REVIEW ARTICLE

The Role of Innate lymphoid cells in health and disease†

Running title: Innate lymphoid cells and Autoimmunity.

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Abstract

Innate lymphoid cells (ILCs) are kind of innate immune cells which can be divided into three main subsets according to their cytokine release profile, transcription factors, and surface markers. ILCs affect the initial stages of immunity in response to microbes and participate in immunity, inflammation and tissue repair. ILCs modulate immunity through resistance to the pathogens and regulation of autoimmune inflammation and metabolic homeostasis. Therefore dysregulation of ILCs may lead to chronic pathologies such as allergies (i.e. asthma), inflammation (i.e. inflammatory bowel disease) and autoimmunity (i.e. psoriasis, atopic dermatitis, rheumatoid arthritis, multiple sclerosis, and ankylosing spondylitis). Regarding the critical role of ILCs in the regulation of immune system, the elucidation of their function in different conditions makes an interesting target for improvement of novel therapeutic approach to modulate an immune response in different disease context. This article is protected by copyright. All rights reserved

Key words: Innate lymphoid cells, Inflammation, Allergy, Autoimmunity.
Introduction

During the past years, a variety of innate lymphoid cells (ILCs) have been emerged which play a crucial role in the modulation of inflammation (Spits et al., 2013). ILCs exert various functions in the initial stages of the immunity in response to microbes (Cella et al., 2009; Moro et al., 2010), tissue repair (Monticelli et al., 2011; Scandella et al., 2008), anatomical containment of microbiome (Sonnenberg et al., 2012), and epithelial barrier function (Sonnenberg et al., 2011a). ILCs neither express lymphoid differentiation lineage markers (LIN-) nor antigen receptors which make them discriminated from T cells and B cells (Hwang and McKenzie, 2013). ILCs are derived from hematopoietic lymphoid precursors and characterized by the lack of recombination activating genes (RAG1 or RAG2) expression (Nowarski et al., 2013). Recent studies demonstrated that the transcription factor Id2 (inhibitor DNA 2) is necessary for differentiation of all innate lymphocytes (Hwang and McKenzie, 2013; Yokota et al., 1999) implying that all innate lymphocytes might be developed from a common precursor. The first ILCs were identified several years ago, including Natural Killer (NK) cells (Jadidi-Niaragh et al., 2012; Pross and Jondal, 1975) and lymphoid tissue inducer (LTi) cells (Kelly and Scollay, 1992; Mebius et al., 1997). Other ILCs were recently recognized which can be divided into three main subtypes, called group 1, 2 and 3 ILCs based on the expression of surface markers, transcription factors (TF) and effector cytokine release pattern (Spits et al., 2013). Each ILC subtype exhibits a specific cytokine release pattern that represents the cytokine-secreting profiles of helper T-cell subsets (Spits and Di Santo, 2011). ILC1 promotes secretion of IFN-γ via T-box, ILC2 generates type 2 cytokines via GATA-binding protein-3 and ILC3 secretes IL-17 and IL-22 via retinoic acid receptor-related orphan receptor-γt (Montaldo et al., 2016; Sanati et al., 2015). Modification of frequency and function of ILCs in various diseases implies a critical role of these cells in human health and disease (Sonnenberg and Artis, 2015). Therefore, dysregulation of these cells can affect chronic pathologies such as allergies, autoimmunity, and inflammation (McKenzie et al., 2014). In this review, we will focus on the role of ILCs in inflammation, allergy, and autoimmune disorders.

Development and heterogeneity of ILCs

ILCs derives from common lymphoid progenitors (CLPs) initially in the fetal liver and then in the adult bone marrow (BM) (Cherrier et al., 2012; Constantinides et al., 2014; Klose et al., 2014). Similar to B and T cells, ILCs develop from the CLPs, but dedicated transcription factors inhibit the generation of B and T cells and promote the development of the various ILCs (Eberl et al., 2015). Transcription factors inhibitor of DNA binding 2 (Id2), nuclear factor interleukin-3 regulated (NFIL3) (Geiger et al., 2014; Klose et al., 2014; Kobayashi et al., 2014; Seillet et al., 2014; Spits et al., 2013; Walker et al., 2013; Xu et al., 2015; Yu et al., 2014), and thymocyte selection-associated high mobility group box (Tox) (Aliahmad et al., 2010; Seehus et al., 2015) are required for differentiation of all ILCs from a CLP (Figure 1).

Type 1 ILCs contain innate lymphocytes expressing T-box transcription factor T-bet and secrete interferon (IFN)-γ in response to interleukin (IL)-12 and IL-18, cellular ligands up-regulated in tissues after infection or wound, and/or pathogen associated molecular patterns (Cooper et al., 2001; Jacobs et al., 2001). In humans, type 1 ILCs have been found in the mucosal associated lymphoid tissues such as tonsils and gut (Bernink et al., 2013; Fuchs et al., 2013), liver...
(Marquardt et al., 2015), endometrium and decidua of the uterus (Vacca et al., 2015), and in the skin (Villanova et al., 2014a).

A new subtype of ILCs have been identified that produce type 1 cytokines especially IFN-γ, but not other signature cytokines including IL-17, IL-22, and IL-5 (Spits et al., 2013; Walker et al., 2013). The first reported subset of ILCs named natural killer cells (NKs). It seems that not only NK cells have cytotoxic function against tumors, but also incorporated into the deletion of viruses and other intracellular pathogens, so explaining them as effector innate lymphocytes (Herberman et al., 1975; Kiessling et al., 1975; Vivier et al., 2011).

Type 2 ILCs (ILC2s) express GATA binding protein-3 (GATA3), secrete IL-13 and IL-5, reply to IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) and involve in the defense against helminthic infections and pathogenesis of allergic inflammation (Bernink et al., 2014; Hoyler et al., 2012b; Kim et al., 2013; Mjösberg et al., 2012; Moro et al., 2010; Neill et al., 2010; Price et al., 2010; Teunissen et al., 2014; Walker and McKenzie, 2013). These cells are also entitled natural helper cells (NHC), nuocyte and innate helper 2 (IH2s) cells (Koyasu and Moro, 2012; Walker et al., 2013). In humans, ILC2s are present in the peripheral blood (Mjösberg et al., 2011), lung (Mjösberg et al., 2011; Monticelli et al., 2011; Wojno et al., 2015), fetal gut (Mjösberg et al., 2011), skin (Dyring- Andersen et al., 2014; Teunissen et al., 2014), tonsils (Bernink et al., 2013), and adipose tissue (Brestoff et al., 2015; Moro et al., 2010).

ILC3s express retinoic acid receptor (RAR)-related orphan receptor RORγt, reply to IL-1β, IL-23, and danger/pathogen signals (Crellin et al., 2010a; Glatzer et al., 2013), and secrete IL-17 and/or IL-22 (Cella et al., 2009; Crellin et al., 2010a; Crellin et al., 2010b; Luci et al., 2009; Sanos et al., 2009; Satoh-Takayama et al., 2008; Sonnenberg et al., 2011b). Human ILC3s from adult persons have been largely found in tonsils (Cella et al., 2009; Cupedo et al., 2009) and lamina propria of the intestine (Cella et al., 2009) and to lesser extent in spleen (Magri et al., 2014), endometrium and decidua (Vacca et al., 2015), skin (Dyring- Andersen et al., 2014; Teunissen et al., 2014; Vacca et al., 2015) and lung (Kim et al., 2014b). An important group 3 of ILCs are LTi cells that were first recognized as CD4+CD3-cells sprinkled among fetal and neonatal lymph nodes (Mebius et al., 1997; Mebius et al., 1996). LTi cells are generated independently of IL-15 (Satoh-Takayama et al., 2010) and require RORγt for their generation and function (Cherrier et al., 2012). LTi critically affects the development of lymphoid tissues (Sonnenberg et al., 2011b). Some ILC3s express natural cytotoxicity receptors (NCRs) which discriminate them LTi (Luci et al., 2009; Spits et al., 2013). Recent studies have explained the role of transcription factor Notch in the generation of ILC3 (Bouskra et al., 2008). It has been proved that Notch signaling cooperates to maximize the efficiency of LTi cell differentiation (Cherrier et al., 2012). Transcriptions factors Runx1 and Tox are also required for development of LTi (Aliiahmad et al., 2010; Tachibana et al., 2011). Additionally, aryl hydrocarbon receptor (AhrR) signals are needed to support development of postnatal emerging of ILC3 subset (Spits and Di Santo, 2011). It has recently demonstrated that a divergent long noncoding RNA (IncRNA), IncKdm2b, exhibited a high expression in ILC3. LncKdm2b enhanced the maintenance of ILC3s in part through promoting their proliferation via activation of the transcription factor Zfp292 (Liu et al., 2017).

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ILCs promote the resolution of inflammation and tissue repair

ILCs directly help to control inflammation by restoring injured tissues, containing the lung, various lymphoid tissues, and the gastrointestinal tract. These procedures are vital to regulate prolonged inflammation, avoiding reinfection and repairing tissues to the homeostasis circumstance (Sonnenberg and Artis, 2015). ILCs seem to be particularly powerful modulators of epithelial barriers. The maintenance and re-formation of barrier unity are necessary for the control of inflammation after infection or inflammatory responses (Klose and Artis, 2016). In addition to advancing immunity and inflammation in some contexts, recent analyses have highlighted an important role of both type 2 and type 3 ILCs in tissue repair and immune homeostasis, either in the steady circumstance or during the of inflammatory responses (Spits and Cupedo, 2012; Spits and Di Santo, 2011).

ILC2s are implicated in the tissue-remodeling through the secretion of amphiregulin (Areg: a ligand of the epidermal growth factor receptor) and IL-13 (Zhang et al., 2013). Tissue repair of the infected airways or injured intestinal epithelium is regulated by amphiregulin produced by IL-33-stimulated ILC2s (Monticelli et al., 2015; Monticelli et al., 2011). ILC2s also increase wound repair in the skin by an as-yet-undefined process (Rak et al., 2016). Harmful effects of ILC2-dependent tissue restoring have been demonstrated in the liver fibrosis after chemical damage, where IL-33-stimulated ILC2s produce IL-13 that induces fibrosis (Mchedlidze et al., 2013) (Klose and Artis, 2016).

ILC3s promote tissue defense and repair responses by production of LTα1β2 and IL-22. Infection of lymph nodes with lymphocytic choriomeningitis virus induced destruction of lymphoid stromal cells (LSCs) (Scandella et al., 2008). ILC3s repair LSCs by LTα1β2 and activation of LTβ receptor on LSCs. IL-22 preserve epithelial cells, mostly by activation of anti-apoptotic pathways. In a model of graft-versus-host disease (GvHD), ILC3s protect intestinal epithelial stem cells from the cell death in part through secretion of IL-22 (Dudakov et al., 2012; Hanash et al., 2012).

ILCs in the immunopathogenesis of mucosal tissue Inflammation

There are various subsets of ILCs in different parts of the body, however most of them are found in mucosal tissues (i.e. skin, intestine, respiratory tract, lymph nodes and etc.) (Kumar, 2014). ILC-derived cytokines can also participate in the immunopathology of diseases such as asthma, inflammatory bowel diseases (IBDs) and gastric adenocarcinoma (Amedei et al., 2014; Yazdani et al., 2015). It has been shown that while RORγt-dependent ILCs are involved in the colitis and IBD, ILC2s participate in allergy (Hwang and McKenzie, 2013). Amedei et al. showed that tumor-infiltrating lymphocytes (TILs) cells from H. pylori infected patients with distal gastric adenocarcinoma produced IL-17 and IL-21 in response to HP0175 (Amedei et al., 2014).

ILCs in the lung Inflammation

Several infectious and allergic stimuli can provoke the expression of IL-33 by epithelial cell and macrophage in the lung. IL-33, IL-2, and IL-7 stimulate ILC2s to secrete autocrine IL-9 and paracrine IL-5, IL-13 and amphiregulin that, depending on the setting, can promote both pathologic allergic airway inflammation and protective airway tissue remodeling (Monticelli et al., 2012). Umetsu and Colleagues discovered that ILCs exert a pathogenic role in inducing
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airway hyper-reactivity after viral infection in the respiratory tract. (Chang et al., 2011). Infection with H3N1 enhanced acute allergic airway inflammation characterized by a fast AHR response that develops in the adaptive immune independent manner (Chang et al., 2011). In addition to having a pathogenic function in the context of allergic airway inflammation, a current report indicated that ILCs could enhance beneficial tissue repair effects in the lung after acute epithelial destruction (Monticelli et al., 2011). Collectively, these reports imply that ILC2s can exert both the protective and pathogenic effects depending on the tissue microenvironment and the nature of the inflammatory signal (Monticelli et al., 2012) (Figure 2).

ILCs in the intestinal immune defense and inflammation
ILCs play also a pivotal role in immune defense against intestinal bacterial infection. For example, recent studies have demonstrated that RORγt+ ILCs or ILC3s play a prominent role in the defense against C. rodentium (Satoh-Takayama et al., 2008; Satoh- Takayama et al., 2011; Sonnenberg et al., 2011a; Tumanov et al., 2011). During the infection with C. rodentium, CD4+ LTi cells act as a major source of primitive IL-22 and this response depends on IL-23 as ablation of IL-23 cause an imperfect innate immune response (Mjösberg and Spits, 2016; Sonnenberg et al., 2011a). In addition, decrease in CD4+ LTi cells stroked out infection-induced expression of IL-22 and anti-microbial peptides (AMPs), making a growth in mortality rate of infected animals. These studies indicated that LTi cells are important for the host to present rich defensive immunity against bacterial infection. This primitive release of IL-22 from intestinal ILCs is stimulated by lymphotoxin (LT) during C. rodentium infection (Bostick and Zhou, 2016; Tumanov et al., 2011). Liu et al. demonstrated that LncKdm2b deletion reduces the expression of all ILC3s in the intestine, which leads to decreased amounts of IL-22 and higher susceptibility to bacterial infection (Liu et al., 2017). Besides the important role of ILCs in maintaining intestinal homeostasis via interactions with commensal microbiome and supporting the formation and function of the GALT, ILCs can act as potent innate immune effector cells that promote resistance to intestinal pathogens (Spits and Cupedo, 2012; Spits and Di Santo, 2011). High amounts of ILC-derived cytokines could lead to intestinal inflammation if produced in the lack of infection-induced tissue damage (Monticelli et al., 2012). It has been demonstrated that intestinal ILCs play a critical role in preclinical models of intestinal inflammation implying their involvement in the pathogenesis of IBD. To date, ILC3, ILC1 and to lesser extent ILC2 are involved in IBD (Goldberg et al., 2015).

Pathogenic ILC1 in intestine
Intra-epithelial CD103+NKP44+ ILC1 and lamina propria ILC1 are likely developed in the ileum of Crohn’s disease patients in contrast with non-inflammatory control patients (Bernink et al., 2013; Fuchs et al., 2013), which implying the pathogenic function of ILC1s in Crohn’s disease (Goldberg et al., 2015). ILCs interact with other important mucosal cells in IBD. In inflamed situation, ILC3 differentiates toward IFN-γ producing ILC1, under the influence of IL-12. IFN-γ activates macrophages and other mononuclear phagocytes. Epithelial stress enhances the expression of ligands that crosslink NKP44, changing the cytokine production by ILC3 from IL-22 to TNF, which enhances several proinflammatory functions, including direct epithelial apoptosis and neutrophil recruitment. NCR-ILC3 secretes...
proinflammatory cytokines including IL-17 (and occasionally IFN-γ) that lead to neutrophils activation and recruitments (Goldberg et al., 2015).

**Pathogenic ILC3 in intestine**

Intestinal ILC3s potently secrete IL-17A and IFN-γ. Reduction of intestinal ILCs or antagonism of their major cytokines in mice led to attenuation of colitis, implying the deleterious function of ILC3s in colitis (Goldberg et al., 2015). Pathogenesis of colitis can not only be affected by the presence of ILC22 cells, a balance status between protective and pathogenic ILCs may also be critical for the pathogenesis of colitis and IBD (Klose et al., 2012). In other studies, innate immune cells derived from colon samples of patients with Crohn’s disease or ulcerative colitis exhibit elevated expression of major ILC3 cytokines (i.e. IL-17A and IL-22), transcription factors (RORγt and the AhR) and cytokine receptors (IL-23R) (Geremia et al., 2011). These studies support this idea that intestinal NCR-ILC3 might have a pathogenic action in chronic intestinal inflammation. Further studies on these cells are needed in human IBD (Goldberg et al., 2015).

**ILCs orchestrate acute inflammation**

Acute inflammation is necessary in order to elevate an efficient immune response to various infectious microorganisms. ILCs were initially determined on the basis of their ability to enhance quick and vital innate immune responses against various kinds of pathogens, in part by regulating local epithelial cell, myeloid cell or granulocyte responses. These cells develop innate immune responses against a number of intra and extracellular pathogens (Sonnenberg and Artis, 2015). ILC1s have a pivotal role in enhancing immunity against intracellular pathogens like promoting immunity against *T. gondii*, by producing TNF and IFN-γ under the influence of DC-derived IL-12. Moreover, they facilitate recruitment of inflammatory myeloid cells. However, little is known about the function of other type 1 ILCs (Klose et al., 2014). Consistently, T-bet deficient mice were highly sensitive to *T. gondii* infection, and adoptive transfer of ILC1s to lymphocyte-deficient mice promoted immunity (Klose et al., 2014).

**ILC2s and extracellular parasites**

ILC2s were initially identified as major innate immune cells responsible for anti-helminth protection (Fallon et al., 2006). The fact that potent type 2 immune responses can be induced by the lack of T cells is reported several times before the recognition of ILC2s (Fallon et al., 2006; Fort et al., 2001). Most of the observations indicate a non-redundant function for ILC2s in parasite infections is against the nematode *N. brasiliensis* (Hoyler et al., 2012a; Moro et al., 2010; Neill et al., 2010), however some observations implied that ILC2s might also involve in the clearance of *Strongyloides venezuelensis* and *Trichuris muris* (Yasuda et al., 2012; Zaiss et al., 2006). IL-25 and IL-33 are necessary for ILC2 activation and worm removal in most conditions (Neill et al., 2010; von Moltke et al., 2015). Tuft cells secrete IL-25 in the intestine and stimulate the IL-13 secretion that increased tuft-cell hyperplasia in return (Gerbe et al., 2016; Howitt et al., 2016; von Moltke et al., 2015). Another important development process in early ILC2 activation is the generation of
IL-9, that acts in an autocrine manner on ILC2s (Wilhelm et al., 2011). Activated ILC2s released IL-4, IL-5, IL-13, and amphiregulin against helminth infection. IL-5 is a prominent factor contributed to eosinophil function, while amphiregulin mediates the repair of epithelial cells; however the mechanisms of amphiregulin’s action in host defense are less defined. IL-13 stimulates smooth-muscle contraction, mucus production by goblet cells, the recruitment of alternatively activated macrophages (AAM) and secretion of eotaxin, which together cooperate worm removal (Artis and Spits, 2015; Moro et al., 2010; Neill et al., 2010; Zaiss et al., 2006).

Production of IL-17 and IL-22 by ILC3s in response to DC-derived IL-23 and IL-1β enhances innate immunity against fungi and extracellular bacteria. IL-17 and IL-22 enhance neutrophil accumulation in the intestine and the generation of antimicrobial peptides from intestinal epithelial cells (IECs), and stimulate the expression of chemokines (Cxc11 and Cxc19) in order to recruit neutrophils to the location of infection (Aujla et al., 2008; Sonnenberg et al., 2011a; Sonnenberg et al., 2010; Zheng et al., 2008). IL-17 that produced by ILC3 modulates neutrophils in neonatal mice, which is vital for resistance to sepsis with gram-negative opportunistic bacteria and is relying on the presence of commensal bacteria (Deshmukh et al., 2014). Collectively, this recommends that the ILC family has a major role in mediating acute inflammation in response to infection, which is important for the control and clearance of different types of pathogens (Sonnenberg and Artis, 2015).

ILCs promote chronic inflammation

Increased levels of IL-25 and IL-33 production in the asthmatic lung tissue lead to some physiological changes in the lungs such as quick type 2 responses increased releasing of IL-5, IL-13 and mucus production, eosinophilia, and hyper reactivity in airways. As mentioned, IL-25 and IL-33 could stimulate the production of type 2 cytokines by ILC2s. IL-33 and ILC2s have a role in the persistence of airway hyper reactivity, and IL-13 that released by ILC2s increases expression of IL-33 in epithelial cells (Kabata et al., 2015). It is also possible that type 2 ILCs represent a major source of IL-13 in chronic asthmatic patients, which may involve in repairing the lung tissue and lung fibrosis (Olman, 2003). Certainly, this feedback loop is expected to be involved in enhancing chronic asthma. ILC2s are effective in development of asthma even in the absence of IL-13 secreted from T cells (Barlow et al., 2012). It has been understood that the promotion of IL-9, IL-17, IL-22 and IL-25 extremely associated with severity of asthmatic symptoms. Additionally, it was revealed that simultaneously elevate in ILC and eosinophil numbers and inflammatory cytokines in asthmatic patients may explain the relation between ILCs, eosinophils and Th cells in initiation and development of allergic responses (Sherkat et al., 2014). Additionally, Mjösberg et al. have shown TSLP increases human ILC2 in order to upregulate GATA3 via STAT5 which causing the release of high levels of IL-5 and IL-13, the type 2 cytokines (Mjösberg et al., 2011). These data are highly related to the setting of asthma, especially in the severe asthmatic patients. These observations are approved by other studies in mouse models (Barlow et al., 2012; Halim et al., 2012; Wolterink et al., 2012).

Furthermore, ILC2s are increased in nasal polyps of patients affected by chronic rhinosinusitis (Juelke and Romagnani, 2016). These patients exhibited the higher amounts of IL-5 and IL-13 transcripts in the polyp tissue, which in turn leads to
eosinophil enrichment in the nasal polyps (Barlow et al., 2012). Epithelial cells of nasal polyps might be able to make high amounts of TSLP and IL-33, which enhanced IL-5 and IL-13 production by ILC2s in patients (Mjösberg et al., 2011). The elevated numbers of ILC2s were detected in the skin of human atopic dermatitis (AD) patients compared to healthy subjects (Kim et al., 2013; Salimi et al., 2013). These cells are induced by TSLP (Kim et al., 2013) and possibly by IL-25 and IL-33, because increased expression of these cytokines have been identified in AD skin lesions (Imai et al., 2013; Kim et al., 2013; Salimi et al., 2013). The lectin inhibitory receptor KLRG1 acts as a regulator of ILC2 activation during AD, because its ligand, epithelial cadherin (E-cadherin), which decreases ILC2 cytokine production, is downregulated in AD lesions (Salimi et al., 2013). Investigations in animal models of atopic dermatitis imply that ILC2s can play a T-cell-independent function in inducing skin lesions (Kim et al., 2013). Additionally, ILC2s can interact with other types of innate immune cells such as mast cells and basophils in order to develop type 2 inflammation in the skin (Kim et al., 2014a; Motomura et al., 2014; Roediger et al., 2013). The skin also contains ILC3s, which in mice has been demonstrated to interact with fibroblasts by IL-22 production in order to mediate wound restoring (McGee et al., 2013). Dermal ILC3 may also mediate pathology. In patients with psoriasis, an increase in NCR1 ILC3s was detected in affected skin, recommending that these IL-22-producing innate cells may participate in the pathology of psoriasis (Hazenberg and Spits, 2014). In mice, intra-epithelial ILC1s and IFN-γ-producing ILC3s can stimulate inflammation, and blocking IFN-γ could improve this disease in some models of colitis (Buonocore et al., 2010; Fuchs et al., 2013). IFN-γ-producing ILCs may also be contributed in human IBD, since ILC1s develop and IL-22-producing ILC3s reduce in inflamed intestinal tissues of patients with Crohn’s disease (Bernink et al., 2013; Fuchs et al., 2013). IL-17-producing ILC3s affect the pathogenesis of inflammatory bowel disease in part through T-cell-independent mechanisms in mouse models (Buonocore et al., 2010; Powell et al., 2012). Collectivity, these findings show that ILC1s and ILC3s can involve in the progress of intestinal inflammation (Artis and Spits, 2015). It is suggested that ILC2s activation causes an overexpression of IL-13 in the gut, which then promotes chronic inflammation and ulcerative colitis (Camelo et al., 2012).

ILCs in allergy and autoimmune disorders

For several years, pathogenesis of allergic diseases was related to the vital function of adaptive Th2 cells via producing IL-4, IL-5 and IL-13, altogether called type 2 cytokines (Aryan et al., 2013; Azizi et al., 2016a; Azizi et al., 2016b). Hallim et al. indicated that ILC2-deficient mice fail to progress allergic lung inflammation after intranasal management of protease-allergen papain (Halim et al., 2014). ILC2s have been demonstrated to be important actors that enhance Th2 generation, production of type 2 cytokines and sensitization to allergens in mucosal or epithelial barriers (Sanati et al., 2015). Type 2 ILCs have been identified as important actors in the allergic diseases, asthma, AD and also chronic rhinosinusitis while ILC1s and ILC3s are related to the pathogenesis of IBD and psoriasis (Sanati et al., 2015). Uncontrolled activation and proliferation of ILCs can involve in inflammatory autoimmune diseases (Hazenberg and Spits, 2014). Dysregulation of RORγt-dependent ILCs and production of IL-17 and IL-22 may also involve in some autoimmune diseases such as psoriasis, rheumatoid arthritis (RA), and IBD (Yamada, 2010).

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Asthma

Asthma is a chronic inflammatory disorder of respiratory tract and asthmatic patients are identified by the existence of chronic lung inflammation, lung infiltration by mast cells and eosinophils, hyper secretion of the mucus, breathing problem (Bronchoconstriction) (Bartemes and Kita, 2012), high amount of IgE and release of mucus that show increase goblet cells activation (Walker and McKenzie, 2012). Immunologically allergic asthma can be diagnosed by higher Th2 immune response in these patients (Kim et al., 2010; Voehringer et al., 2006; Walter et al., 2001). In humans, IL-5- and IL-13-producing innate cells that are similar to ILC2s have been detected in asthma patient’s sputum (Allakhverdi et al., 2009), lung parenchyma and bronchoalveolar lavage fluids of lung transplantation patients (Monticelli et al., 2011).

During the first stage of allergic asthma, type-2 immune response emerged, independent of Th2 immune cells. This finding is prepared by using the Rag-/-mice, that are T cell deficient but display allergic asthma symptoms upon treatment by IL-25 or IL-33 (Bartemes et al., 2012; Kondo et al., 2008). Chang et al. showed that influenza virus-promoted asthma in mice is arbitrated by IL-33 dependent ILC2 and not by the adaptive immunity (Chang et al., 2011). It has been discovered that ILC2s are activated in the lungs after infection by H1N1 influenza A virus. This type of infection stimulates the release of IL-33 (Yazdani et al., 2015) and amphiregulin in order to mediate wound repair (McKenzie et al., 2014) in the lungs and causes airway hypersensitivity and raise in ILC2 counts (Chang et al., 2011) (Figure 3A).

Atopic dermatitis

Atopic dermatitis (AD) has two main properties; imperfect barrier integrity of the skin and dysregulation of the immune system (Boguniewicz and Leung, 2011). AD starts with imperfect skin integrity created by inherited defects in skin-related proteins like filaggrin (Ponińska et al., 2011). Imperfect skin integrity in the epidermis easily causes water loss and improper exposure to environmental allergens (Ponińska et al., 2011). Resident ILCs in mucosal and epithelial barriers are discovered as the major reason of AD pathology. Like asthma, ILC2s have a significant role in AD development (Sanati et al., 2015). Keratinocytes, basophils, DCs and ILC2s promote Th2 differentiation from naive T cells and production Th2-related cytokines (Kinoshita et al., 2009). TSLP, IL-25, and IL-33 regulate ILC2 and adaptive Th2 polarization in patients with AD (Kim et al., 2013; Maródi and Casanova, 2010). Interestingly, ILC2s have been demonstrated to be enriched in biopsies taken from patients with AD compared to healthy individuals (Kim et al., 2013; Kinoshita et al., 2009). The role of ILC2 is significant as they can progress AD even independent of adaptive Th2 cells. Roediger et al. observed that Rag-/- mice that lack adaptive immune responses can advance eosinophilic dermatitis because of ILC2s activation (Roediger et al., 2013). Type 2 cytokines like IL-13 amplify this cycle by activating ILC2s and Th2 cells. Additionally, keratinocyte-derived TSLP can also activate ILC2s without impressing by IL-13 and IL-4 (Kinoshita et al., 2009; Morris et al., 2014). It is important that ILC2s also use anti-inflammatory effects to restrict the exaggerated Th2 responses but these effects are inhibited in patients with AD. Activated ILC2s express KLRG1, which ligates to the E-Cadherin and in this way inhibits secretion of IL-5 and IL-13 from keratinocytes (Salimi et al., 2013). As mentioned, this anti-inflammatory effect of KLRG1 is restricted by downregulation of E-Cadherin in AD patients (Oliphant et al., 2014). Collectivity, ILC2s seem to be as pivotal as adaptive Th2 cells in the pathology of AD (Sanati et al., 2015) (Figure 3B).

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Inflammatory bowel disease

Crohn’s disease and ulcerative colitis are the two main types of human IBD (Qiu and Zhou, 2013), a complicated chronic immune-mediated disease (Goldberg et al., 2015). An absolute role for ILCs in human IBD has not been proved, but various surveys have reported the modified count or function of ILCs in Crohn’s disease. However, the higher IL-17 production by ILC3s has been demonstrated in the patients with Crohn’s disease compared to those from people without IBD (Geremia et al., 2011). One study showed decreased ILC3 number and enhanced ILC1 count in intestinal tissue from patients with IBD compared to non-IBD individuals (Bernink et al., 2013) and these may lead to the progression of intestinal inflammation. There are several reports regarding the tissue-defensive functions of ILC3s in mouse models of intestinal inflammation and reduced ILC3 numbers in IBD patients (Sonnenberg and Artis, 2015). IFN-γ-producing ILCs can lead to enhancement of human IBD, due to the elevation of ILC1 and reduction of ILC22 in inflamed intestinal tissues of patients with IBD (Bernink et al., 2013; Fuchs et al., 2013). ILC22 could contribute in defense against IBD in mouse models (Sanos et al., 2009; Satoh-Takayama et al., 2008). Downregulation of ILC22 might be due to differentiation of ILC3s toward ILC1s in inflamed mucosal tissues. In the setting of defensive role of ILC22, IL-22 activates antimicrobial molecules and anti-apoptotic pathways that are involved in inhibition of tissue injury and tissue remodeling. These activities contribute to the enhancement of intestinal barrier integrity and epithelial innate immunity (Li et al., 2014). ILC17 could be contributed in IBD without T-cell activation mouse models (Buonocore et al., 2010). An important role of IL-17A, IL-17F, IL-22 and IFN-γ in IBD has been indicated. Nevertheless, additional surveys could be done to recognize the role of ILC2s in human IBD (Duerr et al., 2006). It has been shown that NK cells also could be contributed in the pathogenesis of IBD. Takayama et al. reported that intestinal NKp44- NKp46+ NK cells could produce IFN-γ, however NKp44+ NKp46- NK cells released IL-22 in the intestine (Takayama et al., 2010). They have discovered increased IFN-γ-producing NKp46+ NK cells in inflamed mucosa of patients with Crohn’s disease, however, IL-22-producing NKp44+ NK cells are significantly decreased in these patients. Actually, interference of balance between IFN-γ-producing NKp46+ and IL-22-producing NKp44+ NK cells in inflamed mucosa and also increase of IFN-γ-producing NKp46+ cells may involve in the progression of Crohn’s disease (Yazdani et al., 2015) (Figure 4A).

Psoriasis

Psoriasis is an autoimmune disease of the skin that is promoted by IL-17A, IL-17F, and IL-22. Topical presentation of mouse skin to the TLR7 agonist imiquimod leads to skin inflammation that exhibits some similarities to psoriasis and has been used as its experimental model. In this model, IL-17A, IL-17F, and IL-22 involve in disease, and these cytokines were reported to be produced by γδ-T cells and RORγt+ ILC3s (Pantelyushin et al., 2012). In patients with psoriasis, an accumulation of NCR1 ILC3s was observed in affected skin, implying that these IL-22-producing cells may be involved in the pathogenesis of psoriasis (Dyring-Andersen et al., 2014; Teunissen et al., 2014). Attractively, meaningful increased count of NKp44+ ILC3s, not only in the skin lesions of psoriasis patients but also in the peripheral blood (PB) was observed (Teunissen et al., 2014; Villanova et al., 2014b). Some models show that dynamic alterations in ILC
structure are related to psoriatic inflammation (Villanova et al., 2014b). In support of this opinion, one patient who showed a reduction of psoriatic plaques after treatment by treatment with anti-TNF monoclonal antibodies also exhibited a reduce in circulating NKp44+ ILC3s (Villanova et al., 2014b). Studies in mouse models of psoriasis also implied that ILC3s are involved in this disease, since mice treated with the cream consisting of imiquimod had IL-17A, IL-17F and IL-22-producing ILC3s and γδ-T cells in the skin (Pantelyushin et al., 2012) (Figure 4B).

**Rheumatoid arthritis**

RA is a chronic systemic autoimmune disease that generally affects multiple joints and finally causes the destruction of bones and cartilage (Yazdani et al., 2015). In these patients, there is an association between lymph node (LN) activation and ILC imbalance. During the systemic autoimmunity related with RA, ILCs within the LN microenvironment seem to display a shift from a more “homeostatic” profile, identified by a higher frequency of LTi, towards a more “inflammatory/activated” one, identified by a growth in frequency of potentially proinflammatory cytokine producing ILC subsets (ILC1 and ILC3).

The modified early LN activation and ILC distribution within the LN compartment have been reported during the earliest phase of RA. RA patients demonstrate the lower LTi and raised both ILC1 and ILC3 numbers compared with controls. It is interesting that LTi cells were not only changed in frequency, but also their lesser expression of CD69 was discovered in RA patients, implying a link between CD69 expression on ILCs and protective processes. The reduction of LTi counts and decreased CD69 expression is in accordance with its proposed role as marker for cell protection (Shiow et al., 2006). The schematic model demonstrating the role of ILCs in the pathogenesis of RA is shown in the figure 5A. It is important to note the frequency of total ILCs was intact (Rodríguez-carrio et al., 2016).

**Ankylosing spondylitis**

Ankylosing spondylitis (AS) is a spinal arthritic disease that is often related to human leukocyte antigen (HLA)-B27. T cells have been reported to have a vital role in AS pathology (Duan et al., 2017) and IL-23 is considered as a central cytokine in AS (Ciccia et al., 2009; Smith and Colbert, 2014). According to this information IL-23-sensitive entheseal resident T cells (IL-23R+ROR-γt+CD3+CD4−CD8−Sca1+) cells have been detected in a murine model of AS (Sherlock et al., 2012). These cells exhibit a variety of immunological similarities with particular subsets of ILCs. Specifically in the gut of patients with AS, NKp44 expressing ILC3s are significantly increased, secrete IL-22 and induce mucins production and goblet cells hyperplasia (Ciccia et al., 2012). Recently a strong relationship between the presence of gut inflammation and the degree of spinal inflammation in AS has been proved (Van Praet et al., 2014). In this regard, Ciccia et al. showed that a gut–joint/spine axis exists in AS where ILC3 actively differentiates in the gut and moves in extra-intestinal sites where, they may be responsible for the promotion of inflammation by the production of IL-17 and IL-22 (Ciccia et al., 2015).

**Multiple sclerosis**

Multiple sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system (CNS) (Dolati et al., 2017; Gharibi et al., 2015; Mirshafiey and Jadidi-Niaragh, 2010). The pathology of MS affects perivascular immune cell

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infiltration and demyelination of the CNS white matter (Siffrin et al., 2010). Even though the etiology of MS isn’t recognized, it is clear that autoreactive T cells orchestrate the immune-mediated impairment to the myelin sheath around the nerve axons, causing variable neurological loss over time (Jadidi-Niaragh and Mirshafiey, 2011). Meaningful raise in the ILC3s count, and to a lesser extent γδ-T cells, were also detected in the CNS at disease peak (Hatfield and Brown, 2015). Frequencies of circulating LTis and ILC subsets are increased in patients with MS (Bielekova et al., 2006). Additionally, NK-mediated control of T-cell activity has been shown to be damaged in MS (Gross et al., 2016; Laroni et al., 2016).

The results of several researches confirm a protective role for iNKT cells, which were indicated to infiltrate the CNS during experimental autoimmune encephalomyelitis (EAE) (Ghalamfarsa et al., 2013; Mars et al., 2008). Their activation avoided the advancement of EAE either by expression of anti-inflammatory mediators like IL-4 and IL-10 or by interaction with myeloid derived suppressor cells (Jahng et al., 2001; Miyamoto et al., 2001; Oh and Chung, 2011; Parekh et al., 2004; Parekh et al., 2013; Singh et al., 2001). Additionally Ja18-/- mice, which lack iNKT cells, show a more severe EAE disease course (Oh and Chung, 2011). In MS, lymphoid aggregates have been indicated at autopsy within the inflamed meninges of a substantial portion of patients (Howell et al., 2011; Jadidi-Niaragh and Mirshafiey, 2012). One mechanism that has been recommended for the genesis of these lymphoid aggregates is that LTi-like ILC3s, found in the cerebrospinal fluid, begin and sustain genesis of these focal aggregates in the context of MS (Perry et al., 2012). ILC3s are normal residents of the meninges and show disease-mediated expansion and activation in EAE (Hatfield and Brown, 2015). During an MS relapse the balance of cytokines is shifted towards a pro-inflammatory profile, involving IL-17, (Matusevicius et al., 1999) IL-22 (Xu et al., 2013) and GM-CSF (Carrieri et al., 1998). IL-17 expression relates with disease activity,(Matusevicius et al., 1999) and together with IL-22 likely induced blood–brain barrier (BBB) disruption and CNS inflammation via stimulating chemokines in endothelial cells and by downregulating tight junction proteins (Carlson et al., 2008). ILC3 and LTi cells are both prominent source of IL-17 and IL-22 production (Spits et al., 2013; Walker et al., 2013) even at times surpassing T cells during an immune response (Wilhelm et al., 2011), they are tending to affect the initial phases of inflammatory diseases. In addition to secretion of IL-17 and GM-CSF, ILC3s constitutively express CD30L and OX40L, which are required for survival of memory T cells and they are also essential contributors to the chronic inflammation related with autoimmune disease (Devarajan and Chen, 2013; Elyaman et al., 2008). It has been shown that disease-induced trafficking of migrated wild type T cells to the meninges is damaged in ILC3-deficient Rorc-/- (the gene encoding the RORγt) mice. An important role of RORγt in EAE pathogenesis was proved in researches showing Rorc-/- mice are protected from EAE (Ivanov et al., 2006; Yang et al., 2008). Additionally, LTi cells, a c-kit+ ILC3 subset that induce ectopic lymphoid follicle (ELFs) generation, a hallmark of many autoimmune diseases, are decreased in the meninges of EAE-resistant c-kit mutant Kit W/Wv mice (Hatfield and Brown, 2015). Our putative model demonstrating the role of ILCs in the immunopathogenesis of MS is exhibited in the Figure 5B. It is hypothesized that ELFs serve as places for the sequestration and presentation of autoantigen, and for intrathecal (subarachnoid) antibody production, another characterizing feature of MS (Grogan and Ouyang, 2012). Additionally, CXCL13, is an important mediator of LTi cell recruitment (Van De Pavert et al., 2009), and a pivotal chemokine for the generation of ELFs, is increased in MS patients but is meaningfully decreased in Daclizumab (an anti-CD25 (IL-2Ra) antibody) treated patients (Perry et al., 2012). It is

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demonstrated that ILC3s maintain neuroinflammation through enhancing T cell survival and reactivation in the meninges. Significant increases in ILC3s count, and to a lesser extent γδ-T cells, were also detected in the CNS at disease peak. The expansion of total meningeal ILC3 numbers lead to boosts both of c-kit+ (LTi) and c-kit- subsets. ILC3 accumulation during disease is in part related to the cell recruitment. Other RORγt-expressing cells are also important contributors to EAE. CD45+Lin-IL-7Ra+RORγt+ ILC3s in the meninges, and to lesser extent in the CNS, have a main and essential role in these disease-inducing events. ILC3s exert their effect not only by developing local inflammatory responses, but also by preparing an environment that induces the survival and reactivation of encephalitogenic T cells. Although ILC3s are normal residents of the meninges and CNS, there is a powerful accumulation of these cells at disease peak that is related to intact c-kit signaling pathways (Hatfield and Brown, 2015). The results of several studies support a protective role for iNKT cells, which were reported to infiltrate the CNS during EAE (Mars et al., 2008). Their activation prevented the progression of EAE either by expression of anti-inflammatory mediators such as IL-4 and IL-10 or by interaction with myeloid derived suppressor cells (Jahng et al., 2001; Miyamoto et al., 2001; Oh and Chung, 2011; Parekh et al., 2004; Parekh et al., 2013; Singh et al., 2001). In addition, Ja18-/- mice, which lack iNKT cells, show more severe EAE disease course (Oh and Chung, 2011). The amount of CD56-RORγt+ LTi cells was meaningfully get raised in the MS patients, implying a role for LTi cells in the early phases of MS. CSF leukocyte number predicts the amount of LTi cells which means the frequency of ILCs and LTi cells was significantly increased in patients with an increased CSF WBC counts compared to patients with a normal CSF WBC (Degn et al., 2016). Accumulation of CD56bright NK cells in the CSF of MS patients has been shown. CD56brightCD16 NK cells are non-cytotoxic cells making high levels of cytokines (Strowig et al., 2008). Earlier studies have shown an immunomodulatory role of CD56brightCD16 NK cells, and recommended an useful impact in MS via controlling of activated T cells (Bielekova et al., 2006). Furthermore, the observed increase in CD56bright NK cells in patients with early MS, likely illustrates a disease-induced effect (Degn et al., 2016).

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that can influence several organs, and patients can show heterogeneous clinical features. However antinuclear antibodies (ANA) are noticeable properties, no single laboratory diagnostic is pathognomonic for SLE. Increased ILC1-like cells (CD56bright) have been found in the PB of patients with SLE compared with healthy individuals (Schepis et al., 2009). Referred to at the time as ‘NK cells’, these CD56bright cells from patients with SLE produced more IFN-γ than those cells from healthy controls. Noticeably, type I interferons, known to be plentiful and pathogenic in SLE, elevated the counts of these CD56bright cells in vitro (Schepis et al., 2009). Anti-neutrophil cytoplasmic autoantibody (ANCA)-related vasculitis (AAV) is a necrotizing small-vessel autoimmune vasculitis that mostly influences the airways, skin and kidneys. A study has shown that in AAV the ILC1s count is get raised at the cost of ILC2s and ILC3s during acute phases and returns to normal during remission (Braudeau et al., 2016).
Potential therapeutic modulation of ILCs

There are many therapeutics in the clinic or currently under investigation that could affect ILC differentiation, homeostasis or function (Sonnenberg and Artis, 2015). Understanding how ILC responses are dysregulated in the context of infectious, metabolic and chronic autoimmune conditions may imply the therapeutic potential in the treatment of several debilitating diseases (Artis and Spits, 2015) and it will open new preventive and therapeutic approaches based on the regulation of ILC activity (McKenzie et al., 2014). Therapeutic strategies might inhibit ILC activation and/or survival signals, interference with intracellular signaling pathways, neutralization of the effector cytokines that they produce, or disorder of ILC trafficking to target tissues (Goldberg et al., 2015).

The production of IL-17, IL-22 and lymphotoxins by ILC3s is needed for the induction of anti-microbial protection at epithelial barriers. ILC1s and ILC3s in an inflammatory setting, produce IFN-γ, which is efficient against intracellular pathogens and tumors. ILC2s produce IL-5 and IL-13, which are both pivotal effectors against helminth infection. Consequently, strategies for activating ILCs in the first stage of immune response to pathogens, or even late, to support the adaptive immune response to these pathogens, should deliver significant enhancements to immunotherapy directed against infection (Cording et al., 2016).

The approach mentioned above may lead to the progression of a new generation of more-effective vaccines that contain both antigens and adjuvants that involve the suitable ILC subset and consequently choose the suitable type of adaptive response to the target pathogen. To this end, an arsenal of ‘orchestrator adjuvants’ that trigger the ILC subset of choice is eagerly awaited (Cording et al., 2016).

Monoclonal antibodies against surface markers of ILCs make the specific targeting of each type of ILC. Moreover, management of cytokines controlling proliferation and differentiation of ILCs affords a comparatively nonspecific targeting of ILCs (Sanati et al., 2015). For example, targeting the IL-23-IL-17 pathway was successful in psoriasis and RA (Bowman et al., 2006; Genovese et al., 2010; Leonardi et al., 2012; Papp et al., 2012). However, in IBD patients, blockade of IL-17 had restricted efficacy and in some cases promoted disease and susceptibility to fungal infections (Colombel et al., 2012; Hueber et al., 2012; Kaser, 2014). Regarding the role of ILC3s and IL-17 in anti-fungal immunity (Gladiator et al., 2013), targeting IL-17 may have limited efficacy in certain conditions, as it also targeted protective ILC3 (Sonnenberg and Artis, 2015). The activator cytokines IL-12, IL-25, IL-33, IL-1β, and IL-23, effectively stimulate specific ILC subsets, but they also stimulate T cells. Consequently, such cytokines require to be used locally, in a timely manner, to prevent an unwanted systemic regulation of immune responses (Cording et al., 2016). Local and timed approaches will be needed, because ILCs have pivotal roles in maintaining homeostasis. For example, blocking ILC3s during colitis or autoimmunity would decrease containment of the intestinal microbiota and leads to inflammation (Lochner et al., 2010), however blocking ILC2s through allergy or fibrosis would cause homeostasis deficiency in adipose tissues (Lee et al., 2015; Qiu et al., 2014). Selectively targeting of IL-23 is an evident procedure to restrict pathogenic ILC activation, notably in the gut. In the gut, IL-23 strongly induces IL-17A and IL-22 production by pathogenic ILC3 (Buonocore et al., 2010; Geremia et al., 2011; Powell et al., 2012) and might induce IFN-γ production by ILC1 (Takayama et al., 2010). Therapeutic neutralization of IL-23p19 or restriction of
its receptor (IL-23R) attenuates ILC-arbitrated colitis in mouse disease models (Buonocore et al., 2010; Powell et al., 2012). Targeting IL-12p40 provides the benefits of simultaneously neutralizing two key pathways contributed in ILC activation (IL-12-induced ILC1 activation and IL-23-induced ILC3 activation). IL-12p40 neutralization with monoclonal antibodies (ustekinumab and briakinumab) or block of its synthesis with oral factors (STA-5,326) are hopeful treatments for Crohn’s disease and are waiting for assessment in ulcerative colitis (Niederreiter et al., 2013; Sandborn et al., 2012).

An ‘ILC-boosting’ strategy might be moreover applied to remodeling normal tissue function, increase healthy metabolism and stop inflammatory pathology. Procedures for activating ILC2s should support tissue remodeling after damage and should also sustain normal functions of adipose tissue. ILC2s inhibit pathogenic type-3-mediated responses in white adipose tissue and thereby stop the gathering of white adipose tissue (obesity) and growth in blood sugar (diabetes), both disorders that are accessing endemic expanse worldwide. The activation of ILC2s may lead to higher benefits in the regulation of IBD and autoimmunity promoted by type 3 responses such as arthritis and multiple sclerosis. Reversely, activation of ILC3s should block allergic inflammation stimulated by type 2 responses and prevent the invasion of tissues by microbiota during the production of IL-17 and IL-22. Additionally, IL-22 protect intestinal stem cells from injury-induced death by stimulating an anti-apoptotic pathway (Aparicio-Domingo et al., 2015; Hanash et al., 2012).

By the reverse strategy, the activity of ILCs might be inhibited to counter immunopathology. The managing and effector functions of ILC1s and ILC3s in IBD and pathogen-promote colitis, and those of ILC2s in allergy and fibrosis might be targeted during the usage of neutralizing antibodies to the activator cytokines or the effector cytokines produced by ILCs. Nevertheless, here again a more specific approach that targets ILCs is guaranteed to prevent systemic deregulation of immunity (Cording et al., 2016).

**Conclusion**

ILCs play principal role in immune responses, not only as first barrier against pathogens but also for their capability to effect downstream adaptive immune steps (Sedda et al., 2014). It induces lymphoid tissue development, preserves tissue and barrier homeostasis, provides a quick defensive response against infectious agents, and promotes wound healing (Hwang and McKenzie, 2013). Although, ILCs were fundamentally related to acute innate immune responses to infection and tissue restoring, it is now accepted that ILCs play a much extensive role when they are also contributed in the management of adaptive immunity, chronic inflammation, and metabolic homeostasis. Although the frequency of ILCs is low in tissues, their important location at mucosal barriers in relation with epithelial surfaces enables them to modulate the immune homeostasis by balancing destructive immunity and “constructive” repair responses. It is comprehensible that extreme activation may involve ILCs in chronic pathologies such as allergies, autoimmunity and inflammation (McKenzie et al., 2014). Moreover dysregulation of ILCs is also related to disease. RORγt-dependent cells are contributed with colitis and IBD, however ILC2s are related to allergy in the gut and lungs (Hwang and McKenzie, 2013). Current finding demonstrated pathogenic role of these cells in autoimmune disorders , rheumatoid disorders and in tertiary lymphoid organ development in some chronic infection related with inflammation (Neyt et al., 2012). ILC2-derived Amphiregulin, refresh normal lung function and epithelial repair through influenza virus infection associated pulmonary inflammation. Additional researches to identify the role of amphiregulin through IBD or Crohn’s disease may

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give a beneficial tool to repair the intestinal epithelial cell integrity and remodeling of normal intestinal function in patients with intestinal inflammatory disorder (Kumar, 2014). As we find out more about the ILCs, they may come to show usable therapeutic targets to battle such diseases (Hwang and McKenzie, 2013). Therefore, ILCs have bright future in inflammation biology and may determine advantages in offering new tools to demystify the secrets of inflammation and novel therapeutic goals for several autoimmune and inflammatory disorders. Additional investigations focusing on ILCs and inflammation will prepare the unexplained mechanisms of action of accessible immunomodulatory materials used in various immunologic disorders (Kumar, 2014).
Figure legends

Figure 1. Differentiation of ILCs and their anatomical locations
Human Innate lymphoid cells (ILCs) development originate from common lymphoid progenitors (CLPs) via common helper innate lymphoid cell precursors (CHILPs). Each one of transcription factors and effector cytokines can change the fates of cells subtype of ILCs (dedicated transcription factors suppress the B and T cell fates and direct the generation of the different types of ILCs). T-bet and IL-5 promote ILC progenitor (ILCp) toward the ILC1s which can secrete TNF, IFN-γ, granzyme, perforin that are located in the mucosal associated lymphoid tissues such as tonsil, gut, liver, endometrium, skin and decidua of uterus. Effects of GATA3, RORα, Gifi1, IL-17 and Bcl11b on ILCp can lead to ILC2s generation which can release IL-4, IL-5, IL-9, IL-13 and amphiregulin. Group 2 ILCs have been found in lung, skin, fetal gut, tonsils and adipose tissues. ILC3s have been found in lamina propria, tonsil, spleen, lung, endometrium, and skin. ILC3s generated from ILCp in the situation that influenced by RORγt, aryl hydrocarbon receptor (AhR), micro biota and IL-7 which may lead to production of IFN-γ, IL-22, TNF and IL-17 by ILC3s.

Figure 2. The role of ILCs in viral infections
Infection and damage of lung epithelial cells by Influenza viruses type H3N1 lead to secretion of IL-25, IL-33, and TSLP, which stimulated ILC2s. On the other hand, IL-9 which produced by ILC2s increased its proliferation. ILC2s produce Amphiregulin, IL-13, and IL-5 which affect lung epithelial cells and induce its proliferations in order to repair lung tissue but in that way, it may lead to some disorders like airway hyper reactivity (AHR). IL-5 and IL-13 are known to promote mucus production.

Figure 3. The role of ILC2s in Asthma and Atopic dermatitis
A) ILC2s and Asthma. When a body encounters with the allergens, the lung epithelial cells secrete TSLP, IL-33, and IL-25. These cytokines stimulated ILC2s that can secrete three different type of cytokines. One of them is IL-9 that acts as an autocrine cytokine and stimulates ILC2s proliferations. The next one is secreting amphiregulin, an agent that increases lung epithelial proliferation. The last type of cytokines that produced by ILC2s are IL-4, IL-5, IL-13, IL-19, which increase the frequency of alternatively activated macrophages (AAMs), mast cells and eosinophil and increase secreting mucus from goblet cells which lead to the appearance of the asthma symptoms.

B) ILC2s and atopic dermatitis. ILC2s are important cells that promote the development of AD. IL-33, IL-25, and TSLP increase the number of basophils. Basophils derived IL-4 effects on ILC2s in order to secrete IL-13, IL-5, which lead to induction of eosinophil and mast cells. On the other hand, basophils, dendritic cells (DCs) and ILC2s make a shift from naive T cells to T helper 2 and producing type 2 cytokines. All of these processes cause an inflammation of skin epithelial cells and promotion of AD. AD; atopic dermatitis.

Figure 4. The role of ILCs in Psoriasis and Crohn’s disease
A) ILC3s produce higher levels of IL-7 in the patient with Crohn’s disease compared to healthy individuals. The number of ILC3s get reduced and the count of ILC1s get raised in this disease and it leads to an intestinal inflammation. ILC22s

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have a protective role against IBD, therefore a reduction of ILC22s may contribute to higher IBD susceptibility. IBD; inflammatory bowel disease.

B) In the skin of psoriasis patient’s secretion of IL-17A, IL-17F and IL-22 by γδ-T cells and RORγt+ ILC3s contributed to the development of the disease. NCR+ ILC3s derived IL-22 is involved in the pathology of psoriasis. Human skin ILC3s express NKp44, which produce IL-17 and IL-22 in response to IL-1β and IL-23, therefore a significant elevation was shown in NKp44+ ILC3s both in the skin and peripheral blood of psoriatic patients.

Figure 5. The putative model demonstrating the role of ILCs in rheumatoid arthritis and multiple sclerosis

A) Comparison of ILCs population and other cells in healthy individuals and patient with rheumatoid arthritis (RA). In healthy people the number of LTis are high, conversely the levels of ILC1s and ILC3s are low. It is interesting to notice that LTis were not only high in number but also the expression of CD69 on the surface of these cells is high. In normal joints, there are both osteoblast and osteoclast, which respectively lead to the bone formation and resorption so these cells make a hemostatic situation. However in the patient with RA, the number of osteoclasts is more than osteoblasts which lead to bone resorption. On the other hand, there is a link between LN activation and ILC imbalance. During systemic autoimmunity related with RA, ILCs within the LN microenvironment seem to display a shift from a more “homeostatic” profile, identified by a higher frequency of LTi, towards a more “inflammatory/activated” one, identified by a growth in frequency of potentially proinflammatory cytokine producing ILC subsets (ILC1 and ILC3). Additionally, the decrease of LTis and their CD69 which is a protective marker, are the other factors that contribute to create joint inflammation.

B) The role of ILCs in multiple sclerosis (MS). During MS (an autoimmune disease) some changes in immune cells will appear that these alter lead to impairment of myelin sheath around the nerve axons and the symptom of disease will appear. In periphery an increased in ILC3s number was shown. In addition to ILC3s elevation, the expression of OX40L and CD30L (molecules which needed for the survival of T cells) on the surface of ILC3s get to raise. By increase ILC3s, the level of IL-22 will be elevated which lead to disruption of the blood-brain barrier (BBB). During MS, besides the elevation of ILC3s, the level of CXCL-13 (an important mediator of LTi cells recruitment) get to raise, thereafter LTis count increase so the amount of IL-17 and IL-22 which produced by LTis elevate and BBB disruption will induce. The other event that happened after the elevation of CXCL13, is the formation of ELFs (ectopic lymphoid follicles), which increase LTis number can also lead to. During MS in CNS (central nerve system) lesser in iNKT cells lead to the advancement of EAE (experimental autoimmune encephalomyelitis) when iNKT cells numbers decrease, the expression of anti-inflammatory mediators like IL-4 and IL-10 will decrease, too. By decrease in the level of anti-inflammatory mediators and appearance of ILC3s in CNS through BBB disruption, the number of autoreactive T cells gets raise, and myelin impairment will be elevated.
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Human Innate lymphoid cells (ILCs) development originate from common lymphoid progenitors (CLPs) via common helper innate lymphoid cell precursors (CHILPs). Each one of transcription factors and effector cytokines can change the fates of cells subtype of ILCs (dedicated transcription factors suppress the B and T cell fates and direct the generation of the different types of ILCs). T-bet and IL-5 promote ILC progenitor (ILCp) toward the ILC1s which can secrete TNF, IFN-γ, granzyme, perforin that are located in the mucosal associated lymphoid tissues such as tonsil, gut, liver, endometrium, skin and decidua of uterus. Effects of GATA3, RORα, Gifi1, ILA17 and Bcl11b on ILCp can lead to ILC2s generation which can release ILA4, ILA5, ILA9, ILA13 and amphiregulin. Group 2 ILCs have been found in lung, skin, fetal gut, tonsils and adipose tissues. ILC3s have been found in lamina propria, tonsil, spleen, lung, endometrium, and skin. ILC3s generated from ILCp in the situation that influenced by RORγt, aryl hydrocarbon receptor (AhR), micro biota and IL-7 which may lead to production of IFN-γ, IL-22, TNF and IL-17 by ILC3s.
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Figure 4. The role of ILCs in Psoriasis and Crohn’s disease

A) ILC3s produce higher levels of IL-7 in the patient with Crohn’s disease compared to healthy individuals. The number of ILC3s get reduced and the count of ILC1s get raised in this disease and it leads to an intestinal inflammation. ILC22s have a protective role against IBD, therefore a reduction of ILC22s may contribute to higher IBD susceptibility. IBD; inflammatory bowel disease.

B) In the skin of psoriasis patient’s secretion of IL-17A, IL-17F and IL-22 by γδ-T cells and RORyt+ ILC3s contributed to the development of the disease. NCR+ ILC3s derived IL-22 is involved in the pathology of psoriasis. Human skin ILC3s express NKp44, which produce IL-17 and IL-22 in response to IL-1β and IL-23, therefore a significant elevation was shown in NKp44+ ILC3s both in the skin and peripheral blood of psoriatic patients.
For Peer Review

Figure 5. The putative model demonstrating the role of ILCs in rheumatoid arthritis and multiple sclerosis

A) Comparison of ILCs population and other cells in healthy individuals and patient with rheumatoid arthritis (RA). In healthy people the number of LTis are high, conversely, the levels of ILC1s and ILC3s are low. It is interesting to notice that LTis were not only high in number but also the expression of CD69 on the surface of these cells is high. In normal joints, there are both osteoblast and osteoclast, which respectively lead to bone formation and resorption so these cells make a hemostatic situation. However in the patient with RA, the number of osteoclasts is more than osteoblasts which lead to bone resorption. On the other hand, there is a link between LN activation and ILC imbalance. During systemic autoimmunity related with RA, ILCs within the LN microenvironment seem to display a shift from a more “homeostatic” profile, identified by a higher frequency of LTI, towards a more “inflammatory/activated” one, identified by a growth in frequency of potentially proinflammatory cytokine producing ILC subsets (ILC1 and ILC3). Additionally, decrease of LTis and their CD69 which is a protective marker, are the other factors that contribute to create joint inflammation.

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