence from multiple randomized controlled trials (180). By contrast, the oral RORγt inhibitor BI 730357 exhibited only modest efficacy in a phase II plaque-psoriasis trial: At the highest tested dose (200 mg once daily), only 30.0% of patients achieved PASI75 at week 12 vs. 0% with placebo, and the exposure-response relationship plateaued at doses ≥200 mg, suggesting that robust clinical responses are unlikely to be attained even at further elevated drug exposures. Although the safety profile was acceptable during the 12-week induction phase (drug-related adverse events ≤15.8%), long-term development was discontinued as a non-clinical toxicology study identified potential human carcinogenic risks that could not be ruled out (181). As RORγt acts as a shared lineage-defining transcription factor for both Th17 cells and ILC3s, pharmacological inhibition of this protein constitutes an alternative therapeutic approach targeting the IL-23/IL-17/IL-22 axis upstream of direct cytokine neutralization. The modest clinical activity and exposure-response plateau observed for BI 730357 therefore indicate that complete RORγt suppression may be insufficient to fully abrogate IL-17-driven inflammation, while potentially disrupting ILC3-dependent epithelial-barrier protection. These observations underscore the inherent complexity of therapeutically targeting this transcription factor in ILC3-associated intestinal immunopathology (181).

Despite these two drug classes differing in molecular type, both intervene at upstream nodes of the IL-23/IL-17 axis. The

differential efficacy observed between them highlights notable differences between cytokine-targeting strategies (anti-IL-23) and transcription factor-targeting strategies (RORγt inhibitors) in terms of signaling blockade completeness and functional selectivity. A novel small-molecule GPR183 antagonist, which inhibits aberrant ILC3 recruitment mediated by chemotactic signals, has demonstrated dose-dependent intestinal anti-inflammatory activity in a DSS-induced mouse colitis model, supporting its potential for further preclinical development (182). The second category comprises effector molecule-targeted approaches, which regulate downstream inflammatory and tissue repair processes through supplementation or neutralization of specific effector molecules. IL-22-Fc fusion proteins provide exogenous IL-22 and have demonstrated mucosal repair effects in animal models of colitis. However, a phase II clinical trial in UC failed to meet the prespecified primary endpoints. Although target engagement was confirmed by dose-dependent elevations of circulating REG3A biomarker, therapeutic supplementation with IL-22-Fc fusion protein (efmarodocokin alfa) alone proved insufficient to overcome the complex inflammatory mucosal microenvironment (183). This trial enrolled 195 patients with moderate-to-severe ulcerative colitis. At week 8, clinical-remission rates for efmarodocokin alfa were 12, 9 and 12% in the 30, 60 and 90 μg/kg dose cohorts respectively, vs. 9% in the placebo arm. None of these differences met the study-pre-specified statistical threshold for significance of $P<0.2$. Rates of endoscopic healing were likewise comparable to placebo, and the trial was terminated early following pre-defined futility analysis (183). These observations indicate that isolated IL-22 agonism is not sufficient to drive meaningful clinical improvement in moderate-to-severe human ulcerative colitis, despite mechanistic expectation from pre-clinical models. The third category involves microenvironment-remodeling strategies, which indirectly regulate ILC3 differentiation and function through metabolic and neural signals, including SCFAs, vitamin D supplementation and modulation of the GDNF neuroimmune pathway. However, these microenvironment-remodeling strategies remain largely at the preclinical stage, with most evidence derived from murine models. The complexity of *in vivo* regulatory networks, coupled with insufficient tissue-targeting capacity and a lack of validated biomarkers, has limited their translation into human trials. Consequently, human clinical data are currently scarce, and substantial further investigation is required prior to clinical translation.

Collectively, clinical evidence from these three therapeutic categories indicates that current ILC3-targeted translation faces two key challenges: Variable therapeutic efficacy and long-term safety concerns. Anti-IL-23 monoclonal antibodies demonstrate the most favorable safety profile but are mainly applicable to inflammatory conditions dominated by IL-23 signaling. RORγt inhibitors face limitations associated with efficacy ceilings and potential carcinogenic risks. IL-22 supplementation alone appears insufficient to overcome the immunosuppressive microenvironment associated with tumors and chronic inflammation. Collectively, these findings suggest that future ILC3-targeted therapies should move beyond broad-spectrum single-pathway inhibition toward stratified precision interventions guided by the three molecular switches proposed in the present review. Therefore, future clinical trial designs should also incorporate systematic evaluation of long-term safety outcomes, including infection and malignancy risks (Table III).

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Availability of data and materials

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Authors' contributions

JZ and PZ prepared the figures and drafted the manuscript. XL, JL, LQ, JC, XH, MZ, JL, XZ, JD, GT, YPT and YF conceived the present study and performed the literature analysis. YT, LB and PZ edited and revised the manuscript. All authors listed have made notable, direct and intellectual contributions to the present work and approved it for publication. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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