Human Cell (2019) 32:231–239
https://doi.org/10.1007/s13577-019-00257-1

REVIEW ARTICLE

Function of innate lymphoid cells in the immune-related disorders

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Received: 12 March 2019 / Accepted: 5 May 2019 / Published online: 11 May 2019

Abstract
Innate lymphoid cells (ILCs) are a recently described group of innate immune cells that mirror the characteristics of $CD4^+$ T cell subsets. Based on their transcriptional factor and cytokine profile, ILCs family is divided into main subgroups—ILC1s, ILC2s, and ILC3s. Recently, one new subpopulation of ILCs with immunosuppressive characteristics has been described and named as regulatory ILCs. Various roles of ILCs have been confirmed including the role during the response to microbial signals, the role in inflammation and process of tissue repair. Function of ILCs is mediated through the cytokines production and direct cell-to-cell contact. This article summarizes in detail, the relationship between the ILCs and various immune-related disorders.

Keywords Innate lymphoid cells · Cytokines · Inflammation · Tissue repair

Introduction

For years, the immune system was divided into innate and adaptive arm. Innate immunity provides initial defense against microbes, prior to activation of adaptive immune response. The cell types involved in both immune responses differ in many characteristics, such as specificity and in how quickly they respond to infections.

The innate immune system blocks the entry of microbes and eliminates or limits their growth. If microbes successfully pass the epithelial barriers, they encounter other cells of innate immunity, which provide two main types of reactions, inflammation and antiviral defense. These reactions can be effective at controlling and eradicating infections.

However, since many pathogenic microbes have evolved to resist innate immunity, defense against them requires the more powerful and specialized mechanisms of adaptive immunity. There are two types of adaptive immunity, humoral and cellular. In humoral immunity, plasma cells secrete antibodies that may prevent future infections and eliminate extracellular microbes. In cellular immunity, cytotoxic $CD8^+$ T lymphocytes directly kill infected cells, whereas $CD4^+$ T helper 1 (Th1), Th2, and Th17 lymphocytes eradicate microbes via secreted cytokines. One of the main characteristics of adaptive immunity is diversity which provides defense against large variety of antigens, thanks to the clonal distribution of membrane receptors that can distinguish subtle differences between antigens [1].

Recently, a family of immune cells named innate lymphoid cells (ILCs) was discovered. They were characterized that mirror the phenotypes and cytokine profile of $CD4^+$ T cell subsets [2].

The ILC family is divided into three main subsets, ILC1, ILC2, and ILC3. Each of them is defined by distinct transcription factors and cytokine expression, and different functions as well [3]. Though ILCs share developmental origin with T cells, ILCs do not express antigen receptors encoded by rearranged genes nor undergo clonal selection and expansion when stimulated [4]. Instead, ILCs react quickly to stress signals from other cells in the tissue microenvironment or microbial compounds by cytokines production [4]. Since ILC1, ILC2, and ILC3 cells correspond to Th1, Th2, and Th17 subsets, respectively, it is thought that they are involved in the immunity against intracellular bacteria,

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parasites, and extracellular microbes [5]. Recent studies show the role of ILCs in regulation of tissue homeostasis and remodeling, inflammation, lipid metabolism, and body temperature [6–8]. In addition, involvement in pathogenesis of allergy, asthma, autoimmune diseases, and cancer has also been described [9]. During the past year, a new subpopulation of ILCs has been described. It is termed as regulatory ILCs (ILCregs) for its regulatory role in intestinal homeostasis and innate immunological defense similar to regulatory T cells (Tregs) [10].

In this paper, we will briefly describe some key features of ILCs in immune-related diseases.

Classification of ILCs subsets

ILCs are cells with highly expressed plasticity, with phenotype and function shifting depending on their microenvironment, thus making their classification complicated. In addition, discovery of the new ILCregs population should probably extend the nomenclature proposed in 2013 by Spits and colleagues [11].

Group 1 ILCs (ILC1s) consist of conventional natural killer (cNK) cells and intraepithelial type 1 ILCs (ieILC1s). The main transcription factor required for their development is *T-bet*, and commonly they produce IFN-γ as the main effector cytokine [12]. Additionally, ieILCs express transcription factor *eomesodermin* (*Eomes*) and CD103 molecule, and exert cytotoxic activity [13]. Another group of IFN-γ-producing cells with a separate developmental route also belong to the group of ILC1s. They are referred as helper ILCs, and include exILC2s and exILC3s [14]. This type of ILCs differ from cNK cells by the absence of cytotoxic function, lack of expression CD56, CD16, CD94, and transcription factor *Eomes* [12, 15].

Due to the lack of antigen receptors expression, ILCs react to the microenvironment through cytokine receptors. ILC1s secrete IFN-γ as a response to intracellular pathogens and production of IL-12, IL-15, and IL-18 by myeloid cells [4]. Myeloid cells are able to activate ILC1s above secreted cytokines through the engagement of activating natural cytotoxicity receptors (NCRs) on ILC1s surface. Namely, activation of NCRs (e.g., NKp46, NKG2D, NKG2A, or Ly49s) triggers the production of cytokines by ILC1s. Such mechanism presumes a receptor–ligand-mediated mechanism for ILC activation and expression of their effector functions [13].

It is shown that ILC1s accumulate in gut and lung where they contribute to IFN-γ-mediated inflammation, inflammatory bowel disease, and chronic obstructive pulmonary disease, respectively [12]. In order to phenotypically distinguish ILC1s' subtypes in inflamed tissues, a mass cytometry analysis was performed [16]. Results showed that ILC1s do not constitute a distinct or consistent population at the phenotypical or functional levels in any of the tested tissues. In addition, investigated ILC1s expressed T cell markers, such as CD3, invariant TCR-β, CD4, CD5, and CD8. These findings suggest a possibility for the existence of distinct heterogeneous population of innate-like T lymphocytes or T cell-like innate lymphocytes [17]. But these findings need to be additionally evaluated.

Group 2 ILCs (ILC2s) were identified in the human intestine [18], lung [19], and skin [20] where they produce the type 2 cytokines and share involvement in allergic inflammation. Helminthic infections or allergen exposure activate immune cells which produce IL-25, IL-33, TSLP (thymic stromal lymphopoietin), and PGD_2, and in turn trigger ILC2s activation. Type 2 cytokines, IL-4, IL-5, IL-9 and IL-13, stimulate protective mechanisms in helminthic infections, such as mucus production, eosinophilia, goblet cell hyperplasia, IgE isotype switching, and fibrosis [6]. In addition, ILC2s are probably involved in tissue repair and regulation of metabolic homeostasis of glucose and lipids [21]. Similarly to Th2 cells, the development of ILC2s is thought to be dependent upon *GATA-3* expression [22]. ILC2s can be identified in humans from other ILC subsets by the expression of chemoattractant receptor, homologous molecule expressed on Th2 cells, *CRTH2* [16]. ILC2s also express CD25, various levels of c-kit and IL-7R. Since their responsiveness to IL-25, IL-33, and TSLP, ILC2s are presumed to have adequate receptors to these molecules [18]. Existence of G-protein coupled receptors on the surface of ILC2s enables them to facilitate lipid signaling from prostaglandins and leukotrienes [23]. No functional subpopulations of ILC2 cells have been identified in healthy individuals.

The ILC3 group (ILC3s) includes ILC3 cells and classical lymphoid tissue inducer (LTi) cells [24]. Depending on the expression of NCR, ILC3 cells contain the group of NCR^+ and NCR^- ILCs. They are usually activated upon bacterial and fungal infections in the presence of IL-1β and IL-23 produced by myeloid cells [25, 26]. When activated, ILC3s secrete IL-17 and IL-22. IL-17 recruits neutrophils and macrophages to the site of the infection, while IL-22 may have anti-inflammatory effects in inflammatory diseases [27]. ILC3s can exhibit features of antigen presenting cells by accepting and presenting antigens, thus playing the role in adaptive immunity [28]. In addition, ILC3s also produce lymphotoxins and GM-CSF [29], while NCR^+ ILC3s contribute to protective immunity by secretion of proinflammatory cytokines, IFN-γ and TNF-α [30]. Expression of transcription factor *RORγt* is the most important for development and maturation of ILC3s family members [31].

Regulatory ILCs predominantly inhabit the gut where they expand following pathogenic stimulation and suppress intestinal inflammation. These cells are distinct from ILCs and Tregs, without significant gene profile similarity.

Namely, ILCregs lack expression of transcription factors that play important roles in ILC development, such as *T-bet*, *GATA-3, RORγt,* or *Foxp3*. Instead, they express unique *Id3* required for their development [10]. Since ILCregs produce regulatory cytokines, IL-10 and TGF-β, it is most likely that this cell population provides the missing link between ILCs and Tregs. Such autocrine TGF-β is probably required for the expansion of ILCregs [10].

Summarized phenotype of each ILCs subset is presented in Table 1.

In recent years, there has been a rapid advance in understanding of the signals that govern ILC development, which has been nicely summarized elsewhere [32, 33].

ILCs respond to the microenvironment through cytokine receptors, translating signals into effector cytokines and activating adaptive effector functions [4]. It is thought that ILCs regulate adaptive immunity through promotion of T cell activation via regulation of dendritic cells (DCs) [34]. Namely, DCs as central players of immune regulation, recognize, decode, integrate and present information from microbial and stress stimuli to T cells thus stimulating immune response [35]. Positive feedback loop between DCs and cNK cells through the production of IFN-γ and IL-12 promotes the differentiation of Th1 cells [36]. ILC2s lead to the activation of DCs through the IL-13 production and subsequent Th2 differentiation [37]. Finally, DCs produce IL-23 upon ILC3s' membrane-bound lymphotoxin $\alpha_1\beta_2$ stimulation, which in turn promote the activity of ILC3s and differentiation of Th17 cells [38]. However, these mechanisms are not fully elucidated and further research should describe it more accurate.

Although ILCs do not express antigen-specific receptors, they express subset-specific receptors, allowing them to be activated specifically under inflammatory conditions [16]. Each subset, however, shares a group of common receptors important for their activation and regulation during inflammation or infections. These receptors include inducible T cell co-stimulator (ICOS), CD161, and IL-18 receptor (IL-18R) [16].

ICOS receptor was initially described as a co-stimulatory receptor expressed by activated T cells important for their function [39]. Recent findings suggest that ICOS play an important role in activation and survival of ILC2s upon its interaction with ICOS ligand, both expressed by this group of cells [40]. There are papers demonstrating the expression of ICOS by ILC3s, but its function remains to be elucidated [15].

CD161 is a C-type lectin which binds to lectin-like transcript-1 upon activation by numerous immune cells [41]. Differentiated Th1, Th2, and Th17 $CD4^+$ T cells express CD161 where it acts as co-stimulatory or co-inhibitory receptor. All ILC subsets also express CD161, but its activation or inhibition role still needs to be investigated.

The IL-18R binds IL-18 produced by intestinal epithelial cells and macrophages under inflammatory conditions [42]. Human ILC2s and ILC3s express IL-18R [40]. Upon activation by IL-18, ILC2s secrete high amounts of type 2 cytokines, whereas ILC3s produce IL-17 as a response to IL-18 only when provided together with IL-23 [40].

ILCs in pathogenesis of the diseases

Many studies were investigating the role of ILCs in the pathogenesis of various diseases. In this review the current knowledge of ILCs as a part of different immunological disorders is summarized (Fig. 1).

ILC1s

ILC1s subpopulation is probably involved in the immune response against various infections, since these cells mostly

Table 1 Expression of characteristic molecules on human ILCs' surface

ILC1s			ILC2s	ILC3s			ILCregs
cNK	ieILC1s	ILC1s		NCR^+	NCR^-	LTi	
NKG2A	NKG2A	CD127	CD127	CD127	CD127	CD127	CD25
NKp46	NKp46	CD161	CD161	CD161	CD161	CD161	Sca-1
NKp44	NKp44	IL12RB1	IL-7R	CD117	CD117	CD117	CD90
IL12RB1	IL12RB1	KLRG1	CRTH2	NKp46	IL-12RB1	CD25	CD45
CD25	CD122	ICOS	CD117	NkP44	CD25	CCR6	CD127
CD122			IL-17RB	IL-12RB1	ICOS	IL-23R	
KLRG1			KLRG1	CD25	CCR6	IL-1R1	
			ICOS	ICOS	IL-23R		
			CCR6	CCR6	IL-1R1		
			IL-1R1	IL-23R			
			MHC class II	IL-1R1			
			IL-33R	MHC class II			

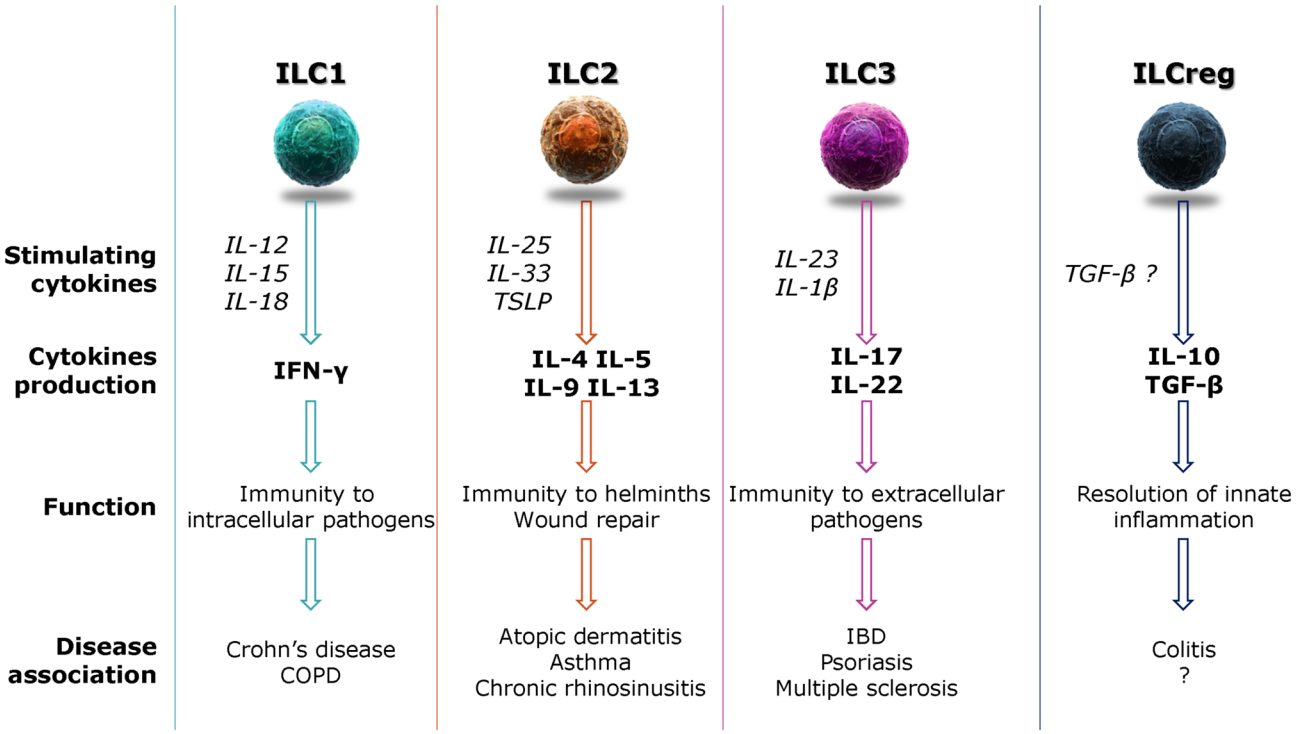

Fig. 1 Innate lymphoid cells: subsets, functions and disease association

inhabit the mucosal surfaces where they meet infective agents [43]. Namely, upon infection, innate immune cells produce different cytokines involved in activation of ILC1s [5]. Following activation, ILC1s secrete mainly IFN-γ, important for protection against infections, such as *Clostridium difficile* [44] and *Toxoplasma gondii* [45].

Numerous studies described the increased number of ILC1s in various inflammatory diseases [46–48]. Intestinal samples from patients with Crohn's disease or bronchoalveolar lavage (BAL) fluid from patients with chronic obstructive pulmonary disease are characterized with great increase of ILC1s versus ILC2s and ILC3s [48]. In addition, a large number of ILC1s are found in peripheral blood of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis, rheumatoid arthritis, systemic lupus erythematosus (SLE), and systemic sclerosis, suggesting the importance of ILC1s in their pathogenesis [47, 49, 50]. Since the role of IFN-γ in inflammation is well established, the usage of IFN-γ blockers can be considered as a promising therapeutic strategy in certain inflammatory conditions. Different anti-IFN-γ antibodies were approved in treatment of Crohn's disease, rheumatoid arthritis, SLE, and systemic sclerosis [48]. Description of their modes of actions overcomes this review and is well-described elsewhere [51, 52].

Involvement of IFN-γ in anti-tumor response is well known as well [53–55]. However, there is no evidence linking IFN-γ-producing ILC1s directly with tumor immunity. There are few ongoing studies investigating the effect of their secreted cytokines and anti-tumor response [55, 56]. The authors described ILC1-like cells expressing granzyme B and TRAIL which can efficiently lyse tumor cells in a mammary tumor model [56]. Further research is required to establish whether an equivalent cell type exists in humans.

ILC2s

Due to its production of Th2 cytokines, ILC2s were considered as a detrimental in numerous inflammatory disorders [5, 57].

Allergic asthma is an airway disease caused by over activated immune response to allergens, such as dust mites, pet dander, pollen, mold, etc., [58]. Inhalation of these allergens leads to airway hyper-responsiveness and inflammation, and sequent bronchoconstriction, excessive mucus production, and airway narrowing [59]. For a long time it was thought that Th2 immune response plays a crucial role in pathogenesis of asthma. However, Kim et al. described involvement of ILC2s, ILC3s, and Th17 cells as well [60]. Recent studies showed increased number of ILC2s in lungs and BAL fluid with up regulated levels of IL-25, IL-33, and TSLP in peripheral blood of patients with asthma [61, 62]. It is thought that ILC2s in cooperation with DCs and $CD4^+$ T cells modulate immune response at mucosal sites and contribute to allergic airway inflammation [63]. In addition,

several genes associated with ILC2s are certified in asthmatic patients, including the gene that encodes RORα, IL-13, and IL1RL1 (component of IL-33 receptor), suggesting a role of ILC2s in asthma pathogenesis [64]. Lungs of asthmatic patients express high levels of IL-9, another Th2 cytokine [65]. It has been demonstrated that this cytokine leads to airway remodeling and mucus hyperproduction. Study by Wilhelm and colleagues [66] revealed possible autocrine or paracrine effect of IL-9 on ILC2s leading to their survival and increased secretion of IL-5 and IL-13, important for asthma symptoms.

Human ILC2s are also involved in pathogenesis of *chronic rhinosinusitis* (*CRS*) [18]. CRS is a persistent inflammatory disease characterized by sinonasal mucosal inflammation lasting at least 12 weeks [67]. High IgE sera levels and eosinophilia are common findings in patients with CRS. Main symptoms of CRS include nasal congestion, headache, and postnasal drip, whose severity is dependent on the size of the nasal polyps and number of ILC2s within [18, 68]. Namely, increased number of ILC2s in polyps following eosinophilia, suggest the potential role of ILC2s in the activation and survival of eosinophils in CRS [69]. Allergic rhinitis is a disease also characterized with involvement of ILC2s, and it is frequently associated with CRS [48].

Atopic dermatitis (AD) is a chronic inflammatory skin disease, mostly seen among children. It is characterized by various signs and symptoms, such as rash in the creases of the elbows or knees, at the neck, wrists, and ankles. Rash is often followed by itchy, scaly patches. Recent studies proposed the role of ILC2s in pathogenesis of AD. Namely, Salimi and colleagues [20] demonstrated increased number of ILC2s in the skin lesions of AD patients followed by high amounts of IL-5 and IL-13. Increased levels of TSLP, IL-25, and IL-33, stimulators of ILC2s, were also detected in these lesions [21]. Interaction between ILC2s and innate immune cell types could have an important role in the pathogenesis of AD as well [70]. Basophils, mast cells, and keratinocytes are marked as cells of great importance. Namely, Kim et al. have demonstrated the presence of basophils in skin lesions of AD patients [71]. Investigating AD in murine model, this group showed that depletion of basophils can reduce skin inflammation and improve the healing. Mast cells and their mediator, PGD_2, could also promote disease symptoms by inducing the migration of ILC2s to the skin lesions. Furthermore, keratinocytes with engaged ligand NKp30 leads to the production of IL-5 and IL-13 by ILC2s, suggesting additional mechanism of ILC2s activation in AD patients [72].

Another important role of ILC2s is reflected through the promotion of immunity against extracellular helminthic parasites [73, 74]. Namely, type 2 cytokines produced by ILC2s, IL-4, IL-5, IL-9, and IL-13, regulate the alternative activation of macrophages, granulocyte response and smooth muscle contractility, inducing parasite expulsion [75]. In addition, study showed that ILC2s express amphiregulin, a member of the epidermal growth (EGF) family of proteins, which mediates anti-helminthic immunity [76]. Amphiregulin also interacts with EGF receptor upon stimulation by IL-33, and promotes the proliferation of epithelial cells, thus contributing to process of tissue remodeling [20, 77].

Some investigations were trying to explain the role of ILC2s in regulation of metabolic homeostasis [78–80]. It is supposed that ILC2s are main responders to nutrient and metabolic stress. For instance, IL-5 and IL-13 produced by ILC2s in murine white adipose tissue maintain eosinophils and alternatively activated macrophages limit induced obesity and insulin resistance [78]. However, these mechanisms are not fully understood and more research needs to be performed.

While activation of ILC1s goes in favor of antitumor immunity, ILC2s are generally associated with tumor progression [70]. This feature is reflected through the production of IL-33 and IL-13. Namely, breast cancer murine model studies revealed that administration of IL-33 increases tumor growth and development of metastases. Such findings were accompanied by the growing number of IL-13-producing ILC2s [81]. Another study showed linkage between high sera levels of IL-33 and liver cirrhosis [82]. Activation and proliferation of liver-resident ILC2s seems to be dependent on IL-33, which in turn produce IL-13 and activate hepatic stellate cells, resulting in hepatic fibrosis. Patients with these conditions are in high risk of developing hepatocellular cancer. Amphiregulin, expressed by ILC2s, can also play a role in tumor progression via activation of Tregs [19]. Activated Tregs, in turn induce immune suppression and inhibit antitumor immune response. Such immunosuppressive role of ILC2s makes these cells an interesting target for cancer immunotherapy and such an idea needs additional investigations.

ILC3s

ILC3s act as mediators of different inflammatory diseases and tumors through cytokine production and antigen presentation [83].

Inflammatory bowel disease (IBD) represents a group of intestinal disorders that cause prolonged inflammation of the digestive tract. It is induced by a dysregulated immune response to intestinal microbiota. The two main types of IBD are ulcerative colitis (UC), limited to the colonic mucosa, and Crohn disease (CD), which can affect any segment of the gastrointestinal tract. Patients with this condition are more prone to the development of malignancy. The main symptoms of IBD refer to diarrhea, constipation, bowel movement abnormalities, abdominal cramping and pain, nausea, and vomiting [84]. The most common ILC subset in human intestine is ILC3s where they produce IL-22, IL-17, and

IFN-γ [85], key cytokines of chronic inflammation which characterizes IBD [86].

Psoriasis is another inflammatory disease where ILC3s have a significant share in pathogenesis. This is an autoimmune disorder, characterized by patches of abnormal skin. It typically affects the outside of the elbows, knees or scalp. Itch, burns, and stings are the main symptoms of psoriasis. Recent studies have demonstrated an increased frequency of NCR^+ ILC3s in psoriatic skin lesions suggesting their important role in pathogenesis of the disease [87]. In addition, IL-22, produced by NCR^+ ILC3s isolated from psoriatic skin, was shown as main inducer of psoriatic plaque formation [88].

Multiple sclerosis (MS) is a chronic disease of the central nervous system, characterized by discrete areas of demyelination and axon injury associated with inflammatory activity [89]. One of the key defining characteristics of MS is dissemination of the lesions in both, space and time. Combination of multiple factors seems to contribute to inflammatory activity. Recent studies showed that Th1, Th9, and Th17 cells are included in autoimmune response of MS [90, 91]. Data supporting ILC3s involvement in MS pathogenesis have been reported [92]. Namely, increased number of ILC3s was found in blood of MS patients compared to healthy individuals. Strong expression of IL-17 in the brain lesions of MS patients supports the potential impact of ILC3s in MS [93].

Regarding the role in tumor immunity, ILC3s are found as a big part. Most of the studies involved investigations in gut, where ILC3s through IL-23/IL-17 cytokine axis play its role in IBD [86, 94]. Langowski and colleagues [95] pointed the significantly high amounts of IL-23 in human colon tumors compared to healthy persons. Involvement of IL-23 in colon carcinogenesis was described through the murine model studies, where IL-23-deficient mice expressed resistance to tumor formation induced by chemicals. Development of human breast cancer, lung cancer, pancreatic and gastric cancer was shown as IL-17 dependent [96–98]. Presence of NCR^+ ILC3s seems to be nice prognostic factor in development of human non-small cell lung cancer [99]. These cells were found in lymphoid infiltrates interacting with tumor cells and tumor-associated fibroblasts, formatting tertiary lymphoid structures. These structures stand in positive correlation with better clinical outcome of the disease, indicating NCR^+ ILC3s as good prognostic factor of human NSCLC.

ILCregs

To date, not many investigations were performed regarding the role of ILCregs in health and disease. Current knowledge indicates their involvement in the regulation of intestinal inflammation [10].

Investigation showed that ILCregs exist in mouse and human intestines, where they exert $Lin^-CD45^+CD127^+IL\text{-}10^+$ profile, validated through immunohistochemical staining and flow cytometry analysis. These cells are able to suppress ILC-driven inflammation in an IL-10-dependent manner. Namely, ILCregs inhibit the activation of ILC1s and ILC3s blocking their production of IFN-γ and IL-17 [10]. It is believed that this suppression is achieved via IL-10 secretion during the innate intestinal colitis. On the other hand, ILCregs do not suppress the activation of ILC2s during the intestinal inflammation. Additional protective role of ILCregs in resolution of innate intestinal inflammation is reflected through the IL-22 production by ILC3s. Namely, the protecting potential of IL-22 in mucosal immunity is well known [100]. Although ILCregs suppress the IL-17 and IFN-γ production, IL-22 secretion by ILC3s is not affected, suggesting beneficial tissue protection in the presence of ILCregs. It remains unclear whether ILCregs can be found in tissues other than intestinal tract where they can have protective effects in inflammatory disorders as well. Therefore, future studies need to be performed.

Conclusion

Ever since they were discovered, ILCs were the subject of many studies. Primarily described in three subgroups, ILCs are now expanded with a new population named ILCregs. ILC1s, ILC2s, and ILC3s, reflect both the phenotypic and the functional characteristics of Th1, Th2, and Th17, respectively. ILCregs probably represents the missing piece connecting ILCs and Tregs.

ILCs have a great part in immunity and homeostasis, but also evince an important role in immune-related disorders, making them an interesting therapeutic target, thus additional research needs to be performed.

Acknowledgements The authors thank the support of the Ministry of Education, Science and Technological Development of the Republic of Serbia (projects numbers 175102, 175056).

Compliance with ethical standards

Conflict of interest The authors declare no competing financial interest.

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