Group 2 Innate Lymphoid Cells

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Group 2 Innate Lymphoid Cells (ILC2s) belong to the family of helper ILCs which provide host defense against infectious agents, participate in inflammatory responses and mediate lymphoid organogenesis and tissue repair, mainly at the skin and mucosal level. Based on their transcriptional, phenotypic and functional profile, ILC2s mirror the features of the adaptive CD4+ Th2 cell subset, both contributing to the so-called type 2 immune response. Similar to other ILCs, ILC2s are rapidly activated by signals deriving from tissue and/or other tissue-resident immune cells. The biologic activity of ILCs needs to be tightly regulated in order to prevent them from contributing to severe inflammation and damage in several organs. Indeed, ILC2s display both enhancing and regulatory roles in several pathophysiological conditions, including tumors.

Keywords: group 2 innate lymphoid cells ; immunity in tumors ; immunotherapy

1. Introduction

Helper Innate Lymphoid cells (ILCs) are classified into four groups (ILC1s, ILC2s, ILC3s and lymphoid tissue-inducer—Lti—cells) mimicking the functional profiles of adaptive CD4+ Th cell subsets. ILC2s are devoted to defending against pathogens, lymphoid organogenesis, tissue repair and type 2 inflammatory response in many immune-mediated disorders, including cancer [1].

Exploiting their multiple receptors, ILC2s can be rapidly activated by signals derived from tissue, thus playing a role as sentinel cells involved in the first line of defense against pathogens [2][3][4][5][6]. The biological activities of ILCs need to be regulated to not improve severe inflammation and damage in several organs [7]. Indeed, ILC2s exert both enhancing and homeostatic activities on several cells, including cancer cells and cells from tumor microenvironments (TMEs). Herein we will summarize the main features of ILC2s, analyze their pro- or antitumor activity in different tumors and discuss the ILC2-targeted strategies to improve cancer immunotherapy.

2. Main Features of ILC2s

ILCs derive from common lymphoid progenitors (CLPs) from which common innate lymphoid progenitors (CILPs) and common helper innate lymphoid progenitors (CHILPs) are generated. Whereas CILPs differentiate into natural killer (NK) cell progenitors (NKPs) which then generate NK cells, CHILPs divide into innate lymphoid cell progenitors (ILCPs) and lymphoid tissue inducer progenitors (LTiPs) [8][9][10][11]. Finally, ILCPs generate helper-like ILC subsets, including ILC2s. The transcriptional repressor Id2 is required and sequentially expressed by ILCPs precursors, which can further differentiate, with lineage-specific transcription factors mirroring the phenotype and the function of adaptive helper T cells subsets [8].

ILC2s mainly reside in the submucosa of lung and gut as well as in derma and fat tissue. In these strategic sites they behave as initiators of type 2 immune response. Importantly, ILC2s also localize at interfollicular regions surrounding B cell follicles at the entry of the afferent lymphatics of lymph nodes where interactions between T and B cells occur. This suggests that ILC2s can influence such interactions or the beginning of humoral immune responses by also exploiting their established antigen presenting cells (APC) function [12].

Tissue-resident ILC2s display a panel of sensors for inflammatory mediators, pathogen- and damage-associated molecular pattern (PAMPS and DAMPS), cell density, neuronal signals, complement and angiogenic factors. They are mainly activated by epithelial cells that secrete inflammatory mediators in response to pathogens or other environmental stimuli, thus starting the local immune response [12][13][14]. Epigenetic regulatory networks allow rapid expression of ILC2s functions in response to microenvironmental cues, thus enabling these sentinel cells to promptly respond by restoring homeostasis and collaborating with other resident cells (tissue-resident T memory cells, unconventional T cells, etc) to

activate local immunity and recruit different type of circulating cells [1]. As for Th2 cells, human ILC2s are a GATA-3-dependent subset, even though other transcription factors (RORα, GFI-1, TCF1, Runx1 and Bcl11b) are essential for their development and function [15][16][17][18][19][20][21].

ILC2s do not express rearranged antigen receptors, but integrate multiple (mainly soluble) signals by expressing several receptors that mediate different functions [22]. Their phenotype is characterized by the expression of the prostaglandin D2 (PGD2) receptor 2 (CRTH2), the IL-33 receptor (ST2) and variable levels of c-Kit [23], as well as the NK cell receptor CD161 [24] and the NCR NKp30 [25], which, when engaged by B7-H6, leads to the activation of skin-derived ILC2s. Moreover, the killer cell lectin-like receptor subfamily G member 1 (KLRG1, a coinhibitory receptor expressed by T and NK cells binding the E-cadherins) arises during ILC2 development [26][27]. Notably, ST2+KLRG1+/− ILC2s, defined as natural ILC2s (nILC2s), are responsive exclusively to IL-33, while ST2− KLRG1^{hi} ILC2s, called inflammatory ILC2s (iILC2s), differentiate during infections. iILC2s are highly responsive to IL-25 [28] and can differentiate/shift into ILC3-like cells under type 3-promoting molecules stimulation [26]. Recently it has been shown that helminth-induced IL-33 promotes the generation of iILC2s through the expression of tryptophan hydroxylase 1 and ICOS [29].

ILC2s are triggered by a wide range of soluble mediators released by different types of hematopoietic or nonhematopoietic cells, (epithelial-, adipose-, mast- and tumor cells) [30][31][32][33][34], through many activating and inhibitory receptors, whose knowledge is crucial to understanding their physiologic and pathophysiologic activity.

The main ILC2-stimulating signals are alarmins (IL-25, IL-33 and thymic stromal lymphopoietin—(TSLP-)), growing cytokines (IL-2, IL-4, IL-9 and IL-7) and eicosanoids (mainly PGD2). Besides alarmins receptors, IL-2Rα- (CD25) and IL-7R are essential for the development, homeostasis and activation of ILC2s. ILC2s can also be stimulated by neuropeptides, such as neuromedin U (NMU) and vasoactive intestinal peptide (VIP), which contribute to cytokine production (mainly IL-5) for the eosinophil homeostasis in the lung and gut [35][36]. ICOS and its ligand ICOSL are coexpressed on ILC2s, and their interaction promotes the proliferation of ILC2s as a self-amplifying mechanism [37]. Among activating receptors, ILC2s express several Toll-like receptors (TLRs) (TLR1, 2, 4, 6): TLR2 can directly activate lung ILC2s, an effect potentiated by some allergens. We have shown that human-circulating ILC2s exhibit higher TLRs expression than autologous Th2 cells, and their stimulation through specific ligands induces IL-5 and IL-13 production [38]. Finally, ICAM-1 and its ligand LFA1 are highly expressed on ILC2s and their progenitors, and IL-33 enhances their expression. In particular, ICAM-1 deficiency impairs ILC2s development and function, contributing to reduce lung allergic inflammation [39].

Among the inhibitory receptors, the calcitonin gene-related peptide (CGRP) negatively modulates ILC2s functions in lung inflammation or during helminth infections [40][41]. The β2-adrenergic receptor, highly expressed by intestinal ILC2s, also acts as a negative regulator of the ILC2-mediated inflammatory response [42]. Other inhibitory receptors are those of IL-27, type I or type II IFNs, PGE2, or regulatory cytokines produced by inducible T regulatory cells (Tregs), each of them controlling ILC2s functions through different mechanisms [43][44].

When activated, ILC2s secrete type 2 cytokines, such as IL-4, IL-5, IL-9, IL-13 and amphiregulin (AREG, a member of the epidermal growth factor (EGF) family), which are involved in tissue repair, airway responses and helminth worms expulsion [45]. AREG enhances the suppressive activity of Tregs by triggering surface EGF receptors (EGFR), tissue repair and upregulating the TGF-β production [45]. Activated ILC2s produce PGD2 that acts in an autocrine way supporting ILC2s function via the receptor CRTH2 [46]. In contrast to murine ILC2s, we have recently shown that human-circulating ILC2s from healthy donors produce IL-4, and that the frequency of IL-4-producing ILC2s is higher in atopic individuals than in healthy donors [39].

ILCs are highly plastic and have the potential to transdifferentiate from one subset into another in response to environmental cues [47]. Whereas IL-4 is crucial for retaining ILC2s identity, in respiratory-related disorders, human circulating ILC2s are shown to shift into functional ILC1-like cells that secrete IFN-γ in response to IL-12 and IL-1β [48][49][50]. ILC2s/ILC1s conversion requires the induction of T-bet and the presence of IL-12R. It isn't known if the shifted ILC1s-modulated cells acquire cytolytic activity particularly in TME or derive from a cytotoxic ILC2s subset coexpressing CRTH2 and CD94, a phenotype rarely observed in normal tissues. However, since CRTH2 is downregulated in ILC2s upon activation, it is likely that cytotoxic CRTH2-negative ILC2s are missed in ex vivo analysis of TME infiltrating cells [51]. Moreover, the exposure of murine ILC2s to Notch ligands-induced RORγt expression and elicited both IL-17 and IL-13 production [52]. In humans a c-kit+CCR6+ILC2s subset can shift into IL-17-producing NKp44− ILC3-like cells expressing RORγt in response to IL-1β and IL-23 [53]. We have recently shown that IL1β and IL-23 can favor human circulating ILC2s shift to express RORC and secrete IL-22 [50]. In vitro, the modulated ILC2s continue to express GATA-3 and type 2

cytokines, which are only partially reduced. Of note, such modulated ILC2s have reduced ability to drive IgE synthesis by autologous B cells, since their expression of CD154 (CD40L) is downregulated [50], whereas the helper activity for IgG, IgM and IgA remains unaltered.

3. Enhancing and Regulatory Function of ILC2s

Preclinical studies have clearly shown that ILC2s promoted Th2-cell differentiation since, in their absence, Th2 response in mice is impaired when challenged with allergens or parasitic worms [54]. Accordingly, in humans, an increased number of ILC2s and activity were observed in patients with Th2-oriented disorders as respiratory allergy, atopic dermatitis, chronic rhinosinusitis and eosinophilic esophagitis [54][55][56][57][58][59][60]. Notably, intrahepatic ILC2s contribute also to the process of fibrogenesis in liver diseases through secretion of AREG [61].

ILC2s are the main producers of IL-5, which play a key role in eosinophilic inflammation promoting the differentiation of eosinophils in the bone marrow, their recruitment and survival in the lung of patients with respiratory allergy. When activated the eosinophil produce toxic mediators, that are crucial in determining tissue damage and remodeling. Among such mediators, EDN has been recognized to stimulate TSLP from myeloid dendritic cells (mDC), which in turn maintains this type of inflammation by increasing the ILC2s' survival [62]. ILC2s have been associated in humans with more vigorous variants of airway type 2 inflammation that occur in older asthmatic patients characterized by high numbers of airway and blood eosinophils but relatively low concentrations of serum IgE [63].

The capacity to produce IL-4 and IL-13 has a greater impact, allowing ILC2s to interact with cells of both adaptive and innate immunity. ILC2s support humoral immunity which includes the proliferation/activation of T cell-independent innate B1-cell response and T cell-dependent acquired B2-cell response in mice. In humans, we have recently shown that activated ILC2s express CD154 and are able to induce in vitro IgE production by autologous B cells. This may explain why allergen-specific IgE is often associated to polyclonal IgE production in allergic disorders. Since ILC2s localize at interfollicular regions of lymph nodes where T-B interactions occur, they can directly stimulate B cells to produce polyclonal IgE, but also may influence specific Th2-B cell cooperation for starting allergen-specific IgE synthesis, exploiting their APC function. Indeed, it has been shown that ILC2s may exert APC activity for naïve CD4+ T cells since they express MHC-Class II and costimulatory molecule OX40L [64]. IL-4 has also trophic activity on basophils and mast cells (MC) which are short-lived circulating cells recruited to inflammatory sites (basophils) or long-lived tissue resident cells (MC).

Finally other molecules, such as IL-13 and AREG from activated ILC2s, collectively elicit mucus production, possess smooth muscle hypercontractility, and possess tissue repair abilities, improving fibrogenesis [65][66].

Concerning their regulatory activity, ILC2s can promote Tregs expansion and downregulate excessive immune responses. Tregs proliferation is induced by direct contact with ILC2s through OX40/OX40L or ICOSL/ ICOS signaling [67]. A subset of IL-9-producing ILC2s expressing ICOSL and GITRL, plays a role by activating Tregs in murine and human arthropathies [68]. An increased proportion of IL-9+ILC2s was observed in the blood and joints of patients in remission with rheumatoid arthritis compared to those with relapsed disease: this suggests that IL-9+ ILC2s are essential for the resolution of process of inflammation likely due to other regulatory cytokines that these cells produce [69].

Another regulatory subset is IL10-producing ILC2s. IL-10 exerts suppressive effects on DC, macrophages and Th2 cells, and stimulates the expansion of Tregs [70]. Interestingly, these cells shift from the fatty acid oxidation pathway conventionally used for proinflammatory effector functions, to the glycolytic pathway for IL-10 production [71]. Few IL-10+ ILC2s have been detected in the intestine where their expression was induced in vitro by IL-2, IL-4, IL-27, IL-10 and NMU. Notably this may link the IL-4 stimulation with the suppressive activity of ILC2s. Secreted IL-10 further increased IL-10 production by ILC2s through a positive feedback loop, while TNF superfamily member TL1A strongly inhibited IL-10 production of intestinal ILC2s [72].

4. Pro- and Antitumor Activity of ILC2s

Considering enhancing and regulating properties of ILC2s, their role in TME is still controversial. Moreover, ILC2s activity in tumors could depend on ILC2s distribution and differentiation in tissues, and molecules release by tumor in TME.

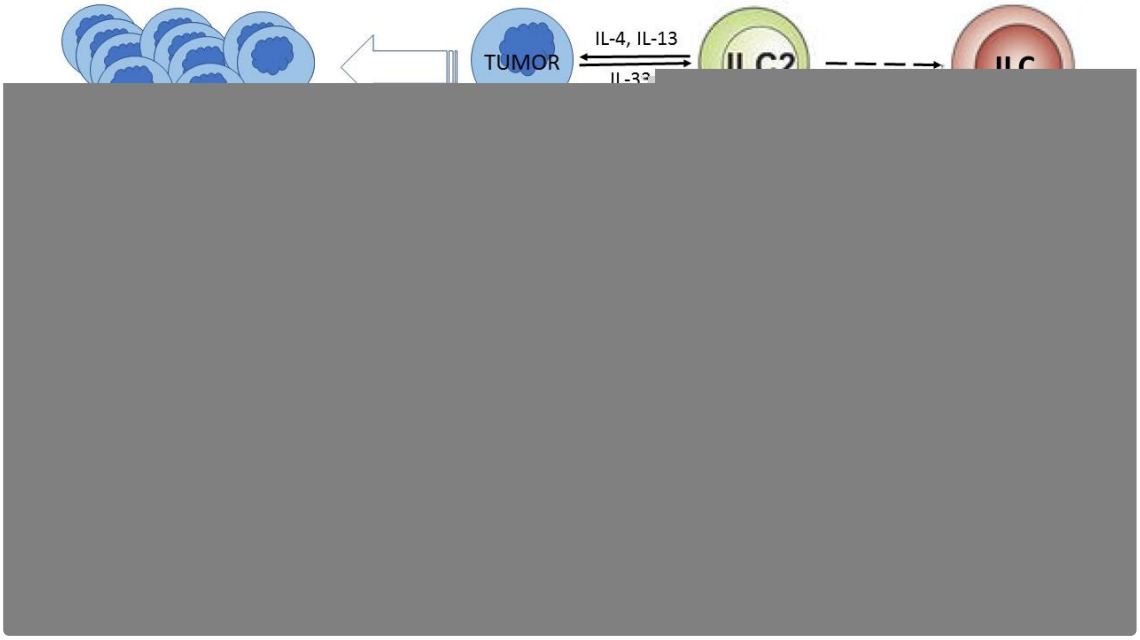
4.1 Protumor Activity

The protumor activity of ILC2s is mainly attributed to IL-33-driven IL-4 and IL-13 production from these cells which have been reported to support tumor development and progression [73]. Depending on the TME and the study models, ILC2s may favor tumor escape through several complementary mechanisms: i. recruitment/activation of myeloid-derived

suppressor cells (MDSCs) and/or Tregs which inhibit antitumor CD8+T cell response, ii. impairment of NK cell-mediated tumor killing, iii. development of type 2 response conditioning TME and tumor cells, iv. induction of epithelial cell proliferation/transformation.

4.2. Antitumor Activity

Some data showing that type 2 shifting is associated with good prognosis in some tumors, such as some types of breast cancers, follicular lymphoma and Hodgkin's lymphoma. In response to the different tissue signals, ILC2s can follow some paths amplifying antitumor type 1-oriented response as the following: i. the recruitment and activation of eosinophils which may induce chemokines (CXCL9, CXCL10, etc) and cytokines (IFN-α) production promoting the recruitment and M1 conversion of macrophages; ii. the production of IL-9 from ILC2s which contributes to M1 shift; iii. the directly activation of tumor-specific CD8+ T cells by ILC2s (exploiting their APC activity) which, in turn, produce IFN-γ, further contributing to amplify type 1 response, including ILC1s conversion from ILC2s.



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