

Deciphering the Role of Innate Lymphoid Cells Group 3 in the Gut Microenvironment: A Narrative Review of Their Novel Contributions to Autoimmune Disease Pathogenesis

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Abstract: Type 3 Innate lymphoid cells (ILC3s) play a crucial role in intestinal immune function by serving as an innate effector that contributes to early-life defense against pathogens and helps protect the intestines from bacterial infections. ILC3s exert their immune function through cytokine secretion, patrolling actions and the generation of memory ILC3s that aid in repairing epithelial tissue and preserving mucosal barrier integrity. Moreover, dysregulation of ILC3s function has been implicated in the pathogenesis and progression of autoimmune diseases. This comprehensive review aims to explore the interactions between gut microbes, gut microbial metabolites, and diet in relation to ILC3s within the context of the gut microenvironment. Furthermore, the gut microenvironment has the potential to influence distant extra-intestinal sites through immunomodulation, thereby modifying their risk of inflammation. The gut has emerged as a significant focus of autoimmune disease research in recent years. However, the relationship between gut ILC3s and autoimmune diseases remains poorly understood. This paper aims to examine the potential association between ILC3s and autoimmune diseases.

Keywords: ILC3s, IL-22, short-chain fatty acids, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis

Introduction

Innate Lymphoid cells (ILCs) represent a group of lymphocytes with important effector and regulatory functions in innate immunity and tissue remodeling, of which ILC3s is an important class.¹ ILC3s are capable of producing IL-17, IL-22 and granulocyte-macrophage colony-stimulating factor (GM-CSF), and are recognized by their expression of the transcription factor ROR γ t.² In addition, transcription factors can also clarify the identity of ILC3 and maintain its function, such as GATA3,³ Zbtb1,⁴ HIF-1,⁵ etc. ILC3s are predominantly localized on mucosal surfaces, including the gut, lung, and skin,^{6,7} serving as crucial innate effect in early-life defence against pathogens. ILC3s primarily produce IL-22 to safeguard intestinal immunity. IL-22 acts as a potent inducer of mucins, large glycoproteins that form a thick, normally impenetrable barrier on the mucosal surface.⁸ Additionally, IL-22 promotes the differentiation and proliferation of Paneth cells through the PI3K/AKT/mTOR axis.⁹ These cells secrete various antimicrobial molecules, including defensins and antimicrobial peptides (AMPs). ILC3s localization exhibit rapid responsiveness to environmental and pathogenic signals. Villous ILC3s, which are predominantly immobile during homeostasis, can acquire migratory “patrolling” properties and enhance cytokine expression in response to inflammation.¹⁰ During bacterial infections, ILC3s-derived IL-22 clears bacteria by regulating the expression of antimicrobial genes in the epithelium.¹¹ Recent evidence suggests that ILC3s possess memory properties, and exposure to pathogenic bacteria results in the generation of a highly functional and persistent ILC3s subpopulation, akin to memory T cells. These memory-like ILC3s exhibit a preferential expansion upon

re-encounter with pathogens and produce substantial amounts of IL-22, thereby contributing to long-term mucosal defense.¹²

ILC3s show a strong correlation with the pathogenesis of autoimmune diseases, such as inflammatory bowel disease (IBD).¹³ However, their mechanism of action in other autoimmune diseases such as Rheumatoid arthritis(RA),¹⁴ Systemic lupus erythematosus (SLE),¹⁵ are fully controversial. This article provides a thorough overview of the role of ILC3s and associated cytokines in maintaining intestinal immune homeostasis, the impact of the intestinal micro-environment on ILC3s functions that may contribute to the pathogenesis of autoimmune disease.

Cell Classification

Lymphocytes are categorized into two groups based on their ability to recognize specific antigens: acquired immune cells and ILCs.¹⁶ ILCs represent a group of lymphocytes with important effector and regulatory functions in innate immunity and tissue remodeling.¹ This innate lymphocyte family includes various subpopulations, including Group 1 ILCs (ILC1s), Group 2 ILCs (ILC2s), Group 3 ILCs (ILC3s), lymphoid tissue inducers (LTi) and Natural killer (NK) cells.¹⁷ Each subtype of ILCs possesses distinct transcription factor requirements and cytokine production capacities, influencing their roles in various immune responses.¹⁸

ILC1s and NK cells constitute closely related subsets within the ILC family, distinguished by their expression of the transcription factor T-bet and their ability to produce Interferon- γ (IFN- γ).¹⁹ Although NK cells and ILC1s have historically been considered as functionally distinct cell types, ILCs are primarily found residing within tissue, in contrast to NK cells, which are mainly circulating in the bloodstream.^{20,21} ILC2s secrete type 2 cytokines, such as IL-5 and IL-13, in response to cytokines like IL-33. These cytokines contribute to tissue repair and defense against helminth infections.²² ILC3s are recognized by their expression of the transcription factor ROR γ t and cytokines such as IL-17, IL-22, and granulocyte-macrophage colony-stimulating factor (GM-CSF).² LTi cells, which emerge early in embryogenesis are involved in secondary lymphoid organogenesis, T-cell tolerance, and T- and B-cell function.²³ Although it has been suggested that LTi could be categorized within ILC3s due to their mutual requirement for ROR γ t expression for both their development and function, LTi/LTi-like cells are now acknowledged as a distinct population. This distinction is based on their unique gene expression pattern and their development from precursors that are different from the precursors of all other ILCs and conventional natural killer (cNK) cells.^{24,25}

ILC3s are derived from fetal liver and bone marrow progenitors that colonize the intestine during embryonic development and early postnatal life.²⁴ ILC3s can be further classified into distinct subgroups with significant differences in tissue localization, transcriptional regulation, cell surface phenotypes and biological functions. The identification of subpopulations of ILC3s for mice is mainly based on the expression of two cellular markers, CD196 (CCR6) and CD335 (Nkp46), and there are three basic populations of mouse ILC3s: Nkp46+CCR6- (NCR+), Nkp46-CCR6- (NCR-) and Nkp46-CCR6+ (CCR6+ LTi-like) ILC3s.^{2,26} NCR+ ILC3s express mainly IL-22 and less IL-17, NCR-ILC3 expresses mainly IL-17 and less IL-22.²⁷ Furthermore, NCR+ ILC3s exhibit transcriptional expression of T-bet, which is essential for the expression of Nkp46 and the production of IFN- γ by ILC1s.²⁸ CCR6+ LTi-like cells are predominantly located within crypt plaques (CP) and mature isolated lymphoid follicles (ILF), and have been demonstrated to promote the formation of lymph nodes and Peyer's patches.²⁹

Transcription Factors

Transcription Growth Factors

ILC3s represent the predominant subpopulation of gut-resident ILCs. The development and function of ILC3s are dependent on transcription factors, including GATA3, ROR γ t, Zbtb1, Id2, and others^{3,30–32} (Table 1).

GATA3

GATA3 is essential for the promotion of the development of multiple ILC subpopulations, including ILC3s, and for the maintenance of ILC1s and ILC2s.³ GATA3 plays a crucial role in maintaining the equilibrium of ILC3s through its influence on IL-7R α expression, which is a pivotal process in the development, maintenance and proliferation of ILC3s. GATA3 binds to a region within intron 2 of the *Il7r* gene, exhibiting a binding pattern that is highly similar to that

Table 1 Transcription Factors Have Been Demonstrated to Promote the Development and Function of ILC3s

Transcription factor	Effect	Reference
GATA3	1. GATA3 is essential for the promotion of the development of multiple ILC3s subpopulations. 2. IL-7R α expression in ILC3s requires sustained expression of GATA3. 3. Gata3 is indispensable for the innate immune response against <i>B. Rodentia</i> infection. 4. GATA3 positively regulates NKp46+ ILC3s-specific genes but negatively regulates most CCR6+ ILC3-specific genes.	[3,33–35]
ROR- γ t	1. The secretion of IL-17 and IL-22 by ILC3s is dependent on the expression of ROR γ t. Furthermore, ROR γ t is a transcription factor that is required for the development of ILC3s.	[30,36]
Zbtb1	1. Zbtb1 has been identified as a crucial transcription factor essential for the generation of NKp46+ ILC3 cells.	[4]
Id2	1. The gene Id2 is expressed in all ILC subpopulations and is essential for their development. It is thought that Id2 plays a pivotal role in determining the fate of ILCs.	[32]
Nfil3	1. Nfil3 plays a pivotal role in the development of ILCs subpopulations, which are crucial for intestinal immunoprotection, as well as the high levels of Nfil3 expression observed in all ILCs populations	[37,38]
Batf	1. Given its pivotal role in ILCs haematopoiesis, Batf exerts a profound influence on the differentiation of all ILC subpopulations, including ILC3s subpopulations	[39]

Abbreviations: GATA3, GATA binding protein 3; ILC3s, Group 3 innate lymphoid cells; IL-7R α , IL-7Ralpha; IL-17, Interleukin 17; Zbtb1, Zinc finger and BTB domain containing 1; Id2, Inhibitor of binding or differentiation 2; Nfil3, Nuclear-factor, interleukin 3 regulated; Batf, Basic leucine zipper ATF-like transcription factor.

observed in ILC3s, ILC2s and Th2 cells.³³ While GATA3 has been demonstrated to positively regulate the expression of genes specific to the NKp46+ ILC3s subset, it has also been shown to exert a negative regulatory effect on the expression of genes specific to the CCR6+ ILC3s subset and lymphoid tissue inducer (LTi)-specific genes in NKp46+ ILC3s. Furthermore, GATA3 is essential for the production of IL-22 in both LTi and NKp46+ ILC3s.³⁴ In the absence of Gata3, there was a reduction in the expression of the antimicrobial peptide Regi γ by intestinal epithelial cells.³³

Zbtb1

Zinc finger and BTB domain containing 1 (Zbtb1) plays a crucial role in lymphocyte development.⁴ Zbtb1 has been demonstrated to prevent DNA damage in cell lines by initiating trans-damage DNA synthesis in response to replication stress. Conversely, deletion of Zbtb1 has been observed to result in increased DNA damage and activation of p53-dependent apoptosis in immune progenitor cells, thereby affecting lymphocyte.⁴⁰ Although Zbtb1 is commonly expressed in different ILC subpopulations, its presence has been shown to significantly impact the production of NKp46+ILC3s. Zbtb1 has been identified as a crucial transcription factor essential for the generation of NKp46+ ILC3s. The deletion of Zbtb1 has been observed to impair the production of IFN- γ by ILC3s, while its absence does not affect the ILC3s' capacity to secrete IL22.³¹

Nfil3

Nfil3 (also known as E4BP4) is a basic leucine zipper transcription factor that has been demonstrated to regulate a range of cellular processes in lymphocyte subpopulations. Nfil3 plays a pivotal role in the development of ILCs subpopulations, which are crucial for intestinal immunoprotection, as well as the high levels of Nfil3 expression observed in all ILC populations.³⁷ Nfil3 is responsible for the development and/or maintenance of ILC3s in a cell-intrinsic manner. The expression of Nfil3 increases continuously from the CLP to the ILCP to the mature ILC3s stages, with the highest levels of Nfil3 observed in intestinal ILC3s. Nfil3 is indispensable for the progression from the CLP to ILCP stages. It can therefore be postulated that the expression of Nfil3 may precede that of ROR γ t and Gata3, and that it may regulate the expression of ROR γ t and Gata3.^{37,38}

Maintenance Function

ILC3s represent the predominant subpopulation of gut-resident ILCs and are instrumental in the pathogenesis of infection and the process of tissue repair. However, the mechanisms by which they adapt to the intestinal environment to maintain tissue residency remain unclear, and some common transcription factors are summarized for reference in this section.⁴¹

HIF-1

One of the principal mechanisms of cellular adaptation to hypoxia is the activation of hypoxia-inducible factor (HIF)-1, which is expressed in the majority of cells within the immune system, as well as in the IEC.⁵ ILC3s are highly prevalent in the intestinal mucosa, and thus the elevation in ROR γ t expression and transcriptional capacity by HIF-1 facilitates the proliferation and activation of ILC3s under hypoxic conditions, which is crucial for maintaining barrier homeostasis.⁴² It has been demonstrated that hyperbaric oxygen therapy reduces the abundance of ILC3s and its IL-22 production, and stimulates the HIF-1 α -IL-22 signalling axis in ILC3s, thereby impairing host immunity.⁴³ Furthermore, HIF-1 α plays a role in the conversion of ILC3s to ILC1s in NKp46+ cells. It has been demonstrated that HIF-1 α can maintain ILC3s status in intestinal NKp46+ cells by reducing T-bet expression when HIF-1 α is absent.⁴⁴ Genetic deletion of HIF-1 α selectively within ILC3s progenitors results in impaired IL-17 and IL-22 secretion *in vivo*.⁴⁰ This deficiency corresponds with reduced expression of epithelial target genes and heightened susceptibility to enteric microbial infections.⁴⁰ In contrast, HIF-1 α ablation solely within NCR+ILC3s precludes conversion to inflammatory ILC1s, thereby preventing dextran sodium sulfate colitis-exacerbated intestinal damage.³⁸

C-Maf

C-Maf has been identified as a pleiotropic regulator of effector programming in adaptive and innate-like lymphocytes.⁴⁵ A transcriptomic analysis of ILC subpopulations revealed that c-Maf was the most highly expressed gene in ILC3s,⁴⁶ suggesting that c-Maf may have a function in this spectrum.

NCR+ ILC3s possess plasticity, undergoing full conversion to ILC1s status upon acquiring a type 1 effector profile.⁴⁷ C-Maf establishes physiological equilibrium between type 1 and type 3 effector states in steady-state NCR+ ILC3s by suppressing type 1 signatures and limiting conversion to physiological ILC1s.⁴⁷ Recent investigations employing ILCs network analyses have demonstrated that c-Maf plays a regulatory role in maintaining the equilibrium between ILC3s and ILC1s populations within the intestinal mucosa.⁴⁸ C-Maf engages in a negative feedback loop with T-bet to solidify ILC3s identity, while also restricting functions of Runx3 and TCF-1 that may drive type 1 transition in wild-type NCR+ ILC3s.⁴⁹

The NF- κ B and Notch signalling pathways, which are activated by IL-1 β and IL-18, respectively, represent potent exogenous enhancers of c-Maf expression in CCR6-ILC3s. And C-Maf forms a negative feedback loop with T-bet to preserve the identity of CCR6 ILC3s.⁴⁹ C-Maf has been demonstrated to enhance ILC3 accessibility and to bolster ROR γ t activity.

Gut Microenvironment and ILC3s

Establishing a balanced gut microbiota interacting homeostatically with the intestinal epithelial barrier proves integral to preserving normal enteric functioning.⁵⁰ However, disturbances stemming from genetic, environmental, dietary shifts or inflammatory states can incite dysbiosis of the resident microbiota.⁵¹ Such disruptions impact crucial programs governing intestinal immunity, including ILC3s development and functional capacities.⁵¹

ILC3s subsets receive regulatory cues from dietary elements through discrete molecular circuits. The AhR, G protein-coupled receptors (GPCRs), and Retinoic acid receptors (RARs) transduce signals influencing ILC3s activation status and cytokine secretion profiles.^{52,53} AhR engagement mediates ILC3s responses to microbial tryptophan catabolites while GPCRs and RARs coordinate detection of microbial metabolites and retinoids, respectively.⁵³

AhR

AhR functions as a key immune cellular sensor of environmental conditions through its dual roles as a cytoplasmic receptor and transcription factor.⁵⁴ Within ILC3s subsets, AhR exhibits high expression and proves indispensable for development and homeostasis.⁵⁴ AhR primarily binds endogenous ligands including tryptophan metabolites derived from gut microbiota, such as indole and indole-3-acetic acid.^{55,56} Such ligand engagement enhances ILC3s secretion of IL-22 while preventing intestinal epithelial cell transformation into a DNA damage response phenotype.⁵⁶ AhR ligands may also exert direct cytoprotective effects on epithelial cells.⁵⁷

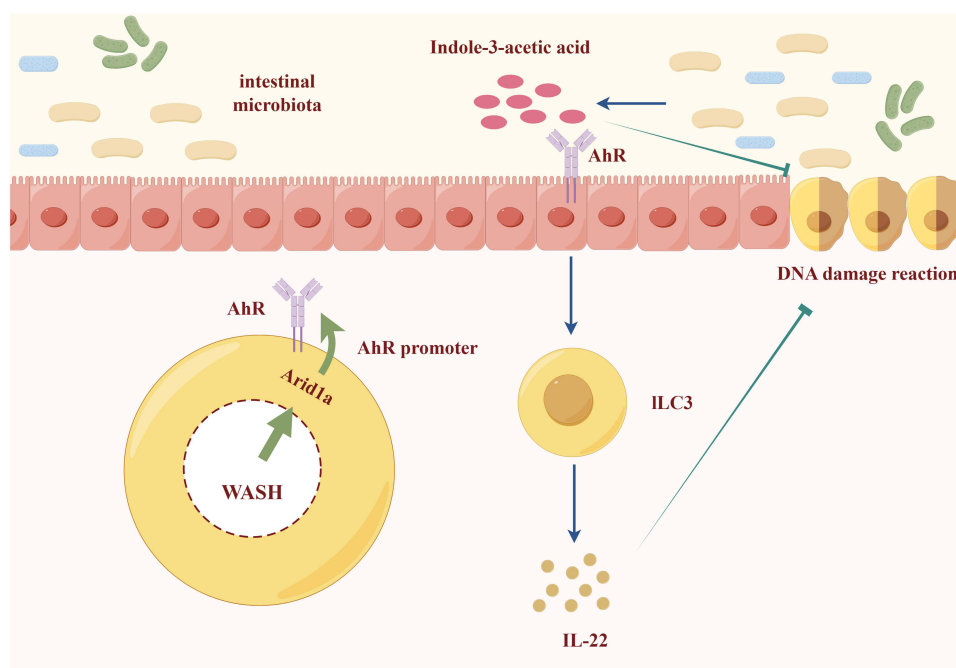


Figure 1 AhR is highly expressed in ILC3s and is required for ILC3s development and maintenance. The gut microbiota-derived tryptophan metabolites indole and indole-3-acetic acid bind to AhR to activate ILC3s and regulate IL-22 production. AhR ligand binds to AhR and enhances ILC3s to secrete IL-22 and prevent intestinal epithelial cell transformation through the DNA damage response (DDR). In ILC3s, WASH recruits Arid1a to the AhR promoter, thereby activating AhR expression.

The WASH protein complex exhibits elevated nuclear expression specific to ILC3s, where it proves necessary to maintain the subset independently of developmental requirements.⁵⁸ Within these cells, WASH recruits chromatin remodeler Arid1a to the aryl hydrocarbon receptor promoter to activate gene transcription.⁵⁸ Meanwhile, the IL-22 receptor exhibits wide distribution across intestinal stem cell membranes and transduces signals crucial for IL-22-mediated responses.⁵⁹ L-fucose significantly increases IL-22R cryptal expression and may engage AhR pathways to promote intestinal IL-22 release⁵⁹ (Figure 1).

Ffar2

Activation of GPCRs, such as free fatty acid receptor 2 (Ffar2) and free fatty acid receptor3 (Ffar3), typically induces expansion of the peripheral ILCs population. Among colonic ILC3s subsets, Ffar2 defines a dominant signalling pathway through regulation of proliferation and function, acting primarily on NCR+ ILC3s.⁶⁰ While dispensable for lymphoid tissue development, Ffar2 expression on ILC3s may contribute to increased abundance within colonic lymphoid aggregates.⁶⁰ Ffar2 activates AKT or ERK signalling through the AKT and STAT3 axis and increases ILC3s-derived IL-22. In addition, the Ffar2 receptor stimulates the activation of PI3K, Stat3, Stat5 and mTOR, promoting colonic ILC3s activation.⁶¹ Activation of the Ffar2 receptor promotes colonic ILC3s proliferation in situ and, in the absence of Ffar2, reduces ILC3s proliferation in situ and the production of derived IL-22, leading to impaired intestinal epithelial function, alterations in mucus-associated proteins and antimicrobial peptides, and increased susceptibility to colonic injury and bacterial infection.⁶²

Retinoic Acid Receptor

Dendritic cells act as the principal source of Retinoic acid receptors (RARs) in the intestine and metabolize vitamin A into its biologically active form, retinoic acid.⁶³ Retinoic acid and vitamin A signaling induces a homing receptor switch allowing ILC3s and ILC1s migration to the intestine independent of retinoic acid effects on ILC2s homing.⁶⁴ Within the intestinal compartment, retinoic acid functions synergistically with IL-2 and other stimuli to induce expression of the homing integrin $\alpha 4\beta 7$ and IFN- γ production in ILC1s and ILC3s.⁶⁵ Specifically, retinoic acid upregulates ILC3s

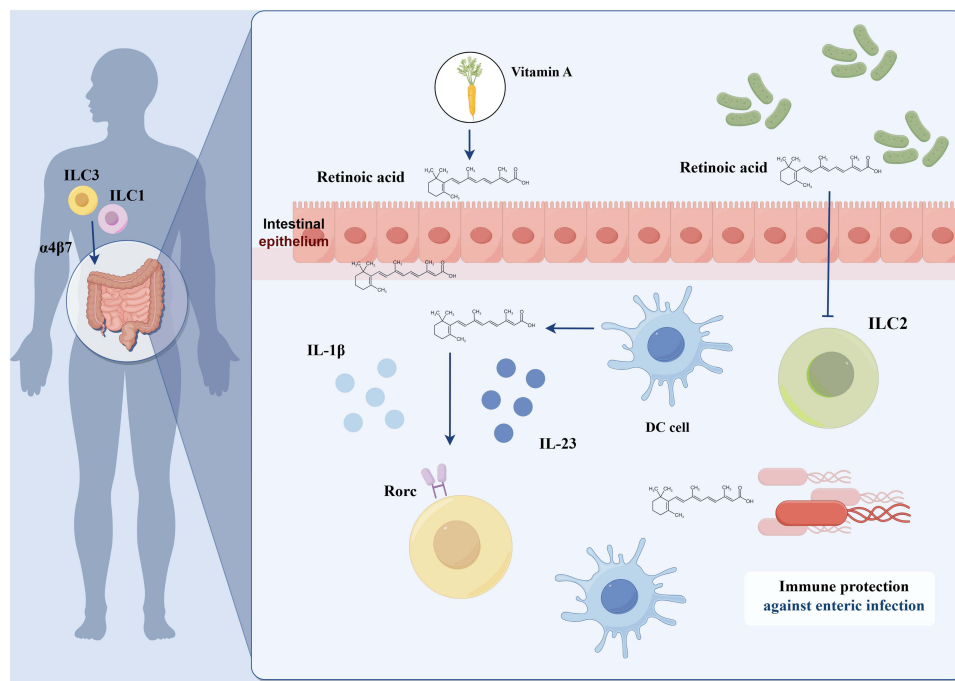


Figure 2 Retinoic acid regulates ILC3s homing and promotes ILC3s growth. Retinoic acid induces a homing receptor switch that allows ILC3s and ILC1s to migrate to the intestine, but ILC2s migration to the intestine is not regulated by retinoic acid. Retinoic acid inhibits ILC2s but increases ILC3s numbers and IL-22 expression, mainly by promoting IL-22 production in IL-1 β - and IL-23-stimulated ILC3s and by controlling LT α upstream of the transcription factor ROR γ t.

abundance and IL-22 expression via promoting IL-1 β and IL-22 generation in IL-3 exposed to IL-23.^{65,66} The cytokine response elicited demonstrates dose-dependency on retinoic acid levels.⁶⁶ Collectively, these mechanisms fine-tune ILC3s developmental trajectories and functional capacities (Figure 2).

SCFAs

Short-chain fatty acids (SCFAs) regulate ILC3s function by activating specific GPCRs, inhibiting histone deacetylases, stimulating histone acetyltransferases, stabilizing hypoxia-inducible factor 1, and GPR43-dependent metabolic regulation.⁶⁷ Acetate and butyrate prove indispensable for colonic ILC3s proliferation and effector cytokine generation, respectively.⁵² Acetate activates Ffar2 on ILC3s and epithelia to boost IL-1 β production, promoting neutrophil-ILC3s cross-talk. The acetate-Ffar2 axis elevates ILC3s IL-1R expression, heightening IL-1 β sensitivity and inducing IL-22/IFN- γ secretion.^{61,67} Acetate inhibits ILC3s-derived IL-17A independently of Ffar2 through direct histone deacetylase inhibition as well.⁶⁷ Under homeostasis, butyrate negatively regulates terminal ileal Peyer's patch ILC3s frequency, correlating with enhanced antigen-specific mucosal immunity.⁶⁸ Acetate promotes ILC3s proliferation primarily via Ffar2 and downstream AKT, STAT3 and mTOR signaling, whereas propionate preferentially induces IL-22 through Ffar3⁶⁹ (Figure 3).

Intestinal Micronutrients

Intestinal micronutrients such as vitamins A and D critically govern ILC3s maturation and functional preservation. Deficient adult vitamin A consumption hampers ILC3s proliferation and secondary lymphoid structure maturation.⁷⁰ Specifically, reduced frequencies of intestinal ILC3s subsets exhibit diminished IL-22 production.⁷⁰ Vitamin A proves essential to maintain intestinal ILC3s pools through ensuring cellular stability.⁵⁷

Vitamin D arises from sunlight or diet and influences food allergy risk.⁷¹ The biologically active 1,25(OH) $_2$ D $_3$ form engages the vitamin D receptor (VDR), highly expressed gut-resident ILC3s, to control lineage commitment and functionality.⁷² VDR deficiency or signaling blockade impairs ILC3s maturation and immunity particularly involving lymphoid tissue inducer cells.⁷² VDR governs IL-22 synthesis by regulating ILC3s proliferation and potentially IL-22

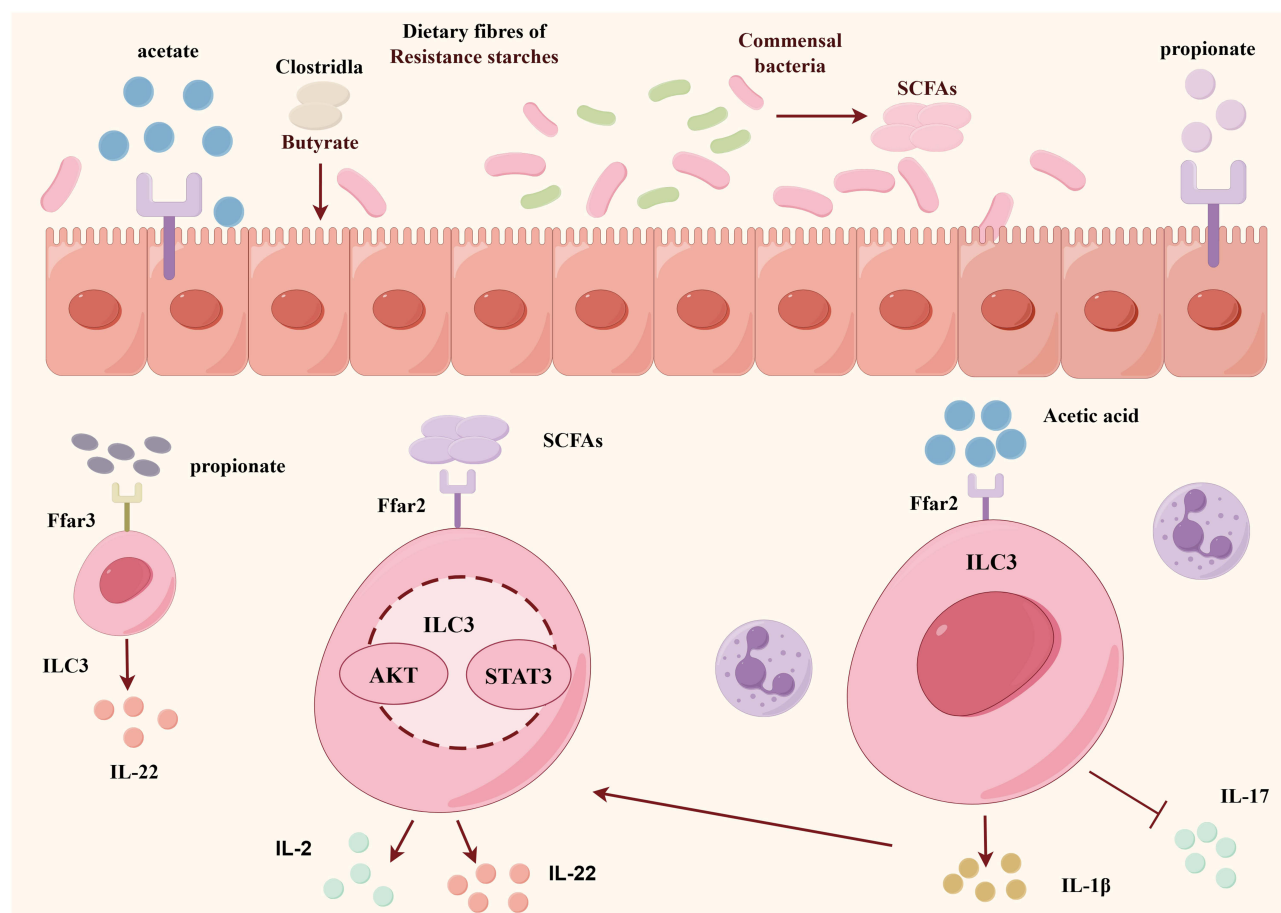


Figure 3 SCFAs are essential for the proliferation and effector function (IL-22 production) of colonic ILC3s to promote intestinal immunity. Gut microbiota ferment dietary fibre to produce SCFAs, which stimulate IL-22 production by ILC3s, mainly through activation of the AKT and STAT3 pathways. SCFAs, including acetate and butyrate, etc. Acetate activates FFAR2 to increase the production of IL-1 β , which in turn increases ILC3s susceptibility to IL-1 β , promotes IL-22 production, and also reduces ILC3s-induced IL-17A levels.

gene transcription independently of symbiotic bacteria.⁷³ Vitamin D ensures colonic ILC3s-derived IL-22 and protective Th17 amplification during infection, as its deprivation elicits prolonged, severe enteric pathogenesis.⁷³ While vitamin D clearly impacts ILC3s physiology, deeper exploration of underlying mechanisms remains necessary.

Gut Microorganisms

SFB

Segmented filamentous bacteria (SFB) are a group of host-adapted symbiotic organisms that are widely distributed in vertebrates, including humans and mice.⁷⁴ *SFB* predominantly colonizes the terminal ileum in mice, where they typically instigate autoimmunity. *SFB* colonization induces transcriptomic shifts within the lamina propria, characterized by surging serum amyloid A 1 and 2 (SAA1/2) production in overlying epithelial cells.⁷⁵ *SFB* engages IL-22-mediated STAT3 signaling in epithelial cells to induce SAA1/2 expression, implicating a homeostatic mechanism coupling barrier integrity maintenance to microbial colonization.⁷⁶ As the principal intestinal source of IL-22, ILC3s express IL-22 at levels exceeding Th17 cells 10-fold.⁷⁷ *SFB* also elicits REG3 γ production and IL-22-dependent phosphorylation of STAT3 in epithelial cells, supporting epithelial renewal.^{78,79} IL-22 stimulated by *SFB* further induces fucose-2 and fucosylation pathways enhancing paneth cell antimicrobial capacity.⁷⁹

Dietary composition intricately shapes *SFB* behavior through regulatory interactions with ILC3s. Nutrient intake sustains *SFB*-associated epithelial morphology via IL-22 signaling, whereas IL-22 blockade or fasting impair intestinal homeostasis and restrict *SFB* expansion in mice.⁷⁹ Work from Japan additionally revealed carbohydrates and insoluble fiber reduce IL-22 production and STAT3 phosphorylation in ILC3s, diminishing epithelial renewal and down-regulating

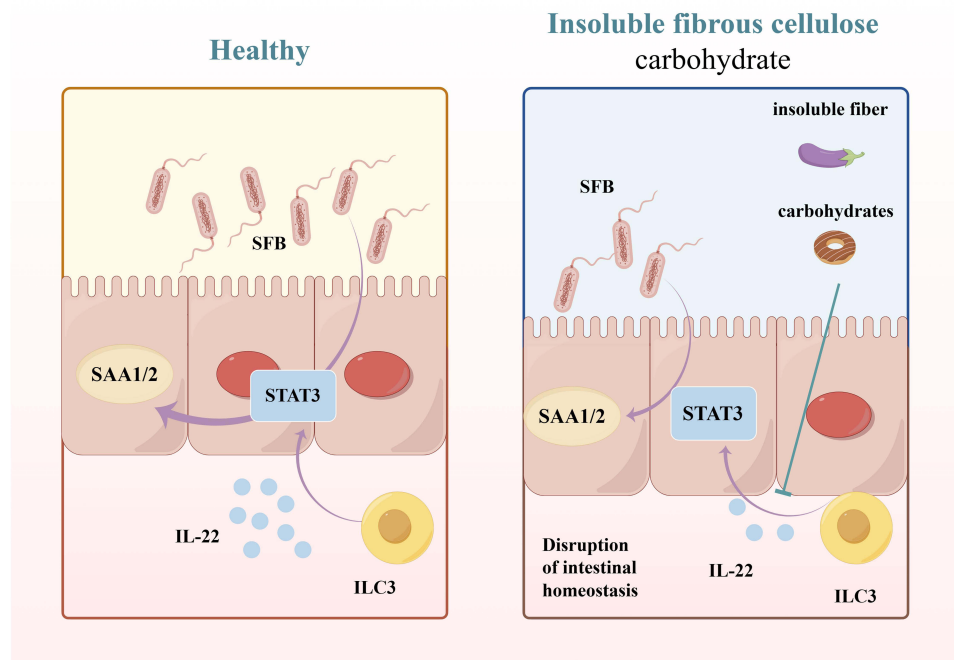


Figure 4 SFB in ILC3s function or homeostasis. SFB colonise epithelial cells and initiate an IL-22-mediated Stat3 signalling cascade leading to local SAA1/2 expression and can also maintain the epithelial cell barrier function in the ileum by promoting the phosphorylation of STAT3 (pSTAT3) in the intestinal epithelium, inducing the production of REG3 γ and contributing to IL-22 production by ILC3s. At the same time, ILC3s express high levels of Sca-1 on its surface in response to SFB colonisation, high levels of Sca-1 in response to SFB colonisation. Diet is also closely related to SFB function, as carbohydrates or insoluble cellulose fibre can affect IL-22 production by ILC3s and STAT3 phosphorylation in the ileum.

the B3gnt7 gene.⁸⁰ Western high-fat diets likewise impact SFB colonization. Such diets induce SFB loss in ILC3s-deficient, but not sufficient, mice, highlighting ILC3s as integral to high-fat diet mediated SFB depletion⁸¹ (Figure 4).

Salmonella

Salmonella typhimurium is a parthenogenetic intracellular pathogen that invades and replicates within host cells, causing gastrointestinal and systemic disease.^{82,83} *Salmonella* establishes mucosal niches by inducing antimicrobial proteins that inhibit commensals while promoting its survival.⁸⁴ During later infection stages, *Salmonella* targets ILC3s, activating IL-22 production through a TLR5-Myd88-IL-23 dependent mechanism enhancing APC-derived flagellin.⁸⁵ Conversely, *Salmonella* directly induces caspase-1 mediated ILC3s cell death independently of flagellin.⁸⁶ Casp1 ablation confers ILC3s survival and IL-22 elevation, exacerbating typhoid infection.⁸⁶

ILC3s also shape the intestinal response to *Salmonella* via effects on epithelial fucosylation.⁸⁷ While luminal colonization proves independent of fucosylation, epithelial fucose restricts bacterial tissue invasion, and its depletion elicits more severe infections.⁷⁹

Akkermansia Muciniphila

Probiotics interact with intestinal immune cells and commensals to modulate immunity through health-promoting and immunomodulatory properties.⁸⁸ *Akkermansia muciniphila* (*A. muciniphila*), a strictly anaerobic, mucin-degrading bacterium comprising 1–4% of the human gut microbiota, safeguards intestinal homeostasis via mucolytic actions.^{89–91} *A. muciniphila* promotes SCFAs (eg propionate, acetate) production and upregulates antimicrobial peptide genes (eg Reg3a, Reg3b, Reg3g), elevating paneth cell numbers yet exacerbating depletion following *Salmonella typhimurium* infection.⁹² *A. muciniphila* abundance modulates ILC3s-T cell balances, inhibits proinflammatory colonic epithelial signaling, and mitigates dysbiosis-driven inflammation⁹³ (Figure 5).

The beneficial bacteria are *Parabacteroides distasonis*, *Barnesiella intestinihominis* in addition to *Akkermansia muciniphila*.⁹⁴ *A. muciniphila* has been shown to enhance the number of ILC3s in the colon, a function that Amplification of this bacterium can be achieved through co-colonisation with *Parabacteroides distasonis*.⁸⁹

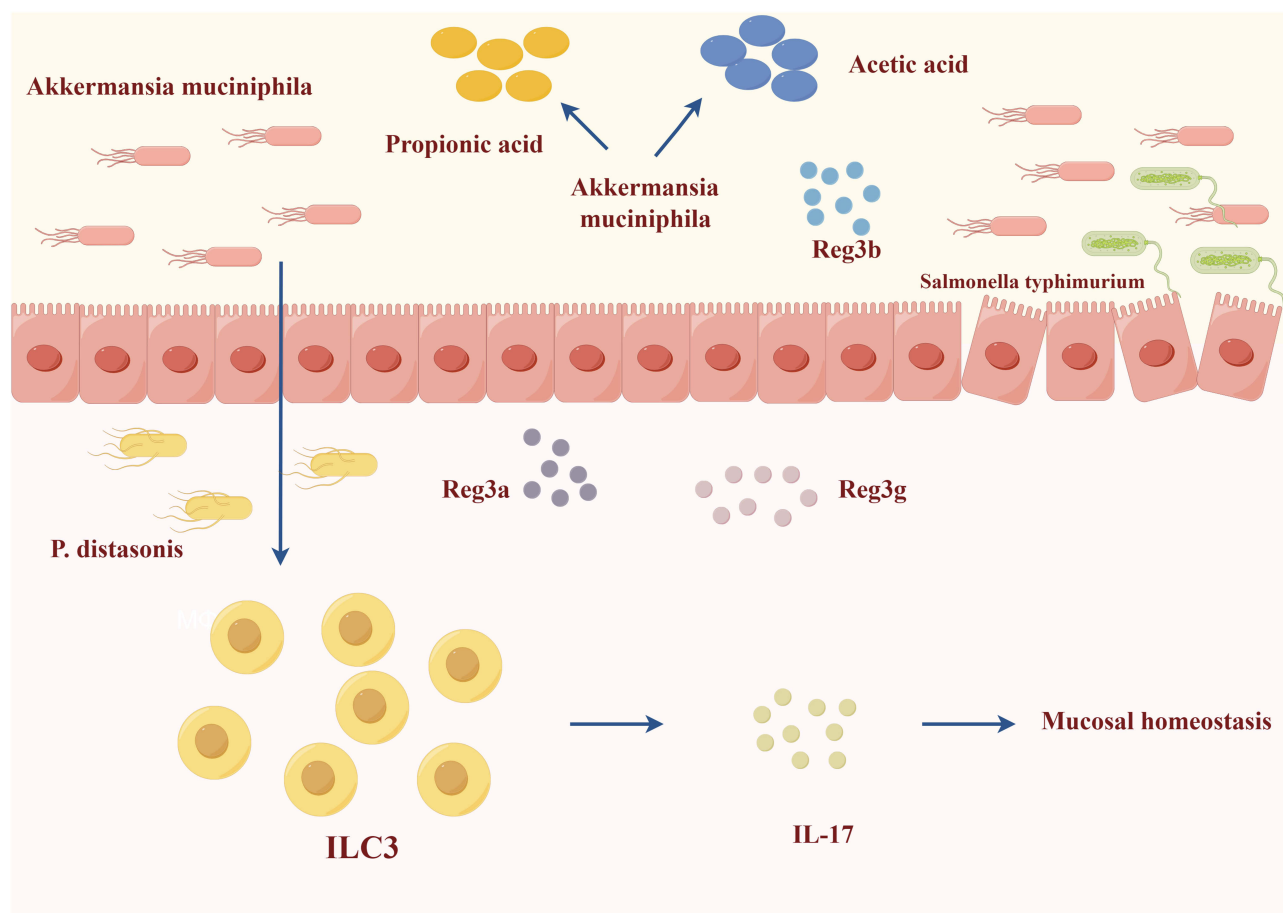


Figure 5 Probiotic *Akkermansia muciniphila* maintains intestinal barrier stability. *Akkermansia muciniphila* promotes the production of SCFA propionate and acetate, and upregulates gene expression of antimicrobial peptides (eg Reg3a, Reg3b and Reg3g). Co-colonisation with another bacterium, *Salmonella typhimurium*, exacerbated the reduction in cuprocytes, but co-colonisation with *P. distasonis* led to an increase in IL-17-ILC3s, reinforcing the interactions between gut microbes and their contribution to the protective immune response.

Administration of *A. muciniphila*, either alone or in combination with *P. distasonis*, has been demonstrated to increase IL-17-ILC3s, thereby enhancing gut microbial interactions.⁹³

These three types of gut microorganisms are all closely associated with human health. If their numbers and functions are not normalised, they will have a deleterious impact on human health. These gut flora are closely related to ILC3s, which can exert a direct or indirect influence on the equilibrium of the intestinal tract and the body's overall health.

ILC3s in Autoimmune Disease

The function of ILC3s and their associated cytokines in maintaining intestinal immune homeostasis, as well as the impact of the intestinal microenvironment on ILC3s activity, have been previously described in detail. These processes may play a role in the pathogenesis of autoimmune diseases. Consequently, we have selected some representative autoimmune disorders for discussion in the following paragraphs.

IBD

Crohn's disease (CD) and ulcerative colitis (UC) are classified as inflammatory bowel disease (IBD), a recurrent, non-specific lesion defined by chronic inflammation of the gastrointestinal system.⁹⁵ A recent study employing single-cell sequencing to ascertain the transformation of immune cells in peripheral blood and colon tissue in patients with ulcerative colitis (UC) during active and remitting periods revealed a notable decline in the proportion of ILC3s.¹³ A reduction in the number of ILC3s, which produce IL-22, has been observed in the guts of patients with Crohn's

disease.⁹⁶ Further analysis of animal studies revealed that ILC3s-deficient mice exhibited severe intestinal mucosal damage and developed colitis.⁹⁷

A recent study has revealed that mice with colitis exhibited a notable elevation in aldosterone levels within the colon. Aldosterone plays a role in accelerating DSS-induced colitis, with ILC3s identified as the key effector cell. The activation of ILC3s by endogenous aldosterone resulted in the protection of mice from DSS-induced colitis. The halocorticoid receptor in ILC3s may play a pivotal role in responding to changes in aldosterone levels within the intestinal micro-environment, and in regulating IL17A stimulation of ILC3s.⁹⁸

There is a correlation between IBD-related immunoinflammatory responses and imbalances in the gut microbiota. The imbalance in the effects of the gut microbiome on the intestinal mucosa and tissues is caused by an increase in the number of harmful bacteria (such as *E. coli*) and a decrease in the number of protective bacteria (such as *bifidobacteria* and *Lactobacillus* genera).^{99,100} *Lactobacillus* may promote intestinal mucous homeostasis by producing L-Orn (L-Ornithine). L-Orn stimulates Trp metabolism to produce AhR ligands in intestinal epithelial cells, thereby inducing the accumulation of ILC3s in intestinal tissues.^{3,101} A review of the literature revealed that the number of *Lactobacillus* with weaker attachments to epithelial cells colonizing the gut in individuals with IBD is less than that observed in healthy individuals.¹⁰² A reduction in the relative abundance of *Lactobacillus*, an increased severity of DSS-induced colitis, and an impairment of ILC3s development were observed.

Rheumatoid Arthritis

In the early stages of RA, the lymph node (LN) microenvironment is impaired, and activation and autoantibody production precede the onset of joint inflammation. It appears that ILCs in the LN microenvironment exhibit a shift from a more “homeostatic” to a more “inflammatory/activating” profile, characterised by an increased frequency of subpopulations of potentially pro-inflammatory cytokine-producing ILCs (ILC1s and ILC3s) in RA patients. It has been demonstrated that ILC1s and ILC3s are capable of inducing inflammation in RA pathogenesis.^{103,104} A clinical study revealed that ILC3s levels were elevated in RA patients and the frequency of ILC3s exhibited a correlation with the progression of RA. Additionally, the study demonstrated that ILC3s were positively correlated with Th1 and Th17 cells in peripheral blood in RA.¹⁴ A further study conducted in a Japanese RA population revealed a positive correlation between the incidence of ILC3s in synovial fluid and both tender joint counts and swollen joint counts.¹⁰⁵ Furthermore, ILC3s were observed to be elevated in the synovium of CIA model mice in murine experiments. It is hypothesized that ILC3s may be involved in the pathogenesis of RA through the production of IL-17 and IL-22.¹⁰⁵ ILC3s are a primary source of IL-22, IL-17 and TNF α .¹⁰⁶ IL-22 plays a pivotal role in the inflammatory and proliferative cascade of various autoimmune diseases, including RA.¹⁰⁷ IL-22 is also expressed as a pro-inflammatory cytokine in fibroblast-like synoviocytes (FLS) and macrophages, and promotes an inflammatory response on the FLS in patients with RA through the expression of IL-22 receptor 1. Other cytokines, such as TNF α and IL-17, also play an important role in synovitis in patients with RA.¹⁰⁸ Although several clinical studies have indicated a potential association between ILC3s and RA exacerbations, the specific role of ILC3s in RA pathogenesis remains unclear.

A notable decline in the Firmicutes population was observed in RA patients, with a concomitant reduction in the production of butyrate-producing bacteria (BPB). Butyrate is a pivotal SCFA that exhibits a greater range of physiological functions than other SCFAs, such as acetate and propionate. The study observed an imbalance between butyrate producers and consumers in the gut microbiome of RA patients, which was found to be associated with levels of anti-citrullinated protein antibodies (ACPA) and joint deformities.^{109,110} The above demonstrates that SCFA is closely associated with ILC3s, which is also closely linked to RA. Consequently, we postulate that the intestinal flora in RA disease may have a certain relationship with ILC3s, which could contribute to the development of the disease.

Systemic Lupus Erythematosus

SLE is a heterogeneous autoimmune disease that predominantly affects women of childbearing age and can lead to damage in multiple organs.^{111,112} The immunopathogenesis of SLE involves various factors such as genetics, environment, hormones, epigenetics, and immune modulation. Autoreactive T cells play a pivotal role in the pathogenesis of SLE. Additionally, Th17 is implicated in the pathogenesis of SLE.¹¹³ ILC3s have been identified as the innate counterpart

of Th17 cells.¹¹⁴ Clinical studies demonstrated alterations in the circulation of ILC in SLE patients with an increase in circulating ILC1s and ILC3s and a decrease in circulating ILC2s, indicating an imbalance in ILC homeostasis.¹⁵ Research by JIANG et al in 2020 found that SLE patients had significantly higher level of circulating ILC1s and ILC3s, with a significantly higher ILC1s/ILC3s ratio. In SLE patients with arthritis, there was a higher frequency of ILC3s and a lower ILC1s/ILC3s ratio, correlating with the presence of arthritis.¹¹⁵ Moreover, the absolute number of ILC3s was elevated in active SLE patients compared to those with inactive disease, and ILC3s levels correlated positively with disease activity and serum anti-dsDNA levels.¹¹⁵

Lupus nephritis (LN) is a serious complication of SLE that affects around 50% of SLE patients and significantly increases morbidity and mortality rates.¹¹⁶ Studies have shown that in LN patients, blood ILC2s levels are decreased, while ILC3s levels are significantly increased. Interestingly, the percentage of circulating ILC3s has been positively correlated with serum anti-double-stranded DNA (anti-dsDNA) antibodies and anti-nuclear antibodies (ANA). Research from mouse experiments has indicated that ILC3s from the intestinal can migrate to the kidneys. Additionally, it has been suggested that the CXCR6/CXCL16 pathway may play a crucial role in regulating the translocation of ILC3s from the intestine to the kidneys.¹¹⁷ These findings provide valuable insights into the potential involvement of ILC3s in the pathogenesis of SLE and LN. Further investigation into the mechanisms underlying the migration and function of ILC3s in LN may offer new therapeutic targets for the management of this severe complication of SLE.

Ankylosing Spondylitis

Ankylosing Spondylitis (AS) is a chronic inflammatory disease of unknown aetiology. In contrast to other systemic autoimmune diseases, the innate immune system plays a dominant role in AS. Aberrant activity of innate and innate-like immune cells, including ILC3s, has been observed in AS patients.¹¹⁸ It has been demonstrated that patients with AS exhibit a notable increase in IL-17-producing cells in the peripheral blood, inflamed bone marrow (BM), and synovial fluid. These cells also secrete high levels of IL-22 and $\alpha\beta7$ integrins, which are primarily responsible for directing immune cells to intestinal sites. In AS patients, The antireceptor of $\alpha\beta7$, MAdCAM1, is significantly upregulated in intestinal high endothelial venules (HEV) and BM in patients with AS, indicating its involvement in the chemotaxis of ILC3s to sites of active inflammation in AS.^{119–121} The correlation between ILC3s and AS disease activity scores suggests that ILC3s play a crucial role in AS pathogenesis and disease progression. The gut is regarded as a potential site of ILC3 differentiation, amplification and initiation in AS.¹²² Dysbiosis of the intestinal flora observed in AS patients may lead to the activation and proliferation of ILC3s, which could subsequently lead to joint inflammation and involvement.¹²³

Other Autoimmune Diseases

A similar correlation has been observed in other immune diseases. To illustrate this point, consider the case of psoriasis, ILC3 has been identified in psoriatic skin samples from both humans and mice.^{124,125} Moreover, a decline in ILC3 numbers has been observed in response to therapeutic compounds, indicating their potential role in the pathogenesis of the condition. It has been demonstrated that tissue-resident ILCs, including ILC2, respond to IL-23 by activating a convergent, pathologically induced ILC3-like programme in Psoriasis. This programme is characterised by the production of cytokines such as IL-13 and IL-22, among other molecules.¹²⁶

In patients diagnosed with type 1 diabetes (T1D), a reduced frequency of ILC3 was identified in the duodenum.¹²⁷ In the pancreas and mesenteric lymph nodes of diabetic NOD mice, low IL-22-producing ILC3 was identified, alongside notably elevated levels of IFN- γ and TNF, but not IL-22. Furthermore, the transition from The transition from pre-diabetic to diabetic in NOD mice was associated with an impaired function of ILC3, which could lead to a reduction in the amount of Treg and suggest a protective effect of IL-22-producing and IL-22-producing ILC3 on T1D.^{128,129}

Furthermore, in psoriatic arthritis, Soare et al observed that patients with psoriatic arthritis (PsA) exhibited elevated levels of circulating ILC3s and ILC2s, and that the ILC2/ILC3 ratio correlated with disease activity.⁸⁷ Furthermore, Leijten et al demonstrated that ILC3s were amplified in the synovial fluid of patients with PsA, but not in peripheral blood.¹³⁰ In ANCA-associated vasculitis (AAV), there is a reduction in the number of ILC2s and ILC3s, while the

number of ILC1s is increased, in comparison to healthy controls or patients with remission-phase AAV. It is not yet possible to draw definitive conclusions regarding the role of ILCs in the pathogenesis of AAV.¹³¹

Discussion

Recent research underscores the pivotal role of ILC3s in modulating innate immune responses. These cells are ubiquitously distributed across the body, with a constant presence at mucosal barrier locales such as the lungs, liver, intestines, spleen, skin, and secondary lymphoid tissues.¹³² Circulating ILCs progenitors, originating from the fetal liver, migrate to the bone marrow (BM) and persist through to adulthood.¹³³ Primarily, ILC3s are drawn to intestinal tissues, moving from the bone marrow to mesenteric lymph nodes in a CCR7-dependent manner, with commensal bacteria potentially directing intestinal ILC3s towards the lungs.¹³³ The lung-specific migration of ILC3s involves CCR4 and CXCR5 signaling pathways, where CCR4 acts as a homing receptor and CXCR5 signaling is essential for lung colonization and subsequent IL-17 production, orchestrating neutrophilic responses.^{134,135} Additionally, ILC3s can be summoned to inflamed skin via a CCR6-dependent route, influencing the equilibrium of commensalism by modulating sebocyte functionality through direct interactions with CD4 T cells.¹³⁶ Within the skin, ILC3s secrete IL-22 to bolster antimicrobial responses by keratinocytes, whereas IL-17 prompts keratinocytes to release IL-33, intensifying inflammation and fostering type 2 immune reactions.¹³⁷

In the blood a considerable number of ILCs progenitors exist, yet mature ILC1s and ILC3s are notably absent.¹³³ Recent discoveries have unveiled an unrecognized ILCs subset within the liver, exhibiting an ILC3s-like phenotype with the capability to produce the ILC2s-specific cytokine IL-13.¹³⁸ Notably, variations in cytokines, such as IL-13, IL-17 and IL-22 across different tissues (intestines, lungs, skin), present substantial challenges in the consistency and correlation of research findings across diverse populations, necessitating further investigative efforts.

In vivo, ILC3s are integral to a myriad of protective homeostatic functions. However, imbalances in ILC3s responses are linked with a range of chronic inflammatory ailments and are progressively acknowledged for their role in the emergence and evolution of autoimmune diseases, including SLE,^{15,115} AS,¹²³ psoriasis,¹²⁶ type 1 diabetes,¹²⁷ Rheumatoid Arthritis.^{107,108} The precise aetiology and pathogenesis of these autoimmune diseases in relation to ILC3s remain unclear. Despite the existence of clinical evidence suggesting a correlation between ILC3s and the aforementioned autoimmune diseases, there is a distinct lack of scientific literature that clarifies the specific interactions between ILC3s and them. Furthermore, a plethora of autoimmune diseases, including vitiligo, pernicious anaemia, have not yet been clinically linked to ILC3s, thus representing a relatively novel perspective that merits rigorous study and exploration.

The microenvironment exerts a substantial influence on immune cell plasticity, with cytokines and transcription factors playing a pivotal role in the differentiation and maintenance of ILCs. These factors also influence the distribution of ILCs subpopulations, which may consequently alter the trajectory of the disease. Current data can suggest that ILCs can be utilised as biomarkers to assess disease severity or treatment response. Recent technological advances have enhanced our capacity to monitor and characterise ILC3s dynamics in the gut microenvironment, thereby facilitating the development of personalised therapeutic strategies. Single-cell RNA sequencing (scRNA-seq) and mass spectrometry cell counting (CyTOF) now enable high-resolution analyses of ILC3s heterogeneity, unveiling subtype-specific functional states in autoimmune environments.^{13,139,140} The following experiment will utilise spatial transcriptomics and multiphoton imaging to track ILC3s interactions with gut microbiota and epithelial cells in real time in a living organism.^{141,142} These innovations have the potential to assist in the stratification of patients according to ILC3s characteristics, thus facilitating the development of targeted interventions such as cytokine modulation (eg anti-IL-23 therapy) or microbiota-directed therapies. However, the standardisation of these technologies in clinical applications remains challenging, particularly with regard to cost-effectiveness and longitudinal monitoring. The development of organoid-ILC3s co-culture models in conjunction with AI-driven biomarker discovery may serve to bridge this translational gap in the future.

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Disclosure

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