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Innate Lymphoid Cells, Diversity of Functions and Plasticity

Editorial

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Innate lymphoid cells (ILC) in addition to being cooperative cells are important protagonists in tissue homeostasis and inflammation. In the manner of T helper cells (Th), ILCs are classified according to the expression of dominant transcription factors and effector cytokines, thus ILC-1 depends on the transcription factor TBET for IFN-ɣ production; ILC-2 relies on GATA3 for the production of IL 5 and IL-13; and ILC-3 on the retinoid-related gamma-t orphan receptor (ROR gamma-t) and in the aryl hydrocarbon receptor (AHR) for the production of IL-17 and IL-22.

Recent studies have shown that human ILCs are highly plastic cells and can be transformed into other cells of the same lineage with different functions, depending on the microenvironment that surrounds them, that is, an alteration such as an inflammation or any other antigenic insult can alter their phenotype and function to meet prevailing needs [1].

For example, plasticity has been demonstrated between ILC-3/ILC-1, ILC-3 loses the transcription factor ROR gamma-t and acquires TBET, over-regulating IFN-gamma and diminishing the production of IL-22. This conversion is reversible, since an ex-ILC-3 can be differentiated back to ILC-3 if cultured with IL-2, IL-23 and IL-1ß. Similarly, it has been shown that human ILC-2 shows plasticity towards ILC-1 during type 1 inflammatory conditions, such as Crohn's disease and chronic obstructive pulmonary disease (COPD) [1].

Currently, helper ILC-2s are believed to be a very heterogeneous group of cells. These cells have been detected in the intestine, nasal tissue, peripheral blood, adipose tissue, lung and skin. Their main physiological function is the immunological defense against helminthes as demonstrated in mice. They are also associated with skin repair, increasing in density during wound repair.

Two subgroups, functionally and phenotypically distinct from ILC-2s, have been described in mice. The natural ILC-2 described as a homeostatic cell, which resides in the lungs and responds to IL-33, and another called inflammatory ILC-2, which is activated by IL-25, and is a product of inflammation [2]. The latter has not yet been detected in humans. However, heterogeneity can only be detected in type 2 inflammation.

In human, a subgroup the regulatory ILC -2 has also been identified; these develop under the influence of retinoic acid (RA) and express IL-10 and CTLA-4, being able to suppress the activity of CD4+ T cells and effector ILC-2s [3]. Another subgroup is the dermal ILC-2 (dILC2) that expresses CD103 and has been associated with immunosurveillance of the skin through an unknown ligand-receptor pair that interact with mast cells and suppress mast cell activation through the secretion of IL-13 [4]. IL-13-primed mast cells produce lower levels of proinflammatory cytokines (IL-6 and TNF) in response to allergens. These dILC2s may also stimulate mast cells to produce immunomodulatory cytokines (IL-10 and TGF-β) through unknown receptor and IL-13R signaling. A study shows that mast cells-derived IL-10 is essential to inhibit skin inflammation [5]. Therefore, a general consequence of this regulatory network seems to prevent uncontrollable tissue inflammation.

ILC -3s are activated by IL-1ß and IL-23 to produce the effector cytokines IL-22 and, to a lesser extent, IL-17A and IL-17F. In humans, these cytokines are secreted by different subpopulations of ILC -3, with IL-22 being produced by NKp44+ ILC-3. Similar to mouse, human NRP1+ ILC -3 produces significant concentrations of IL-22 and IL-17A. However, it remains unknown whether these cells are different from the helper ILC-3, characterized in mice [6].

The main characteristic of ILCs is their plasticity making them some sort of super-cells, with variable and redundant functions whose roles when elucidated will allow their manipulation in variable therapeutic schemes for countless diseases.

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