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Innate Lymphoid Cells: The Hidden Actors in Skin Disorders

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Review Article

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Abstract

Innate lymphoid cells (ILCs) is a collective term that defines a population of lymphoid cells that do not express the typical rearranged receptors, but depends on the common c-chain of IL-2 receptor. The innate lymphocytes includes NK cells and the non-NK ILC: ILC1, ILC2 and ILC3. ILCs groups are categorized based on certain transcription factors and the cytokine production, in an homologous fashion to T cells effector Th1, Th2 and Th17. ILCs play an important role in the lymphoid organogénesis, initiation of inflammation in response to infection and tissue remodelling. They participate in the transition from innate to adaptive immunity and ILCs are involved in the regulation of the chronic inflammation. The dysregulation of their function plays an important role in inflammatory skin diseases, allergies, autoimmunity and cancer. In the present manuscript, we outline the biology of ILCs and review their role in homeostasis and in skin diseases.

Keywords: ILC; Innate lymphoid cells

Introduction

The innate lymphoid cells (ILCs) are a novel type of lymphocyte subfamily, that mediate early immune defense at mucosal and non-mucosal sites, inflammation, and tissue repair in different anatomical compartments, in particular the barrier surfaces of the skin, airways and intestine. They are distinguished from the adaptive immune system by their lack of cell lineage markers associated with T, B, NK or myeloid cells. Different categories of ILCs have been defined based on transcription factor expression and their effector cytokines [1,2]. In an analogous fashion, ILC subsets represents the innate counterparts of CD4+ helper T-cell subsets Th1, Th2 and Th17 [3]. ILCs could influence adaptive immune responses as they reside in the interface of T and B cell zones in the splenic follicles. They express costimulatory molecules for T cell to survive, including CD40 ligand and CD30 ligand. All three ILC subsets have been identified in healthy human adult skin, where a certain group called ILC3 cells are the most abundant. ILC have been also implied in skin conditions such as atopic dermatitis, wound healing and psoriasis and their role in melanoma is not yet entirely revealed [2,4].

ILC classification

Spits et al. [2] categorize ILCs into three groups based on the cytokines they produce and the transcription factors involved in their development and functions (Figure 1):

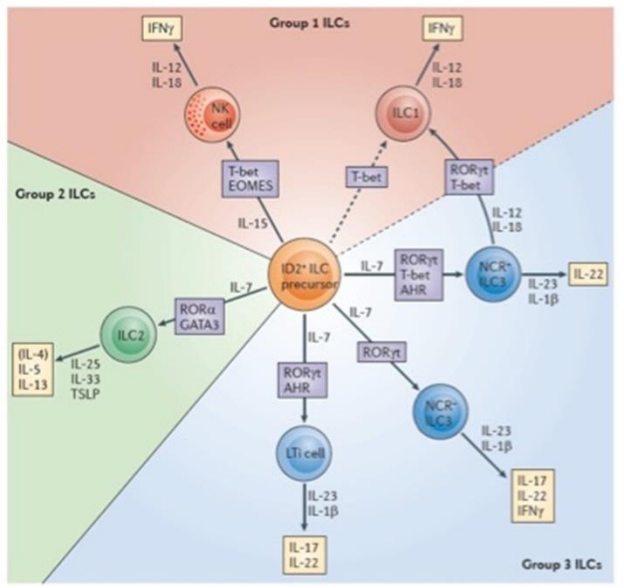

Figure 1: ILC Groups. ILCs are classified into 3 groups: Group 1 ILCs that produce IFNγ: ILC1 and NK cells. Group 2 ILCs, defined by ILC2, which synthesizes Th2 cytokines and depends on RORα and GATA3. Group 3 ILCs is an heterogeneous group that consists on LTi cells and NCR+/- ILC3 cells. This group depend on RORγt and these cells are able to produce or IL-17 and/or IL-22. NCR+ILC3 has the plasticity to become ILC1 under the influence of IL-12 and IL-15. Adapted from Spits et al. (2013) [2].

Group 1: Includes ILCs that produce IFNγ with the inability to produce Th2 and Th17 cytokines. There are two ILC group 1 subsets: the classic cytotoxic NK cell and ILC1, a non-cytotoxic group of cells that produce IFNγ. The Th1 transcription factors T-bet and eomesodermin regulate the development and functions of NK cells. NK cell subsets include cytolytic effectors of the innate immune system and they produce IFNγ, TNFα, MIP1α (macrophage inflammatory protein 1), MIP1β and RANTES (regulated on activation, normal T cell expressed and secreted). They are responsible for defense against intracellular pathogens, tumors and viruses, although they may contribute to aberrant inflammation in certain settings [5]. On the other hand, ILC1 lacks of granzyme B and perforin but express CD103 and CXCR3 (CXC chemokine receptor). ILC1s produce IFNγ in response to IL-12 and they can be found in inflamed mucosal tissue such as tonsils, intestine and in diseased tissue including the lamina propria of patients with Crohn's disease [6].

There are two possible paths to give rise to ILC1. The first would imply ChILP under a repression of PLZF (Promyelocytic leukaemia zinc finger protein) transcription factor. In the second path, ILC1 can be originated from NKp44+ (Natural killer 44-kD surface molecule) group 3 ILC under the influence of IL-12 and IL-15, so they are known as ILC1 ex-RORγt, as the expression of this transcription factor is inhibited [7].

Group 2: Involves ILCs that produce Th2 cytokines such as IL-4, IL-5 and IL-13 in response to stimulation with IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) [2]. They depend on GATA-binding protein 3 (GATA3) and retinoic acid receptor related orphan receptor (RORα), and require IL-7 for their development. ILC2 play a key role in host resistance against nematodes and they are involved in repairing the respiratory tissue, damaged by an acute infection with influenza virus. Activation of skin resident ILC2 promotes amphiregulin production, a ligand for epithelial growth factor receptor and regulates proliferation and migration of epithelial cells to induce wound healing and tissue repair. Human ILC2s express CD45, IL-7Rα, prostaglandin D2 receptor (CRTH2), CD161, c-Kit, CD25 and inducible T-cell costimulator (ICOS) [7-9].

Group 3: Includes all ILC subtypes that produce or IL-17 and/or IL-22 and IFNγ and depend on the transcription factor RORγt and IL-7Rα for their development and functions. Group 3 ILC population is heterogeneous and although it is represented by distinct stable cell populations, these subsets could be part of the same plastic cell type. They play an important role in inflammation, anti-microbial protection, mucosal immunity and homeostasis [10].

The prototypical group 3 ILCs are lymphoid tissue inducer (LTi) cells, which are crucial for the formation of secondary lymphoid organs during embryogenesis. LTi cells express c-Kit, IL-7Rα, IL-1R, IL-23R and lymphotoxin-β receptor (LTβ), CCR6 and aryl hydrocarbon receptor [11].

Another subtype of group 3 ILC is ILC3. They differ from LTi cells as ILC3 cells express the natural cytotoxicity receptor (NCR) NKp44 in humans or NKp46 in mice; therefore they are called NCR+ ILC3s. The NCR(+) ILC3s produce IL-22 but not IL-17A, and they are also known as NK22 cells, NCR22 cells, NKR-LTi cells or ILC22s. IL-22-producing ILC3s are crucial for the IL-22-mediated innate immune response against certain bacteria in the gut [12]. NCR+ ILC3s have the plasticity to transform into ILC1 in the presence of RORγt and T-bet transcription factors and IL-12 and IL-18, as it was mentioned above.

The last subtype found so far, called NCR(−) ILC3, lacks of NCR expression and produces IL-17. Stimulation of NCR(-) ILC3s with IL-23 induces production of IL-17 and IFNγ. This group can regulate adaptive immune responses, as they can process and present antigens [13].

ILC Ontogeny

In the most supported lymphopoiesis model, adaptive and innate lymphocyte subsets derive from the same common lymphoid progenitor (CLP) and their development depends on four stages (Figure 2): [14,15].

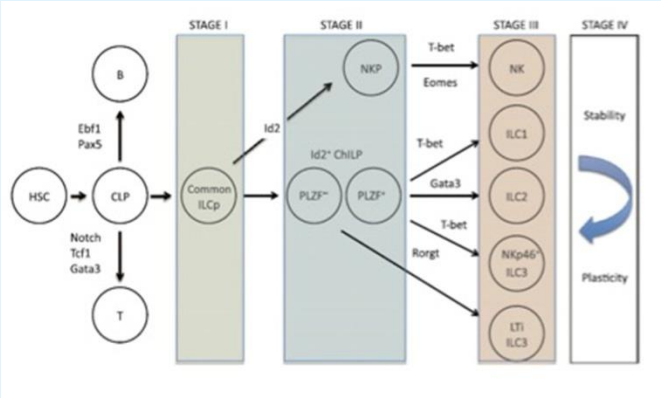

Figure 2: ILC ontogeny. ILCs have a CLP that derives from HSC in bone marrow. The ILC ontogeny can be divided into 4 groups. A common ILCp may differentiate into NKp that madures to NK, or into a ChILP that gives rise to different types of ILC. If ChILP expresses PLZF protein, it can lead to ILC1, ILC2 and NKp46/p44+ differentiation. When ChiLP is PLZF negative, it may become LTi ILC3. Plasticity and phenotypic changes could be observed between stage III ILCs when the microenvironment is adequate. Adapted from Di Santo et al. (2014) [15].

ILC development stage I: The pathways of B- and T-cell depend on several transcription factors, but ILC development is regulated by the transcriptional repressor "inhibitor of DNA binding 2" (Id2). Id proteins inhibits E-proteins, a group of transcription factors essential to develop adaptive immune system, allowing CLP to differentiate in a common ILC precursor [15,16].

ILC development stage II: In this stage, the ILCp divide into helper-like (ChILP) and killer ILCp (NKp) [15]. In the adult bone marrow, NKp could only give rise to NK cells, but not to adaptive immune cells and NKp potential to generate other ILC, it is not yet known [17]. On the other hand, ChILP cellsare able to generate a subset of ILC1, ILC2, and both NKp46+ and LTi cells [18]. Constantinides et al. evaluated the transcription factor PLZF in ILCp and they found two populations in mice. The ILCp PLZF+ give rise to multiple ILC subsets, except LTi cells and NK, whether ILCp PLZF- are related only to LTi development [19].

ILC development stage III: This process involves the functional diversification of ILC and the upregulation of the transcription factors that helps to identify ILC groups. As it was mentioned above, T-bet is essential for ILC1 development, GATA-3 and RORα for ILC2, and RORγt for ILC3. Although ILC lack of antigen receptor, they express a variety of cytokine receptors, costimulatory molecules and retain downstream signaling cascade, which could be involved in the differentiation of distinct ILC subsets [20].

ILC development stage IV*:* The final stage of ILC development is defined by the stability of effector functions within the mature ILC compartment. ILC, as well as T cell helpers (Th) adaptive cells, may exhibit functional plasticity depending on the environmental context [21]. Epigenetic modifications would play a pivotal role to determine stability or plasticity, all along with the regulation of transcription factors and the cytokine [22].

Physiologic functions

Inflammation induction and infection control

- Group 1 ILCs have a crucial role in promoting immunity against intracellular pathogens. NK cells are in charge of the immune response after exposure to multiple intracellular pathogens. ILC1 cells produce IFNγ after the infection with oral *Toxoplasma gondii*, to recruit myeloid cells to control the infection [18,23].

- Group 2 ILCs have a fast response after the exposure to multicellular parasites, such as *Nippostrongylus brasiliensis*. The immunity against helminth infections lead to the induction of type 2 immunity required to control the infection. ILC2s produce IL-13 that induce mucus production and enhance contractility in the gastrointestinal tract, both of which would contribute to the expulsion of the parasites [24,25].

- Group 3 ILCs respond to either extracellular bacteria or fungi infection. NCR+ ILC3s produce IL-22 in the presence of Gram-negative enteric pathogen *Citrobacter rodentium*. IL-22 acts in intestinal epithelial cells and it induces the production of antimicrobial peptides, mucus production and epithelial fucosylation to limit the replication and dissemination of *Citrobacter rodentium* [12].

-Group 3 ILCs located in the oral mucosa promote immunity to fungal infection such as *Candida albicans* in mice. IL-17 and IL-22 promote antimicrobial peptide production and they induce the expression of chemokines to recruit neutrophils to the site of infection [26]. ILC3-derived IL-17 also stimulates neutrophils to achieve resistance to *E. coli* K1 sepsis and is dependent upon the presence of commensal bacteria [27].

Wound healing

ILC2s take part of a host-protective skin reparation in order to restore the skin barrier after an acute injury. In an excisional wound model, where healing is primarily mediated by granulation tissue formation and re-epithelialization, IL-33 mRNA was significantly increased in wounds compared to non-wounded skin within 72 hours. IL-33 can elicit an specific response in wounds, which may result in a selective recruitment and proliferation of ILC2s. IL-13 is a cytokine that derives from active ILC2s and it can transform M2 macrophages into adipose tissue. M2 macrophages promote angiogenesis in wounds, the resolution of inflammation and support efficient wound closure [28].

Thermogenesis and metabolism

ILC2s produce IL-5 and IL-13 by stimuli such as cold or IL-33. Both IL-5 and IL-13 induce the production of IL-4 in eosinophils, in order to recruit M2 macrophages to induce the synthesis of catecholamines and activate the thermogenic program in adipocytes. In addition, IL-4 stimulates the proliferation of bipotential adipocyte precursors and induce their differentiation into beige adipocyte, induces the thermogenesis, protects against insulin resistance and regulates metabolic homeostasis [29,30].

Other immunological functions

ILC are part of many other important immunological aspects. ILC3 group LTi cells induces the lymphoid tissue organogenesis during fetal life and it is essential during the formation of secondary lymphoid tissues such as lymph nodes and Peyer's patches [31-34]. The RORγt ILC group 3 are involved in the regeneration of epithelial cells in the thymus after radiation damage [35].

ILCs contribute to the resolution of inflammation and the repair of damaged tissues after viral infection and as a result of this, IL-33 induces the production of amphiregulin, a mitogen that promotes the growth of normal epithelial cells [23,36].

Pathologic implications

Psoriasis

Psoriasis is a systemic chronic inflammatory disease characterized by inflamed and scaly lesions in the skin, a result of the hyperproliferation state of the epidermis and prominent inflammatory infiltrates. There is a genetic susceptibility combined with environmental risk factors, that triggers a pathogenic cross-talk between innate and adaptive immune cells [37].

Teunissen et al. [37] and Villanova et al. [38] demonstrated an incremental in the NKp44+ ILC3 population in involved and uninvolved psoriasis skin and also in peripheral blood. This population produces IL-22 and possibly IL-17A, two cytokines known to be implicated in psoriasis. A favorable response to treatment of psoriasis with adalimumab, an anti-TNF antibody, was related to a significant reduction of NKp44+ ILC3s in the peripheral blood, suggesting that frequency of circulating NKp44+ ILC3s might reflect disease severity and/or response to treatment with anti-TNF therapy [37-39].

Crohn's disease (CD) is one of the signature inflammatory bowel diseases related to psoriasis, where the homeostasis of the intestinal immune system is impaired. Nevertheless, the role of ILC1 subset in CD is more relevant than in psoriasis. This kind of ILC subsets dysregulation could explain the symptomatic polymorphism in psoriasis, along with certain gene mutations [37-40].

Atopic dermatitis and allergic states

Atopic dermatitis (AD) is an inflammatory, chronically relapsing, pruritic skin disease that is highly prevalent in children. The pathogenesis of AD is linked to a dysregulated type 2 immune responses that includes Th2 cells, IgE-producing B cells, mast cells, eosinophils and basophils. Furthermore, skin ILC2 cells infiltrate AD lesions and they exhibit an activated phenotype [41].

TSLP is a key cytokine secreted by epithelial cells in AD and in mouse models, intradermal or over-expressed TSLP by itself triggers AD. TSLP activates human ILC2 by directly upregulating GATA3, resulting in the production of high amounts of type 2 cytokines, in particular IL-13 [42,43].

The filaggrin mutations contribute to epithelial barrier dysfunction, an important step in AD pathogenesis. In response to barrier damage, keratinocytes produce IL-33 and IL-25, which can trigger cytokine production IL-5 and IL-13 by ILC2 cells. However, in normal skin, ILC2 activity

is suppressed by the interaction with E-cadherin expressed on epithelial cells and Langerhans cells [44,45]. Allergic states linked to AD such as asthma and chronic rhinosinusitis are characterized by a type 2 cytokine signature, in the same manner as in the skin. Not only Th2 cells but also ILC2s are the cellular source of type 2 cytokines in the airway epithelium and lamina propria of asthmatic patients [23,42,46].

Melanoma

It is well known that chronic inflammation and genetic susceptibility are related to cancer development. Although the role of ILCs other than NK cells is not entirely revealed in cancer, different ILC subsets may be involved in the promotion, maintenance or clearance of neoplasms. The immunosuppressive environment in cancer depends on the predominance of Th2 phenotype and correlates to the poor prognosis in cancer. The expression of IL-5, IL-4, IL25 and IL-33 may contribute to the ILC2 polarization and an imbalance in favor to Th2 phenotype, that induce progression of neoplasms in an immunosuppressive status [47].

As an example of ILCs antitumoral effect, the growth of B16 melanoma cells, are repressed by the antitumoral function of IL-12. This cytokine contributes to the upregulation of endothelial adhesion molecules, leukocyte surveillance and elimination of melanoma cells, through the activation and polarization of Th1 cells and NK cells. In murine models that lacked of T and B cells, IL-12 was produced by NCR+ ILC3, dependent on the transcription factor RORγt [48].

The key role of innate immunity in melanoma has not yet been fully understood, although Moskalenko et al. found that the depletion of CD90+NK1.1(-) ILC in mice, limited the chemo-immunotherapy effect and the macrophages infiltration in B16 melanoma. Both in melanoma and normal melanocytes, TRP1 (tyrosinase-related protein 1) forms part of a group of intracellular antigens in melanosomes, but it is also a tumor-cell surface antigen in melanoma. The monoclonal antibody antiTRP1 protects against melanoma B16 in mice. When administered with cyclophosphamide, antiTRP1 clears also melanoma engraftment. In order to achieve its effect, antiTRP1 depends on competent ILCs and Fc receptors, and the absence of the adaptative immunity does not interfere in the tumor clearance [49].

Conclusion

The innate lymphoid cells, a new group of immune cells, have been recently discovered and they have a big impact over the homeostasis, as well as over inflammatory skin diseases and melanoma. ILCs established a major advance in the understanding on how mammalians cope with inflammation, wound healing, lymphogenesis and metabolism. In addition, ILCs are capable of overcoming microbial infections and regulating inflammation and their dysregulation contributes to chronic diseases such as psoriasis, atopic dermatitis, inflammatory bowel disease and asthma. Less is currently known about their involvement in cancer, but it is suggested that ILCs may promote pro and anti-tumoral immune responses. Not only are mandatory more studies dissecting the complexity of ILCs to fully understand their role, but also ILC-specific markers are required for therapeutic interventions.

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