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REVIEW

Innate Lymphoid Cells in Inflammatory Bowel Disease

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Abstract
Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is a complex chronic inflammatory condition of the human gut of unknown causes. Traditionally, dysregulated adaptive immune responses are thought to play a major role; however, accumulating evidence suggests that innate immunity also contributes to this process. Innate lymphoid cells (ILCs) are recently identified important components of innate immunity. They have critical roles in immunity, tissue development and remodeling. Numerous researchers have linked ILCs to the pathogenesis of IBD. In this review, we describe recent progress in our understanding about the phenotype and function alterations of ILCs as well as its interactions with other key mucosal cells in the gut of IBD patients. A better delineation of the ILCs' behavior in the human intestine will contribute to our understanding of ILCs biology and provide valuable insights for potential therapeutic target selection for IBD patients.

Keywords Innate lymphoid cells · Inflammatory bowel disease · Mucosal homeostasis · T-cells

Introduction

Inflammatory bowel disease (IBD), which comprises Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, relapsing–remitting inflammatory disorder of the human gut. The precise pathogenesis of IBD is still not completely understood yet. Dysregulated immune responses towards the commensal microbiota in genetic susceptible individuals are believed to be responsible for the persistent tissue damage among IBD patients. Both innate and adaptive immune system contribute to this process. Innate lymphoid cells (ILCs) are recently characterized as innate immune cells that perform various functions in immune defense, inflammation and tissue remodeling. They are derived from common lymphoid progenitor, but do not express antigen-specific T- or B-cell receptors. According to their specific key transcription factor expression and cytokine production, ILCs are classified into different groups: Cytotoxic natural killer (NK) cells, ILC1s, ILC2s and ILC3s. NK cells and ILC1s are known as T-bet$^+$-interferon (IFN)-γ-producing subset, ILC2s are GATA3$^+$-interleukin (IL)-5 or IL-13-producing cells, while ILC3s are RORγt$^+$-IL-17A or IL-22-producing subset (reviewed in: Mjosberg and Spits 2016). They exhibit certain levels of functional diversity and plasticity. ILCs are localized mainly in mucosa-associated tissues such as gut and contribute to barrier integrity. Emerging evidence suggests the involvement of ILCs in the pathogenesis of IBD (Bernink et al. 2013; Fuchs et al. 2013; Glatzer et al. 2013; Li et al. 2017a; Mizuno et al. 2014; Takayama et al. 2010). The focus of this review is on the recent progress regarding the role of ILCs in IBD.

Inflammatory Bowel Disease

IBD, consisting mainly of CD and UC, is a chronic and inflammatory disorder of the human intestine and can cause abdominal pain, diarrhea and anemia. Its incidence and prevalence has been increasing in Western countries (reviewed in Ananthakrishnan 2015). Patients typically suffer from frequent and chronic relapsing flares interspersed by inactive disease and remission. It can even be complicated by the development of stricture, fistulae, fissure or perianal disease. Most patients need long-term medications and many require hospitalization and surgery (reviewed in Baumgart and Sandborn 2012; Ordas et al. 2012). Unfortunately, the exact etiology of IBD is still largely unknown. This multi-factorial process includes genetic factors, microbiota, immune system

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and environment. According to the current conceptual framework of the pathogenesis of IBD, genetic defects and environmental factors are responsible for the impaired barrier functions along the intestinal mucosa which then lead to translocation of commensal bacteria and microbial antigens from the lumen to the submucosa. These invading pathogens activate immune effector cells which then release numerous proinflammatory cytokines to clear infection. However, if there is a failure of the regulatory mechanisms to suppress the acute immune responses, chronic intestinal inflammation will develop which may cause complications (reviewed in de Souza and Fiocchi 2016).

During this process, various components of the mucosal immune system have been shown to be dysregulated and adaptive immune responses have been the focus of IBD research. Recent progress in mucosal immunology indicates that innate immunity also plays an essential role in the pathogenesis of IBD. The innate immune responses represent the first line of defense against invading pathogens (reviewed in Bevins and Salzman 2011). Innate effector cells, such as dendritic cells, macrophages and intestinal epithelial cells, can sense the microbial antigens and initiate rapid and effective responses. Moreover, they can acquire, process and present microbial antigens to T-cells to induce adaptive immune responses. For the IBD patients, there are some signs of aberrant innate immunity, for example, compromised epithelial barrier, defective anti-microbial responses and autophagy (reviewed in Bonen and Cho 2003). In addition, some evidence points to the fact that intraepithelial lymphocytes, especially γδ T-cells and other unconventional T-cells also play an important role in the recurrent inflammation and ulcerations of IBD patients (Andreu-Ballester et al. 2011; Kadivar et al. 2016; Mann et al. 2012; McCarthy et al. 2015; McVay et al. 1997). Given the complex pathophysiology of IBD, evaluation of the individual cell functions as well as interactions between various players of the innate and adaptive immune system can contribute to our knowledge about the immunologic signature in IBD patients.

NK Cells in the Gut of IBD Patients

NK cells represent the prototypical member of the ILCs family. They are crucial in host defense against transformed cells and virus-infected cells through potent IFN-γ production and cytotoxicity (reviewed in: Vivier et al. 2008). It is a link between innate immunity and adaptive immunity (reviewed in: Moretta et al. 2008). Multiple lines of evidence suggest their involvement in the pathogenesis of IBD (Egawa and Hiwatashi 1986; Fort et al. 1998; Steel et al. 2011; Takayama et al. 2010). Genome-wide studies have linked many NK cell receptors (killer immunoglobulin-like receptors) and their HLA alleles with IBD susceptibility (Diaz-Pena et al. 2016; Hollenbach et al. 2009; Wilson et al. 2010). In tissues, Steel et al. (2011) reported that the frequency of $CD16^+$ NK cells was increased in the colonic lamina propria of IBD patients compared to controls. Ng et al. (2009) identified a $CD56^+$ $HLA\text{-}DR^+$ NK cell subset that was associated with intestinal inflammation in the colonic lamina propria of UC patients. Takayama et al. (2010) showed that the balance of $NKp44^+/NKp46^+$ NK cells was disrupted in the intestinal mucosa of CD patients and concluded that $NKp46^+$ NK cells might mediate the pathogenesis of CD by producing IFN-γ. Yusung et al. (2017) recently showed the immunosuppressive drug 6-mercaptopurine therapy could decrease the number of NK cells in the colon of CD patients. Regarding how NK cells mediates its pathogenic role in the gut of IBD patients, on one hand, excessive presence of proinflammatory cytokine IFN-γ can directly break the tight junction of the intestinal epithelial monolayer to disrupt the barrier function (Bruewer et al. 2005; Patrick et al. 2006). On the other hand, NK-derived-IFN-γ can regulate adaptive responses directly and indirectly. Directly, this early source IFN-γ promotes $CD4^+$ T-cell differentiation into Th1 helper cells (Laouar et al. 2005; Martin-Fontecha et al. 2004; Morandi et al. 2006). Indirectly, NK cell-produced-IFN-γ induces maturation of dendritic cells, leading to increased IL-12-production and assisting Th1 cell polarization (Gerosa et al. 2002; Mocikat et al. 2003). All these information makes NK cells become very attractive immunotherapy targets for IBD patients.

ILC1s' Phenotype and Function in the Gut of IBD Patients

Human ILC1s are generally defined as lineage markers (–) $CD127^+$ $T\text{-}bet^+$-IFN-γ-producing cells. They play a crucial role in host defense against intracellular pathogens in the gut by their secretion of IFN-γ and tumor necrosis factor (TNF)-α at the steady state. However, under inflamed conditions, several human ILC1s subsets have been found to expand and produce excessive cytokines. Geremia et al. (2011) observed a significant and selective increase of IL-23-responsive $CD127^+$ $CD56^-$ ILCs in the inflamed intestine of CD patients but not UC patients. Fuchs et al. (2013) identified the expansion of $CD103^+$ ILC1s which were also $CD56^+$ in the intraepithelial compartment of CD patients' gut. Bernink et al. (2013) reported the IFN-γ-producing $CD127^+$ ILC1s, which accumulated in the inflamed ileum of CD patients. In our study, we noticed the expansion of IFN-γ-producing-$CD127^+$ ILC1s in the inflamed gut was associated with disease severity (Li et al. 2016b, 2017a). Bernink et al. (2015) further proposed that IFN-γ-producing $CD127^+$ ILC1s came from the conversion of $NKp44^+$ ILC3s under the control of IL-12 and IL-23. However, Simoni

et al. (2017) used mass cytometry including a broad range of surface markers and transcription factors to profile human ILCs across healthy and inflamed tissues and were not able to detect ILC1s in any of the tissues assessed. Their high-dimensional analysis allowed for clear phenotypic delineation of ILC2s and ILC3s (Simoni et al. 2017). The controversy of ILC1s identifies might partially due to the lack of consistently expressed specific markers for this subset. Additionally, the diversity and heterogeneity of ILC1s across tissues and organs makes it even more difficult to study. Better integration of the knowledge and information from various groups and studies would shed light on the development of therapeutic targets for restraining the initiation and progression of chronic intestinal inflammatory diseases.

ILC3s in the Maintenance of Human Intestinal Homeostasis

Human ILC3s include lymphoid tissue inducer (LTi) cells, NKp44$^+$ ILC3s and NKp44$^-$ ILC3s. In the fetal gut, LTi cells are the first hematopoietic cells to be recruited to the sites of lymphoid tissue development (Cupedo et al. 2009). In the adult gut, NKp44$^+$ ILC3s and NKp44$^-$ ILC3s are the two major ILC3 subsets (Bernink et al. 2013). The former mainly produces IL-22, while the latter secretes IL-17A under most circumstances (Cella et al. 2009; Hoorweg et al. 2012; Li et al. 2016a). NKp44$^-$ ILC3s are the precursors of NKp44$^+$ ILC3s (reviewed in: Mjosberg and Spits 2016). At steady state, 60–75% of the total non-cytotoxic ILCs are NKp44$^+$ ILC3s in the lamina propria of human gut whose frequencies are reduced dramatically under inflamed conditions (Bernink et al. 2013). They are the major innate source of IL-22 for mucosal immunity (Cella et al. 2009; Sawa et al. 2011). The IL-22 can promote epithelial cells to produce antimicrobial peptide, for example Reg1α, to initiate the early host defense against invading bacterial pathogens (Zenewicz et al. 2008). It can also induce the epithelial fucosylation to strengthen the barrier function in mouse models (Goto et al. 2014; Pickard et al. 2014). In addition, IL-22 can activate Stat3 in the epithelial cells to promote its proliferation which is crucial for tissue repair and mucosal healing process (Cella et al. 2009; Li et al. 2017b). Especially, there is still no cure for IBD and a typical disease course of IBD is a progressive and destructive process. Even under clinical remission stages, the subclinical inflammatory activities continue which lead to the accumulation of bowel structure damage and loss of normal bowel function. The mucosal healing is an important therapeutic goal for the treatment of IBD patients (reviewed in: Torres et al. 2017). Furthermore, IL-22 can also induce epithelial cells to secrete another important anti-inflammatory cytokine IL-10 to restrain inflammatory activity (Cella et al. 2009). In our study, we found that NKp44$^+$ ILC3s from the inflamed ileums of CD patients produced less IL-22 and acquired certain levels of IFN-γ-producing-ability compared to NKp44$^+$ ILC3s isolated from unaffected areas (Li et al. 2017a). Interestingly, multiple lines of evidence also suggests that intestinal ILC3s play a role in the regulation of adaptive immunity, especially CD4$^+$ T-cell responses (Hepworth et al. 2013, 2015). Overall, ILC3s are crucial players in the maintenance of human intestinal mucosal homeostasis. Intriguingly, in mice lacking T-cells, Song et al. (2015) found that NKp46$^+$ ILC3s could promote intestinal inflammation through marked production of granulocyte macrophage colony-stimulating factors which caused inflammatory monocyte accumulation. Further studies are needed to understand the phenotypic and functional heterogeneity of ILC3s in the gut.

ILC2s' Role in Gut Homeostasis and Intestinal Inflammation

Traditionally, ILC2s provide an early source of Th2 cytokines (IL-5 and IL-13) to induce protective immune responses against parasites and helminth infection in the gut (Nausch et al. 2015; Wilhelm et al. 2016). Recently, various other roles of ILC2s in the gut homeostasis are being identified. In mouse studies, Bruce et al. (2017) demonstrated that restoration of ILC2s could treat and prevent acute gastrointestinal graft-versus-host disease in the lower gastrointestinal tract by the generation of IL-13 and amphiregulin. Monticelli et al. (2015) revealed a tissue-protective function of ILC2s in the intestinal tract through the IL33-ILC2s-amphiregulin pathway. In their model, ILC2s mediated tissue protection during intestinal injury by limiting inflammation and promoting epithelial repair through amphiregulin secretion (Monticelli et al. 2015). Furthermore, von Moltke et al. (2016) showed that tuft cell constitutively expressed IL-25 to sustain ILC2s homeostasis in the resting lamina propria. After helminth infection, the IL-25 further activated ILC2s to produce IL-13 which could act on epithelial crypt progenitors to induce differentiation of tuft and goblet cells in the small intestine (von Moltke et al. 2016). However, there is still very limited human data available regarding the role of ILC2s in gut inflammation. Bailey et al. (2012) revealed a possible involvement of ILC2s-derived-IL-13 in the collagen accumulation through down-regulation of fibroblast MMP synthesis among CD patients. More human studies about ILC2s in the gut are urgently needed. Since UC is characterized by the Th2 immune responses, it is very interesting to speculate the potential involvement of ILC2s in the pathogenesis of UC, especially in the colon.

ILCs' Interactions with T-Cells

As mentioned earlier, ILCs can also regulate adaptive responses, particularly those of $CD4^+$ T-cells. First of all, ILCs can influence T-cells differentiation by their rapid and substantial cytokine-producing capabilities (Pelly et al. 2016). Furthermore, ILCs can interact with T-cells through direct cellular contact. In mouse studies, Oliphant et al. (2014) showed that MHCII-expressing ILC2s interacted with antigen-specific Th2 cells to investigate a dialog that contributed to their mutual maintenance, expansion, and cytokine production. This interaction appeared to augment dendritic cell-induced T-cells activation (Oliphant et al. 2014). Halim et al. (2014) reported that ILC2s were required to mount a robust Th2 cell response to the protease-allergen papain. Interestingly, Hepworth et al. (2013) showed that ILC3s also expressed MHCII and could process as well as present antigen to T-cells. Rather than inducing T-cell proliferation, ILC3s acted to limit commensal bacteria-specific $CD4^+$ T-cell responses (Hepworth et al. 2013). Selective deletion of MHCII in mouse ILC3s resulted in dysregulated commensal bacterial-specific $CD4^+$ T-cell responses that promoted spontaneous intestinal inflammation (Hepworth et al. 2013). Later on, they discovered that $MHCII^+$ ILC3s directly induced cell death of activated commensal bacteria-specific T-cells by lack of co-stimulatory molecules and withdrawal of the essential cytokine IL-2 in the surrounding environment (Hepworth et al. 2015). Furthermore, immunofluorescence staining revealed that mesenteric lymph node ILC3s were only present within the inter-follicular region and interface between B-cell and T-cell zones which were key regions through which lymphocytes, as well as other immune cells, trafficked during different stages of adaptive immune responses (Mackley et al. 2015; Withers et al. 2012). Mackley et al. (2015) showed that constitutive trafficking of ILC3s from the intestine to the draining mesenteric lymph nodes was CCR7 dependent. Besides that, Martin et al. (2017) demonstrated that ILCs restricted T-cell homeostasis in lymphoid organs by competing for and consuming IL-7 through a hematopoietic cytokine sink. It seems likely that the outcome of ILCs and T-cell interaction is context-dependent. The differential co-stimulatory molecules expression among ILCs might also contribute to this. ILC3s reported an absence or very low levels of CD80 and CD86 expression (Hepworth et al. 2013). ILC2s were shown to express ICOSL and OX40L which might facilitate its cellular contact with T-cells (Maazi et al. 2015; Withers et al. 2009). In the human studies, ILC3s isolated from human small bowel and colon expressed MHCII at reduced levels in pediatric IBD patients. This reduction was associated with increased Th17 cells in the inflamed colon of those patients (Hepworth et al. 2015). Consistent with this finding, we observed that the decrease of the $NKp44^+$ ILC3s in the inflamed terminal ileum of CD patients was associated with an increase of pathogenic IL-$17A^+$ IFN-γ^+ and IL-22^+ IFN-γ^+ T-cell subsets (Li et al. 2017a). Of course, it is not surprising that many essential questions remain regarding the interaction between rare subset ILCs and effector -cells, for example, how the ILCs acquire and process antigen, where exactly this interaction occurs, and so on. More research is needed to answer those basic questions and help us to gain more insights into the complex interactions between innate and adaptive immunity.

Conclusions and Future Directions

Over the past few years, ILCs have been shown to play important roles in promoting immunity to pathogens, tissue repair, and anatomical containment of commensal bacteria and regulation of adaptive immune responses. These discoveries in mouse models have laid solid foundation for our understanding of ILCs field. However, deciphering the mechanism of ILCs' function, maintenance and development in human has lagged behind. In-depth comparison of the characteristic of ILCs in diseased human tissues with those in healthy human tissues will help to further discover their possible roles in disease and to determine whether targeting ILCs will help to prevent or treat these diseases. Emerging evidence reveals the involvement of ILCs in the pathogenesis of IBD (summarized in Table 1). However, most of the research have been focusing on CD patients. The data regarding various ILCs in the gut of UC patients is missing. Also, patient stratification according to intestinal inflammation condition is absolutely necessary to fully elucidate ILCs composition in IBD. Furthermore, future studies about the exact location of ILCs in the lamina propria of the human gut as well as its traffic pattern are needed to help us further investigate the interactions between ILCs and other key mucosal immune cells. Overall, the dramatic changes of human intestinal ILCs' phenotype and function under the chronic inflammatory conditions make it an attractive therapeutic target. We could target their cytokines production, such as IFN-γ and TNF-α, or surface adhesion markers expression, for example integrins, or pathways that regulate ILCs' phenotype switch, such as IL-12/IL-23 pathway. Actually, they might have already contributed to the benefits that some current treatments for IBD, for example anti-TNF-α monoclonal antibody (adalimumab) and anti-IL-12/23 p40 monoclonal antibody (ustekinumab). One CD patient in our study showed signs of mucosal healing after 5 months of ustekinumab treatment accompanied by the decrease of ILC1s and recovery of ILC3s in the ileum (Li et al. 2016b).

Table 1 Innate lymphoid cells (ILCs) in inflammatory bowel disease (IBD)

Cell type	Surface markers	Transcription factors	General functions	Findings from human IBD studies	References
Cytotoxic NK cells	CD16, CD56, NKp46	T-bet and Eomes	Resistance to virus infection and cytotoxicity for tumor cells	Increased numbers in the inflamed gut of patients with IBD	Steel et al. (2011), Takayama et al. (2010)
ILC1s	CD127 (lamina propria) or CD103 (intraepithelial compartment)	T-bet	Resistance to intracellular pathogens (bacteria)	Increased numbers in the lamina propria and intraepithelial compartment of inflamed ileum of patients with CD	Bernink et al. (2013), Fuchs et al. (2013), Li et al. (2016a, 2017a)
ILC2s	CD127, CRTH2, KLRG1, CD25	GATA3	Host defense against parasites and helminth, epithelial repair at mucosal tissues	Possible involvement in the fibrosis of patients with CD	Bailey et al. (2012), Monticelli et al. (2015)
ILC3s	CD127, CD117, NKp44$^{+/-}$	RORrt and AHR	Epithelial integrity, antimicrobial peptide production against bacteria and regulation of adaptive responses	Reduced numbers in the inflamed ileum of patients with CD. Reduced MHC II expression on colonic ILC3s in pediatric patients with IBD	Bernink et al. (2013), Hepworth et al. (2013, 2015), Li et al. (2017a)

Anti-IL-12/23 p40 strategy might be able to reverse ILCs' phenotype in the inflamed gut of IBD patients for better prognosis.

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Compliance with Ethical Standards

Conflict of Interest The authors declared no conflicts of interest in this study. Sarah Glover, DO is a consultant for AbbVie, Janssen and Takeda. Sarah Glover, DO has received grant support from AbbVie, Bristol Myers Squibb, Celgene, Gilead, Janssen, Genentech, Millennium, Pfizer, Receptos, Takeda and UCB.

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