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Innate lymphoid cell-derived cytokines in autoimmune diseases

Sirui Li [a, b, c, 1], Di Yang [b, 1], Tingwei Peng [a, b, c], Yuzhang Wu [b, **], Zhiqiang Tian [b, *], Bing Ni [a, b, ***]

[a] Department of Pathophysiology and High Altitude Pathology, Third Military Medical University, Chongqing 400038, PR China
[b] Institute of Immunology, PLA, Third Military Medical University, Chongqing 400038, PR China
[c] Battalion 3 of Cadet Brigade, Third Military Medical University, Chongqing 400038, PR China

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ABSTRACT

The most recently recognized types of immune cells, the innate lymphoid cells (ILCs), have been subdivided according to respective distinct expression profiles of regulatory factors or/and cytokines. ILCs have also been shown to participate in a variety of beneficial immune responses, including participation in attack against pathogens and mediation of the pre-inflammatory and inflammatory responses through their production of pro-inflammatory cytokines. As such, while the ILCs exert protective effects they may also become detrimental upon dysregulation. Indeed, recent studies of the ILCs have revealed a strong association with the advent and pathogenesis of several common autoimmune diseases, including psoriasis, inflammatory bowel disease (IBD) and multiple sclerosis (MS). Though the ILCs belong to lineage negative cells that are distinctive from the Th cells, the profiles of secreted cytokines from the ILCs overlap with those of the corresponding Th subsets. Nevertheless, considering that the ILCs belong to the innate immune system and the Th cells belong to the adaptive immune system, it is expected that the ILCs should function at the early stage of diseases and the Th cells should exert predominant effects at the late stage of diseases. Therefore, it is intriguing to consider targeting of ILCs for therapy by targeting the corresponding cytokines at the early stage of diseases, with the late stage cytokine targeting mainly influencing the Th cells' function. Here, we review the knowledge to date on the roles of ILCs in various autoimmune diseases and discuss their potential as new therapeutic targets.

Contents

Abbreviations: ILCs, innate lymphoid cells; IBD, inflammatory bowel disease; MS, multiple sclerosis; AS, ankylosing spondylitis; Th, T helper; CLP, common lymphoid progenitor; CD, Crohn's disease; UC, ulcerative colitis; NKT, natural killer T; AIH, autoimmune hepatitis; HSCs, hepatic stellate cells; RA, rheumatoid arthritis; SS, Sjögren syndrome; SLE, systemic lupus erythematosus.

* Corresponding author. Institute of Immunology, PLA, Third Military Medical University, 30 Gaotanyan St., Dist. Shapingba, Chongqing 400038, PR China.
** Corresponding author. Institute of Immunology, PLA, Third Military Medical University, 30 Gaotanyan St., Dist. Shapingba, Chongqing 400038, PR China.
*** Corresponding author. Department of Pathophysiology and High Altitude Pathology, PLA, Third Military Medical University, 30 Gaotanyan St., Dist. Shapingba, Chongqing 400038, PR China.
E-mail addresses: wuyuzhang@tmmu.edu.cn (Y. Wu), tzhiq009@163.com (Z. Tian), nibing@tmmu.edu.cn (B. Ni).
[1] Contributed equally to this work.

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1. Introduction

The recent discovery of a previously unrecognized population of immune cells, the innate lymphoid cells (ILCs) [1], has stimulated a vigorous field of research to characterize their functions in normal physiology and pathogenesis of immune-related diseases. The ILCs have been defined as innate immune cells that primarily function in mucosal immunity, and have been found to be mainly located in mucosal tissues and organs [2–4]. At these sites, the ILCs have been shown to secrete polarized cytokines and chemokines in rapid reaction to pathogens and infections, thereby contributing to maintenance of homeostasis [5–8].

Although the ILC population does not include T cells or B cells, or any of the markers of other classical cells of the immune lineage, it does include cells that express cytokines associated with the T helper (Th) cells (i.e. Th1, Th2 and Th17). This finding has led to the ILCs being classified into the following three groups [1]: Group 1 ILCs (ILC1s), similar to Th1 cells and mainly producing IFN-γ and TNF [9,10] in response to IL-12 and IL-15 stimulation [11]; Group 2 ILCs (ILC2s), similar to Th2 cells and producing IL-4, IL-5, IL-9 and IL-13 [12–14] and primarily recognizing signals from IL-25, IL-33 and thymic stromal lymphopoietin [15,16]; and Group 3 ILCs (ILC3s), similar to the Th17 cells and producing IL-17A, IL-17F and IL-22 [17], along with other Th17-associated cytokines, with control by IL-23 [18].

ILCs are proposed to differentiate from a common lymphoid progenitor (CLP). Yet, detailed studies of CLPs have indicated that distinctive precursor subsets of CLPs may lead to the development of the three types of ILCs. Studies of the functions of ILCs have demonstrated multiple beneficial effects, including protection from infection, maintenance of homeostasis, repair of tissue, and mediation of normal inflammatory responses [6,19]. However, studies have also discovered pathogenic roles for the ILCs, particularly in autoimmune diseases (Table 1), such as psoriasis and inflammatory bowel disease (IBD) [20]. The various ILCs produce numerous pro-inflammatory cytokines (i.e. IFN-γ, TNF and IL-17). This feature represents an intriguing potential for therapeutic targeting, through which the ILCs may act to suppress inflammation and attenuate the symptoms of autoimmune disease by generation of anti- and pro-inflammatory cytokines (i.e. IL-4 and IL-13) [21].

Herein, we review the latest knowledge of ILCs and autoimmune disease, and discuss the potential mechanisms that ILCs may use to participate in the pathogenesis of autoimmune disease and which may be manipulable for creating novel efficacious therapies.

2. Autoimmune diseases

2.1. IBD

IBDs, including the forms of Crohn's disease (CD) and ulcerative colitis (UC), have emerged as common autoimmune diseases worldwide. At present, CD is generally believed to be closely related to Th1 cells [22,23]and Th17 cells [24], which mainly secrete IFN-γ and IL-17 [25–27]. Th17 cells have also been found to play important roles in UC [27–29]. The most recent studies, however, are finding clues to the contribution of ILCs for both of these forms of IBD.

In a study by Bernink et al. [30], ILCs in microorganism-free fetal gut were characterized; nearly all of these ILCs expressed c-Kit and were NKp44$^+$ but very few ILC1s were detected. The authors also analyzed ILC1s in patients suffering from CD and in healthy persons (as controls), and discovered that the CD patients harbored substantially more ILC1s expressing IFN-γ and CXCR3, and that these ILC1s were accumulated in the regions affected by severe colitis [9]. Further studies provided support for the theory that ILC1s contribute to CD and that this effect is caused by the cells' production of IFN-γ [9,11]. Many research studies have shown that ILC3 cells can change into ILC1s upon stimulation by IL-12 [9,31,32]. Thus, ILC1s may be able to promote inflammation in gut.

Studies have shown that ILC3s can directly participate in intestinal pathogenesis of IBD as well, particularly through IL-23-stimulated release of IL-17, which acts to promote inflammation [33]. Furthermore, Geremia et al. [34] demonstrated that the elevated IL-17A in patients with IBD (vs. healthy controls) was expressed by the ILC3 population which secretes type 3 pro-inflammatory cytokines dependent upon IL-23 signaling. Buonocore et al. [18] reported that Thy1$^+$ ILC3s expressing IL-23R could be regulated by IL-23, leading to generation of IL-17 and IFN-γ that subsequently drives the tissue towards a colitis state. Reducing the quantity of ILC3s, by administration of anti-Thy1 antibodies, inhabited the development of colitis. In another study, IL-23 was shown to induce intestinal inflammation though its control of cells of both the innate and adaptive immune system and, similarly, the gut inflammation of patients with IBD became attenuated upon treatment with IL-23 antibody [35]. Findings from Powell et al. [22] supported the significant role of IL-23 in the pathogenesis of IBD, especially UC, through its ability to stimulate production of IL-17A from IL-7Rα$^+$ ILC3s. Another important feature to consider in this role is that IL-7R can be inhibited by T-bet, which in turn influences the stabilization of IL-7Rα$^+$ ILC3s. Since T-bet and IL-23 cooperate to influence the function of ILC3s, T-bet might be another factor to target as treatment for UC (with the aim of modulating the disease-promoting features of ILC3s).

It is necessary to consider the contradictory findings reported by O'Connor et al. [36], which show the benefit of IL-17A in colitis of IBD. Specifically, the authors demonstrated that IL-17A inhibits the differentiation of Th1 cells, thereby suppressing intestinal inflammation and the pathway of IL-17, at least partially, which is controlled by the IL-23/IL-17 axis. Despite this unique finding, the bulk of the evidence reported in the literature to date has indicated that IL-17 produced by ILC3s is harmful to patients with IBD.

Zenewicz et al. [37] found that knockout of IL-22 caused disorder of the microorganism profile in mouse intestine, and that insufficient levels of IL-22 could aggravate colitis. Sawa et al. [38] used dextran sodium sulfate to induce damage to the intestinal epithelium of mice and confirmed that the IL-22 produced mainly by ILC3s could repair the gut damage. Meanwhile Eken et al. [39,40] reported that mice with anti-CD40-induced acute innate colitis were protected from colitis upon neutralization of IL-22 (by an antimicrobial peptide) and that restoring the IL-22 led to the colitis