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Innate Lymphoid Cells, their Biological Characteristics and Role in Immunopathological Processes

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ABSTRACT

Innate lymphoid cells (ILCs) are among the most recently identified cell populations that contribute to immune responses. ILCs lack antigen-specific receptors that characterise T and B lymphocytes. In contrast to cells of adaptive immunity, ILCs lack somatic rearrangement of antigen-specific receptors and do not express T-cell or B-cell receptors (TCRs or BCRs). ILCs arise from hematopoietic common lymphoid progenitors in the bone marrow; however, full ILC maturation occurs in non-lymphoid tissues, where immature ILCs take up residence. ILCs are under-represented in lymphoid tissues, but parenchymal tissues, especially mucosal surfaces, show substantial enrichment for ILCs. In the mucosa of the intestine and lungs, ILCs seem to be particularly important regulators of epithelial barriers. Because of their strategic location, ILCs are among the first immune cells to respond to pathogens, inducing infection-related responses and shaping the adaptive immune response. Innate lymphoid cells are divided into three groups, ILC1, ILC2, and ILC3, each of which performs specific functions and cooperates with other cells of the immune system, thereby supporting immune defence and homeostasis. ILC cells also contribute to the inflammation and tissue damage in some diseases by producing cytokines that drive inflammatory responses.

Innate lymphoid cells (ILCs) belong to a recently identified population of immune system cells that contribute to the body's defences. They originate from a common lymphoid progenitor (CLP) in the bone marrow, leave the bone marrow as immature cells, and mature in peripheral tissues. They are found in all tissues, but are most abundant in the skin, respiratory and gastrointestinal tracts, and are relatively few in peripheral blood. Morphologically, they resemble B and T lymphocytes but lack their antigen-specific receptors. The second significant difference between lymphocytes of adaptive immunity is that they are not activated in peripheral lymphoid organs and subsequently do not migrate to tissues and organs. On the contrary, they are primarily localised there and respond to stimuli immediately, rather than after clonal expansion. They are not activated by antigen-presenting cells, but rather by a variety of stimuli, including cytokines, alarmins, lipids, and hormones released by stromal, epithelial, and myeloid lineage cells. Thus, ILCs are physically and functionally primed to serve as immediate sources of cytokines in peripheral tissues, alongside other rapidly responding cells residing there, such as NKT cells, γδ T cells, and resident memory T cells. The minimal requirements for their activation enable them to serve as first responders in the early phases of the primary immune response and to produce cytokines in response to subtle perturbations of homeostatic processes[1,2]. In 1987, Mosmann and Coffman identified the T_{H1} and T_{H2} subpopulations

of helper T lymphocytes[3,4]. Two decades later, in 2005, another subpopulation, T_{H17}, was added[5,6], followed by the discovery of three others. Later, when innate lymphoid cells (ILCs) emerged, it was found, quite surprisingly, that these new cells had properties similar to those of T_H lymphocyte subpopulations, especially in production of their cytokines (Table 1). This allowed them to be divided into distinct populations, also based on their different cytokine synthesis and function. So, nowadays we recognise three groups: ILC1, ILC2, and ILC3. These resemble polarised subpopulations of T helper lymphocytes. Thus, ILC1 cells functionally resemble T_{H1}, ILC2 cells resemble T_{H2}, and ILC3 cells resemble T_{H17} lymphocytes. Similarly, they utilise the same transcription factors for differentiation as polarised T_H lymphocytes: T-bet (ILC1), GATA3 (ILC2), and RORγt (ILC3)[7,8] (Fig. 1). Experimental results indicate that ILC cells play a redundant role in a fully functional adaptive immune system in humans. The question arises as to why such functional redundancy exists. On the one hand, the organism may benefit from this in the form of an increased immune response and faster elimination of the intruder as the hallmark of ILCs is prompt, antigen-independent activation. Also, sometimes it is sufficient for ILC cells to respond on their own, without the help of T_H lymphocytes, thereby preventing excessive activation and the subsequent development of autoimmune processes[9,10].

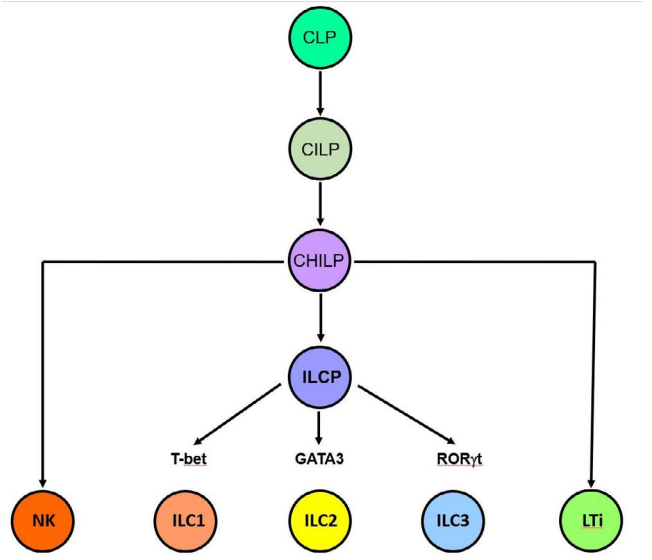

Figure 1: Differentiation of innate lymphoid cells (modified according to Yao et al. 2025[28])
ILCs originate from lymphoid progenitors CLPs (common lymphoid progenitors). They give rise to CILPs (common innate lymphoid progenitors), which serve as the earliest precursors within the ILC lineage. CILPs differentiate to CHILP lineage (common helper lymphoid progenitors), giving rise to NK (natural killer cells), LTis (lymphoid tissue inducers) cells and ILCPs (innate lymphoid cell precursor). ILCPs differentiate further into ILC1s, ILC2s, and ILC3s with distinct functions.

Table 1: Cytokines produced by subpopulations of T helper lymphocytes

Cytokine	T_{H1}	T_{H2}	T_{H17}	T_{H9}	T_{H22}	T_{FH}
IFN-γ	++	-	-	-	-	-
IL-2	++	-	-	-	-	-
TNF	++	+	+*	-	-	-
IL-4	-	++	-	-	-	+
IL-5	-	++	-	-	-	-
IL-6	-	-	+	-	-	-
IL-13	-	++	-	-	-	-
IL-9	-	+	-	++	-	-
IL-10	+	++	+	++	+	-
IL-17	-	-	++	-	-	-
IL-21	-	-	+	-	-	+
IL-22	-	-	+	-	++	-

*Not typically, but they can produce it under specific circumstances
Modified according to common textbooks

Populations of ILC cells and their physiological properties

The ILC1 group includes ILC1 cells and natural killer (NK) cells. NK cells were among the first cells to be characterised as ILCs; they were discovered 50 years ago[11,12]. However, some authors object to their inclusion in the ILC1 group, considering them an independent population[13,14]. ILC1 cells, unlike NK cells, are not cytotoxic and produce substantial amounts of IFN-γ and TNF. We can also distinguish them based on the expression of the transcription factors T-bet and EOMES. While NK cells express both, ILC1 cells only express T-bet. Moreover, ILC1 cells express CD127 (alpha receptor for IL-7; IL-7Rα), whereas NK cells do not. Another difference is that while NK cells recirculate, ILC1 cells, like other ILC cells, are sessile, meaning they dwell in tissues and renew themselves through self-replication rather than deriving from ILC1 cells in the blood or their precursors in the bone marrow. Another characteristic marker of ILC1 cells is CD103, an integrin protein[7,14] (Table 2). ILC1 cells are not a uniform population. We recognise subsets present in the intestinal mucosa, liver, salivary glands and female reproductive tract. Moreover, ILC1 cells can arise by transdifferentiation of ILC2 and ILC3 cells[8].

The physiological role of ILC1 cells is to combat certain bacteria and parasites (*Clostridium difficile*, *Salmonella enterica*, *Toxoplasma gondii*) and to participate in immune surveillance of malignant processes, although distinguishing ILC1 cell participation from that of NK cells in individual cases remains challenging[13,14].

The ILC2 group is characterised by activation by IL-33, IL-25, or TSLP, which are produced by macrophages, mast cells, and NKT cells at the beginning of the immune response, or by epithelial cells when they are damaged (hence they are also referred to as epithelial cytokines). After activation, they begin producing typical T_{H2} cytokines

Table 2: Basic characteristics of ILC cells

ILC1 subset	
NK cells	Eomes, T-bet, NKp80, CD16, CD45, CD56, CD294, KIR, IFN-γ
ILC1 cells	T-bet, NKp46, CD45, CD90, CD103, CD127, CD49a, IFN-γ
ILC2 subset	RORα, GATA3, TSLP, NKp30, CRTH2, CD25, CD45, CD127, ICOS, IL-17RB, IL-5, IL-6, IL-9, IL-13, amphiregulin
ILC3 subset	
LTi cells	RORγt, LTα1β2, CD45, CD127, CD252, CXCR5, CCR6, CCR7
NCR+ (ILC22)	RORγt, AHR, NKp44, CD45, CD127, CD161, IL-22
NCR+ (ILC17)	RORγt, AHR, CCR6, CD45, CD161, IL-17
ILCreg subset	
ILCreg	CD45, CD127, CD90, CD25, IL-10

HR – aryl-hydrocarbon receptor, CRTH2 – chemoattractant receptor expressed on T_{H2} cells, KIR – killer inhibitory receptor

(IL-4, IL-5, IL-9) and amphiregulin. ILC2 cells also express class II HLA molecules, which allows them to participate in adaptive immune mechanisms. In contrast to groups 1 and 3 ILCs, no functional subpopulations of ILC2 cells have been identified in healthy individuals[14,15]. Under physiological conditions, ILC2 cells primarily function to fight helminths. When they invade the gut, tuft cells are among the first to sense their presence and start producing IL-25. It stimulates ILC2 cells to produce IL-13, which subsequently induces tuft cell hyperplasia, thereby increasing IL-25 synthesis and activating ILC2 cells. Another amplification mechanism for the early activation of ILC2 cells involves IL-9 production by ILC2 cells themselves. It acts autocrinally, activating them. Activated ILC2 cells synthesise IL-5, IL-13 and amphiregulin. IL-5 is a growth and activation factor for eosinophils, while amphiregulin maintains epithelial cell homeostasis. IL-13 induces smooth muscle contraction, mucus production by goblet cells and the attraction of M2 macrophages. All these factors contribute to the expulsion of worms from the intestine (a process referred to as "weep-and-sweep reaction")[16,17]. ILC2 cells play a significant role in the development of type I hypersensitivity reactions. They contribute to their development by producing type 2 cytokines, including IL-4, IL-5, IL-9, and IL-13, which are crucial in promoting the type 2 immune response, characterised by the activation of mast cells, eosinophils, and basophils. IL-4 and IL-13 promote B cell class switching to produce IgE antibodies. They bind to the FcεRI receptors on mast cells, sensitising them to allergens. Upon re-exposure to the allergen, the sensitised mast cells degranulate, releasing histamine and other inflammatory mediators. The cytokines produced by ILC2s further amplify this inflammatory response, leading to the symptoms associated with allergic reactions. By producing IL-5, they recruit and activate eosinophils, which substantially contribute to tissue damage and inflammation[18,19]. ILC2 cells also play important roles in limiting tissue damage after infection by producing ligands for the epithelial growth factor receptor, such as amphiregulin. It has been shown to control the proliferation and differentiation of epithelial cells, which are required for epithelial repair following influenza infection[20,21]. This property of ILC2 cells supports the hypothesis that the type 2 immune response (Box 1) evolved to repair damaged tissues and protect against harmful xenobiotics. It suggests that ILC2 cells maintain mucosal barriers under continuous exposure to environmental allergens, remaining fully functional by initiating a low-grade type 2 immune response, including mucus production and tissue repair. Based on the above, we can infer that ILC2 cells may protect us from the development of an allergic response mediated by the adaptive immune system by providing the first line of defence against allergens[21,22].

Box 1 Types of immune responses

Innate and adaptive immunity, working together, ensure the individual's defence against external and internal threats to its integrity. Their mechanisms can be divided into three types. **Type 1 immune responses** provide defence against intracellular pathogens such as *Mycobacterium tuberculosis* and viruses. Additionally, this type of immunity plays a role in immune surveillance of malignant proliferation. T_{H1} lymphocytes, cytotoxic T lymphocytes (CTLs), NK cells, NKT cells, and ILC1 cells are the main effector cells of type 1 immunity, while IgM, IgG1, IgG2, and IgG3 antibodies and interferon-gamma (IFN-γ) are the main humoral factors. **Type 2 immune responses** provide defence against large extracellular parasites by increasing mucosal barrier function. Additionally, participants in this type of immune response play a crucial role in maintaining metabolic homeostasis and supporting the repair of damaged tissue. The principal effector cells and mediators include T_{H2} lymphocytes, ILC2 cells, eosinophils, basophils, mast cells, alternatively activated macrophages (M2), IgE class antibodies, and cytokines such as IL-4, IL-5, IL-9, IL-13, IL-25, IL-33, and TSLP. **Type 3 immune responses** are directed against extracellular bacteria and fungi and are characterised by the involvement of T_{H17} and ILC3 cells, with IL-17 as the signature cytokine and neutrophils as the primary effector cells[23].

The ILC3 group is characterised by CCR6 expression and is divided into three subpopulations. The first one includes lymphoid tissue inducer cells (LTi), which, like NK cells, were discovered before ILC2 and ILC3 cells. LTi cells play a crucial role in the formation of lymph nodes during embryogenesis and are also important for the development of intestinal lymphoid structures in the postnatal gut. They express the lymphotoxin heterotrimer (LTα1β2) in their membranes. After lymphotoxin beta (LTβ) binds to their receptor on stromal cells, it induces the synthesis of

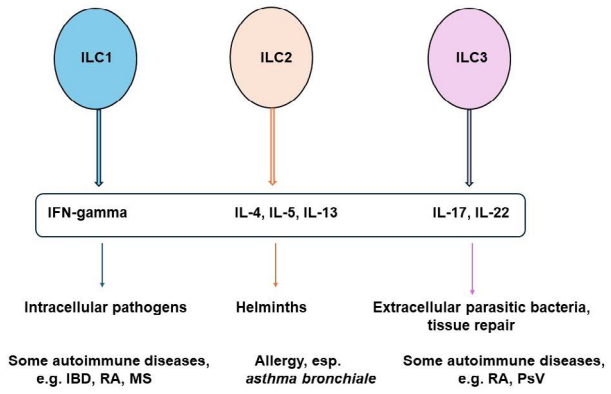

Figure 2: Physiological and pathological functions of ILC cells
After stimulation, ILC cells release their characteristic cytokines, which ensure their physiological functions, i.e. in fighting intracellular pathogens, parasites and extracellular pathogens, or participate in their repair, whether during self-renewal or after damage. However, excessive production of their cytokines during inflammation determines their participation in the development of autoimmune diseases (ILC1 and ILC3 cells), or in the development of allergic processes, especially in bronchial asthma (ILC2 cells).
Legend: IBD – inflammatory bowel disease, MS – multiple sclerosis, PsV – *psoriasis vulgaris,* RA – rheumatoid arthritis

chemokines in them, which attract lymphocytes to form secondary lymphoid organs, namely lymph nodes, Peyer's patches and isolated lymphoid follicles (but not the spleen or nasal associated lymphoid tissue - NALT[2,4,8] Some authors distinguish LTi cells, like NK cells, from the group of ILC3 or ILC1 cells, respectively and classify them as a separate population that develops from different precursors[8,10] (Figure 1). The second and the third subpopulations differ in their production of IL-22 and expression of NKp44 receptor. If they produce their principal cytokine IL22 and express NKp44, they are referred to as **ILC22 cells**. If they are characterised by significant IL-17 synthesis and are NKp44-negative, they are referred to as **ILC17**. IL-22 promotes the synthesis of antibacterial substances and promotes the proliferation of epithelial cells. IL-17, by activating neutrophils, is involved in antibacterial immunity in the skin and mucous membranes[13]. The physiological and pathological function of ILC cells is schematically shown in Figure 2.

Recently, **regulatory innate lymphoid cells (ILCreg)** have been added to the growing family of regulatory cells, which includes tTreg, pTreg, Tr-1, Tr35, T_{H3}, and Breg cells[25,26]. Unlike ILC1s, ILC2s, and ILC3s, ILCreg cells originate from the common helper-like innate lymphoid precursor (CHILP) (Fig. 1) and express Id3 (inhibitor of DNA binding)[3], which is required for their development and maintenance. This $CD127^+CD90^+CD25^+$ population was detected in the small and large intestines and produces IL-10. However, regulatory ILCs fail to express the transcription factor FOXP3 as tTreg cells do. The biological role of regulatory ILCs remains unclear, but these cells appear to have a potent capacity to suppress intestinal inflammatory responses *in vivo*[27,28].

At the very end, one can ask why ILC cells evolved when T lymphocytes already perform the same functions? The answer can be based on the following facts: 1. Early defence: ILCs provide a first line of defence before the adaptive immune system is activated. This is especially important in mucosal tissues through which pathogens often enter. 2. Tissue homeostasis: ILCs help maintain barrier integrity and promote tissue repair – functions that go beyond pathogen defence. 3. Developmental flexibility: Some ILCs may even arise from thymic progenitors, suggesting a shared lineage with T cells but a divergent functional path. 4. Because of speed matters. In evolutionary terms, organisms that could mount a quick response to infection had a survival edge. 5. ILCs also operate in environments where antigen presentation is limited, making their innate responsiveness essential[1,2,29].

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