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Review

Brief introduction of Type-2 innate lymphoid cells (ILC2) and its related airway diseases: asthma and chronic obstructive pulmonary disease (COPD)

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Type-2 innate lymphoid cells (ILC2) belong to innate lymphoid cells (ILCs) family, a distinct arm of the innate immune system that is regulated by multiple endogenous mammalian cell-derived factors. ILC2 cells were originally described as producing mainly IL-5 and IL-13 to promote type-2 inflammation in a large variety of inflammatory disorders. In this review, we summarize the recent findings of type 2 innate lymphoid cells (ILC2) in airway diseases, such as allergic asthma and COPD. Furthermore, manipulation of ILC2 cells may represent a new therapeutic target for diverse airway diseases.

Keywords: Type-2 innate lymphoid cells, allergic asthma, COPD

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What is ILCs

Innate lymphoid cells (ILCs), an indispensable part of the innate immune system, are a newly identified population of lineage negative immune cells. ILCs express subunits of cytokine receptors including IL-2 receptor (CD25) and IL-7 receptor (CD127), but unlike adaptive T and B lymphocytes, ILCs lack expression of somatically rearranged antigen receptors and do not exhibit any degree of antigen specificity [1]. ILCs consist of three distinct subpopulations: type 1 (ILC1), type 2 (ILC2), and type 3 (ILC3) – based on their cytokine production. ILC1 cells express T-bet and produce IFN-r and TNF-a. By contrast, ILC2 cells were characterized as an IL-5 and IL-13-producing cells which require the transcription factors ROR-a and GATA-3. Finally, ILC3 are ROR-rt dependent and include three different subtypes, lymphoid tissue inducers (LTi), natural cytotoxicity receptor (NCR)+ and NCR- ILC3 that express IL-22 alone or in combination with IL-17 respectively [2-4]. Collectively, ILC subsets exhibit their diverse functions without antigen specificity, in similar with T helper cell subsets in terms of cytokine expression and potential effector functions.

ILCs localization in tissues

ILCs have been widely identified in embryonic tissues, bone marrow, secondary lymphoid organs, peripheral blood, and other non-lymphoid organs, such as lung and small intestine, and a growing body of evidence suggests that ILC subsets are strategically localized in specific tissues in a manner that relates to their role in immune and inflammatory responses [5]. However, how ILCs maintain their presence in lymphoid and non-lymphoid organs is currently unknown. To address this question, Gasteiger and colleagues recently identified all ILCs, unlike conventional NK cells and T cells, in both lymphoid and non-lymphoid organs as tissue-resident cells that are maintained and expanded locally under physiologic conditions and during acute helminth infection, suggesting ILCs exert as sentinels of body function, especially non-lymphoid organs [6].

All ILC subsets have been identified in lymphoid organs, such as bone marrow, spleen, and lymph node [7, 8]. Regarding to non-lymphoid organs, ILCs exhibit

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organ-specific distribution. ILC1 are the dominant ILC subset in intestinal intraepithelial compartment. By contrast, ILC2 are the dominant ILC subset in the lung, especially in collagen-rich interstitial tissue. And ILC3 are the majority population of ILCs in lamina propria of small intestine [5]. Although each ILC subset has their preference to locate, it does not mean that these cells exert functions in a tissue-resident manner. IL-25 induces rapid proliferation of intestinal ILC2 cells and changes their sensitivity of chemotaxis, leading to lymphatic entry, blood circulation, and accumulation in many non-gut sites [9]. Presumably, circulating ILC2 might be associated with other diseases, such as viral myocarditis. Viral myocarditis is an important cause of heart failure and dilated cardiomyopathy, and commonly associated with Coxsackievirus B3 infection [10-14]. Molofsky *et al* demonstrated that ILC2 stimulate the production of eotaxins from cardiac fibroblasts, enhance the ability of eosinophils to traffic to the heart [15]. Taken together, these findings suggest that tissue-specific distribution of ILCs may contribute to many organ-specific diseases.

Upstream regulation of ILC2s

ILC2 cells were first identified as non-B/non-T cells that produced IL-5 and IL-13 in response to IL-25 [16]. In 2010, three independent studies further characterized the phenotype and function of Th2 cytokine producing non-B/non-T cell populations that are now termed ILC2 [17-19]. More recently, ILC2 cells have been shown to be detrimental in a large variety of inflammation disorders. ILC2 cells both respond to and are activated by a number of different molecules, including cytokines and other inflammatory mediators.

IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) have emerged as important activators of type 2 immunity, including ILC2 cell. These cytokines are mainly produced by epithelial cell and other local stromal compartments upon cellular damage and stress caused by pathogens invasion, allergens challenge, and chemical irritants exposure [20, 21]. Consistently, ILC2 cells have also been shown to express receptors in response to these epithelium-derived cytokines [22, 23].

IL-25, a member of IL-17 family, is stored in and released from cytoplasmic compartments. It is well known that IL-25 is constitutively expressed in epithelial cells and is released upon exposure to proteases [24]. And there is a growing body of evidence suggested that the release of IL-25 could have important implications in allergic diseases. Sharkhuu *et al* reported that administration of IL-25 resulted in attenuated airway hyperresponsiveness, eosinophilic inflammation, mucus hyperdsecretion and the production of Th type 2 cytokines in the lung, and removal of IL-13 and its signal transduction pathway prevents IL-25-induced airway inflammation and AHR [25]. Ballantyne *et al* demonstrated that blocking IL-25 reduced the levels of IL-5 and IL-13 production, eosinophil infiltration, goblet cell hyperplasia, and serum IgE secretion, and prevented AHR [26]. Clinically, serum levels of IL-25 were found higher in allergic and non-allergic asthmatic patients as compared to control individuals [27]. Recently, Hong *et al* demonstrated elevated expression of airway epithelial cells-derived IL-25 and the expansion of IL-13-producing ILC2 cells were observed in neonates mice during RV infection. Administration of anti-IL-25 neutralizing antibody attenuated ILC2 expansion and AHR, suggesting IL-25 signal is indispensable for ILC2-mediated Th2 immune response in RV-induced asthma in neonates [28]. Additionally, IL-25 and ILC2 have also been shown to exert an important role in other pulmonary disease. Hams *et al* found increased expression of IL-25 and elevated population of ILC2 in both pulmonary fibrosis mice and patients, which occurs independently of T-cell-mediated antigen-specific immune responses [29].

IL-33 is a member of IL-1 family cytokines that includes IL-1a, IL-1b, and IL-18 which signals through the IL-1R homolog ST2L. IL-33 is constitutively expressed in and released from the nucleus of epithelial and endothelial cells upon necrosis or cell damage. Thus, IL-33 can be considered to be an 'alarmin' that alerts the immune system to tissue damage [30]. Oshikawa *et al* observed elevated levels of soluble ST2 as well as IL-33 mRNA in the serum and lung tissues in an OVA-induced murine asthma model of airway inflammation [31]. Similar to IL-25, IL-33 has been shown to be a potent activator of lung ILC2 cells. Barlow *et al* demonstrated that IL-33 more acutely induces expansion of IL-13-producing ILC2 cells and increases methacholine-induced airway contraction, whereas IL-25-induced responses are slower and less potent, suggesting a crucial role for IL-33 in an acute allergic lung response [32]. Furthermore, Salimi *et al* demonstrated IL-33, as well as IL-25, is the predominant ILC2-inducing

cytokine in response to skin challenge, with TSLP having a less marked role in comparison [23]. Recently, Rak *et al* observed IL-33-dependent ILC2 responses upon cutaneous skin injury. In the absence of IL-33, ILC2 responses and wound healing were significantly impaired [33]. Together, these data suggested that IL-33/ILC2s axis has an important role in regulating epithelium-immune interactions.

TSLP, an IL-7-like cytokine, is mainly expressed by epithelial cells in response to danger signals such as mechanical injury, pro-inflammatory milieu and proteases. And it is already known that TSLP is associated with the induction of Th2 immune responses and generation of allergic inflammation [34, 35]. TSLP expression was significantly increased in airway epithelium of asthmatic patients, particularly in patients with severe asthma [36]. In recent years, there have been several studies focusing on the role of TSLP in ILC2 cells. Halim *et al* demonstrated that *in vitro* stimulation of ILC2 cells with TSLP significantly increased the production of IL-5 and IL-13 [37]. Remarkably, unlike ILC2 cells are critically regulated by IL-25 and IL-33 in the lung, ILC2 responses in the skin and skin-draining lymph nodes were independent of these canonical cytokines but were critically dependent on TSLP [22]. Collectively, these studies demonstrated an essential role of TSLP in ILC2 cells activation and function.

IL-25, IL-33, and TSLP have all been independently reported as activators of ILC2 cell. Furthermore, combinatorial blockade of all three mediators significantly reduced the population of ILC2s [38, 39]. However, their potency as standalone stimulators of ILC2 is unclear. Recently, Camelo *et al* showed the roles of IL-25, IL-33, and TSLP individually, or in combination, in the phenotype and activation status of ILC2 in an *in vitro* culture system without the presence of other feeder cells. TSLP is important for ILC2 survival, while ILC2 proliferation and activation are more dependent on IL-33, especially when in combination with TSLP. Notably, IL-2 alone was not able to induce significant activation of ILC2s, however, when combined with any other epithelial cytokine, especially IL-33, it amplified the ILC2 response, leading to an increase in IL13 and GM-CSF production [40].

Aside from these three epithelium-derived cytokines, more other activation mediators of ILC2s have been identified. IL-1b was reported to activate human ILC2s directly[41]. IL-1b was known for its capacity to activates ILC3s in the presence of IL-23, and it could also transdifferentiates ILC1s into ILC3s in combination with IL-23 and retinoic acid [42-44]. Besides, ILC2s also express the receptor for IL-1b [45]. Further, Bal *et a*l demonstrated that IL-1b in combination with IL-2 significantly stimulated the production of IL-5 and IL-13 by ILC2s. The production of IL-5 induced by IL-2 and IL-1b was even higher than that induced by the combination of IL-2 and IL-33 or IL-2 and TSLP [41]. Barnig *et al* demonstrated that PGD2 which binds to CRTH2 expressed on human ILC2s potentiated IL-13 production of peripheral blood ILC2s *in vitro*. And this effect was reversed upon the addition of lipoxin A4 suggesting lipoxin A4 has an inhibitory effect on human ILC2s[46]. Further, Doherty *et al* demonstrated that mouse lung ILC2s express the cysteinyl leukotriene 1 receptor (CysLT1R) which is preferentially activated by leukotriene D4. Addition of Leukotriene D4 induced Th2 cytokine production from lung ILC2s *in vitro*, and increased ILC2s proliferation and eosinophilia *in vivo*[47]. Yu *et al* have reported that TL1A, a member of TNF superfamily which binds to Death receptor 3 (DR3), also directly activates ILC2 and synergizes with IL-25 in vitro to promote cytokine production and expand ILC2s population[48]. Although molecular pathways have been discovered that control the development and function of ILCs which we discussed above, the epigenetic mechanisms that regulate ILC are unclear. Epigenetic modification control gene expression patterns in a cell which involves the pathogenesis of many diseases, such as autoimmune disease and cancer [49-52]. Recently Antignano et al have identified a role for the lysine methyltransferase G9a in regulating ILC2 development and function [53].

ILC2s in allergic asthma

The lung is a unique immune site because it is constantly exposed to potential pathogens. Innate lymphoid cells that are capable of rapidly responding to infections are probably important for the lung immune system. Asthma is now recognized as a heterogeneous syndrome, which is associated with the differences in the influence of genes and environment. A growing body of evidence demonstrated that lung-resident ILC2 contributed to airway inflammation and hyperresponsiveness by responding to IL-25, IL-33, and TSLP [26, 29, 32, 39, 40]. In addition to

mediating acute type-2 inflammation, ILC2 can also influence adaptive immunity [54]. ILC2-deficient mice show an impaired Th2 response to allergen administration, and this could be rescued by ILC2 reconstitution by adoptive transfer. And this defect was due to a deficiency in ILC2-derived IL-13 that was shown to be important for induction of Th2 response. As we described above, IL-25, IL-33, and TSLP can all activate ILC2, but whether there is any specificity in the cytokine elicited in response to a particular allergen remain poorly elucidated. For instance, IL-33 is the most prominent cytokines in response to certain allergens, but IL-25 also plays a role in ILC2 expansion and airway inflammation [32, 55]. Even though ILC2 fit well into an eosinophil-dominated allergic asthma, the elements regulating non-allergic asthma are less clear.

ILC2s in COPD

Chronic obstructive pulmonary disease (COPD) is an airway disorder defined by irreversible and progressive decline in lung function caused by airflow obstruction, destruction of parenchyma, and physema[56]. Cigarette smoke (CS), a major risk factor for the development and pathogenesis of COPD, induces chronic lung inflammation and is presumed to be central to the altered responsiveness to recurrent infection in COPD patients[57, 58]. Other risk factors include exposure to air pollution, occupational dust and chemicals, a history of childhood respiratory infections, and socioeconomic status [59]. The hallmark of COPD is chronic inflammation involving the activation of structural and inflammatory cells in the lung microenvironment[60]. For example, CS activates airway epithelial cells; reduces cilia; and constitutively activates alveolar macrophages. These activated cells release potent inflammatory cytokines and chemoattractants in the lung microenvironment that collectively induce a state of chronic inflammation[61]. Chronic inflammation not only contributes to lung damage, but also compromises innate and adaptive immune responses, and facilitates the recurrent infection of respiratory tract. Hence a fine balance between the induction of immune responses and immunosuppressive networks is needed to minimize lung inflammation without compromising immunity against respiratory infections, which raises the possibility that the plasticity of immune cells might confer to the imbalance of immune responses in COPD patients.

Early studies of T helper cells demonstrated that effector functions were not fixed but rather could be manipulated by extrinsic signals such as cytokines and growth factors[62]. ILCs, critical mediators of mucosal immunity, have also been shown to have plastic properties modulated by microenvironmental signals in a similar pattern. For example, ILC3s→ILC1s plasticity was promoted by extrinsic signals (IL-12, IL-18) and prevented by IL-7[63] and ILC1s→ILC3s plasticity was promoted by IL-1b and IL-23 in human and mouse [43]. Recently ILC2s plasticity has been demonstrated that IL-1b and IL-33 stimulated ILC2s elevate T-bet expression and production of IFN-r in an IL-12-dependent manner. Although there is no evidence that ILC2 contribute to the pathogenesis of COPD, innate lymphoid cells (ILCs) are critical mediators of mucosal immunity, and group 1 ILCs (ILC1 cells) and group 3 ILCs (ILC1 cells) have been shown to be functionally plastic. Overall, chronic inflammation and compromised immunity to respiratory pathogens are strongly associated with the induction of immune suppressive networks that likely contribute to COPD pathogenesis.

ILC2s and antibody engineering

Antibody engineering offers a potential and effective way in cell blocking and depletion as well as depletion of harmful cytokines [64, 65]. Anti IL17a monoclonal antibody has been characterized in animal experiments, and results are encouraging and lid a light in monoclonal antibody isolation against IL5 and IL13 released by ILC2 [66]. It has been reported that naive B cell can be blocked by antibodies to reduce its function [67], and evidences are also raised that B cells can be primed by epitopes, which also indicates the potential role of functional cells blocking by antibodies [68, 69]. Currently there are panels of approaches in functional antibody isolation and characterization against immunogens, including virus particles, tumor markers, as well as cytokines [70-73]. The approaches of large scale of antibody production are full of diversity. Plant expressing antibodies have been proved applicable in treatment of Ebola. The functional activity and yield of monoclonal antibodies produced by plants are both meet the requirement in clinical treatment. In addition, the transgenic plants with drought, cold, or heavy metal resistance displayed a big potential for functional antibody production for they can growth in severe environment

[74-77]. These observations are offering indications in antibody engineering against ILC2 caused diseases.

Conclusion

Type-2 innate lymphoid cells (ILC2), serving as a distinct arm of the innate immune system, has been reported related with many airway diseases, including allergic asthma and COPD. Manipulation of ILC2 cells may represent a new therapeutic target for these airway diseases. Antibody engineering may provide a novel approach for ILC2 blocking or depletion, which lid a light in treatment of ILC2 related airway diseases.

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