

Review

Dual immune functions of IL-33 in inflammatory bowel disease

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Summary. Interleukin-33 (IL-33) has emerged as a critical regulator in a variety of diseases, including inflammatory bowel disease (IBD). IL-33 can be produced by various tissues and cells, and typically induces Th2-type immune responses via binding to the receptor ST2. In addition, accumulated data have shown that IL-33 also plays a modulatory role in the function of regulatory T cells (Tregs), B cells, and innate immune cells such as macrophages and innate lymphoid cells (ILCs). IBD, including Crohn's disease and ulcerative colitis, are characterized by aberrant immunological responses leading to intestinal tissue injury and destruction. Although IL-33 expression is increased in IBD patients and correlates with the patients' disease activity index, mechanistic studies to date have demonstrated both pathogenic and protective roles in animal models of experimental colitis. In this review, we will summarize the roles and mechanisms of IL-33 in IBD, which is essential to understand the pathogenesis of IBD and determine potential therapies.

Key words: Interleukin-33, Inflammatory bowel disease, ST2, Innate immune, Adaptive immune

Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are characterized by chronic uncontrolled inflammation affecting the function of the gastrointestinal tract (Abraham and Cho, 2009). The pathophysiology and etiology of IBD remain elusive, but aberrant immunological responses have been implicated in the development of intestinal inflammation (Baumgart and Carding, 2007). Interleukin-33 (IL-33), a member of the IL-1 family, has emerged as a regulator of both the innate and adaptive immune responses (Schmitz et al., 2005; Lloyd, 2010; Flaczyk et al., 2013; Schwartz et al., 2016). Similar to IL-1 α and high mobility group box 1 (HMGB1), IL-33 is an alarmin protein, which is released in response to danger signals resulting from infection or tissue damage. IL-33 functions as both an intracellular nuclear protein and as an extracellular cytokine, and it exerts its functions by binding to the receptor ST2 (Cayrol and Girard, 2018). It has been demonstrated that the IL-33/ST2 pathway plays critical roles in several human diseases and experimental disease models (Duan et al., 2013; Liu and Turnquist, 2013; Wasmer and Krebs, 2016; Drake and Kita, 2017), including IBD (MacDonald et al., 2012; Nunes et al., 2014). However, the contribution of IL-33 to the pathogenesis of IBD

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remains controversial. Here, we review the dichotomous role of the IL-33/ST2 signaling pathway in the pathogenesis of IBD.

Overview of IL-33

IL-33, also called nuclear factor from high endothelial venules (NF-HEV) and interleukin-1 family member 11 (IL-1F11), is broadly expressed by many cells and tissues. Through the screening of gene expression profiles in different tissues, it has been shown that IL-33 is mainly expressed in the central nervous system and the gastrointestinal tract (Schmitz et al., 2005) suggesting that IL-33 plays important roles in both intestinal inflammatory diseases and neurological disorders (Pastorelli et al., 2013; Abd Rachman Isnadi et al., 2018). Similar to other IL-1 family members, the initial translation product of IL-33 is a precursor, which can be cleaved into a mature protein by caspase-1 and then released outside the cell (Arend et al., 2008; Zhao and Hu, 2010). However, recent studies have reported that the processing of mature bioactive forms of IL-33 in humans is not dependent on caspase-1 (Talabot-Ayer et al., 2009; Lefrancais et al., 2012). In addition to its function as an extracellular cytokine, IL-33 may also function in the nucleus, hence it has been demonstrated that nuclear IL-33 can associate with chromatin (Haraldsen et al., 2009).

IL-33 signaling is initiated when IL-33 binds to its specific receptor, ST2, and subsequently involves the adaptor proteins MyD88, IRAK1, IRAK4, and TRAF6 (Liew et al., 2010; Smith, 2011). IL-1R accessory protein (IL-1RAcP) is indispensable for IL-33/ST2 signal transduction, as IL-33 fails to induce IL-6 production in IL-1RAcP^{-/-} mouse-derived mast cells (Chackerian et al., 2007; Lingel et al., 2009). ST2 is mainly expressed on the surface of Th2 cells, mast cells, basophils, eosinophils, and NKT cells, and is not expressed on Th1 cells (Lloyd, 2010). Recently, ST2 expression was also detected on the surface of T regulatory cells (Tregs), group 2 innate lymphoid cells (ILC2), macrophages, B cells, and neutrophils (Peine et al., 2016). IL-33 exhibits complex biological functions, and it may have completely distinctive effects on different cell types. Interestingly, IL-33 not only can directly affect the ST2+ immune cells, but it can also indirectly induce Th1/Th17 immune response via the activation of innate immune cells (Milovanovic et al., 2012b). While the extracellular interaction with various cell types is mediated through the ST2 receptor, intracellular interaction via full-length IL-33 (fl-IL-33) can play another critical role in the immune response. The intracellular interaction of fl-IL-33 with nuclear factor (NF)- κ B subunit p65 has been shown to impair NF- κ B activity by interfering with DNA binding activity and p65-driven transactivation (Ali et al., 2011). Overall, it is now well-understood that NF- κ B transcription factor can rapidly amplify inflammatory response by promoting the production of many mediators and

proinflammatory cytokines. Exogenous recombinant IL-33 can enhance the inflammation by expression of the LPS receptor components MD2, TLR-4 and the MyD88 adaptor molecule (Espinassous et al., 2009), however, overexpression of intracellular fl-IL-33 can reduce the NF- κ B target genes such as I κ B α , TNF- α , and C-REL. This suggests that intracellular IL-33 can exert an anti-inflammatory function.

The soluble form (sST2) and membrane-bound form (ST2) are two isoforms of the IL-33 specific receptor ST2, which are generated by alternative splicing (Lohning et al., 1998). Although sST2 can serve as a decoy receptor for IL-33, sST2 exhibits an IL-33-independent function by directly binding to the surface of macrophages, which in return can lead to inhibition of LPS stimulation to produce pro-inflammatory cytokines (Sweet et al., 2001; Takezako et al., 2006). Recently, this inhibitory effect of sST2 was also observed in dendritic cells (DCs). The production of cytokines in DCs pretreated with sST2 was impeded after LPS stimulation. Furthermore, the ability of DCs to promote the proliferation of naive T cells was also significantly inhibited by soluble ST2 pretreatment. This inhibition may be related to the regulation of LPS signaling via sST2 internalization (Nagata et al., 2012). Taken together, IL-33-deficient and ST2-deficient mice might exhibit a complex phenotype in the development of diseases (Kamradt and Drube, 2013). ST2 gene knockout can lead to a sST2 depletion that can affect both extracellular stimulatory and intracellular suppressive role. Therefore, the choice between ST2 and IL-33 deficient animals requires careful consideration in an experimental model.

Dichotomous roles of IL-33 in IBD

IL-33 is present in normal intestinal tissue, and its expression is higher in inflamed tissue (Pastorelli et al., 2013; Hodzic et al., 2017). Early studies showed that IL-33 is mainly expressed by colonic epithelial cells, especially during active UC (Beltran et al., 2010; Pastorelli et al., 2010; Seidelin et al., 2010). In addition, subsequent studies have shown that IL-33 co-localizes with fibroblast markers in the intestinal tissue of UC, which suggests that ulceration-associated myofibroblasts may be another source of IL-33 (Kobori et al., 2010; Sponheim et al., 2010). Although IL-33 was induced in the cultured fibroblasts by inflammatory cytokines, including TNF α and IL-1 β , the data from this study suggest that de novo induction of IL-33 is a critical factor for wound healing, which indicates a protective role for the elevated IL-33 expression in these conditions (Sponheim et al., 2010). Similar to other studies, our previous study also showed a markedly increased expression of IL-33 in the colonic tissue of mice with TNBS-induced colitis when compared with the control group. However, we found that IL-33 was mainly expressed in the cytoplasm of infiltrating immune cells in the lamina propria and submucosa, and the infiltrating

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cells showed morphological characteristics of macrophages. Through immunofluorescence double staining of colonic tissue *in vitro*, we further confirmed that infiltrating macrophages were the major source of IL-33 in the colonic tissues of TNBS-treated mice (Duan et al., 2012).

IL-33 exhibits complicated, often contradictory roles in immune-related diseases. Beneficial roles for IL-33 have been established in atherosclerosis (Miller et al., 2008; McLaren et al., 2010), sepsis (Alves-Filho et al., 2010), and experimental autoimmune encephalitis (EAE) (Jiang et al., 2012; Milovanovic et al., 2012a; Chen et al., 2015). However, it has also been demonstrated that IL-33 can be detrimental during the development of asthma (Drake and Kita, 2017), rheumatoid arthritis (Xu et al., 2008, 2013; Palmer et al., 2009), and other autoimmune diseases (Theoharides et al., 2015). Genetic studies have shown that IL-33 polymorphisms contribute to the risk of developing IBD (Latiano et al., 2013). Additionally, IL-33 expression is increased in experimental Th1/Th2-mediated enteritis and its expression positively correlates with disease severity (Pastorelli et al., 2010). On this basis, IL-33 was previously considered a pro-inflammatory cytokine in the context of IBD. However, in DSS-induced experimental colitis, the body weight was markedly decreased in IL-33^{-/-} mice when compared with wild type mice during recovery. Furthermore, expression of the neutrophil chemoattractants KC and macrophage inflammatory protein-2 (MIP-2) were decreased in IL-33^{-/-} mice, which might contribute to the delayed resolution of tissue damage during DSS-induced colitis (Oboki et al., 2010). Our previous studies showed that an increased expression of IL-33 was observed in mice with TNBS-induced experimental colitis, and a significant beneficial effect on experimental colitis was observed with rIL-33 treatment (Duan et al., 2012). Therefore, the IL-33/ST2 signaling pathway might play a dichotomous role in the pathogenesis of IBD. Below we review the complicated roles of IL-33 in the development of IBD.

IL-33 as a pro-inflammatory cytokine

IL-33 promotes Th2-type immune responses

IL-33 plays a pivotal role in asthma by inducing the expression of Th2-type cytokines such as IL-4, IL-9, and IL-13. In a murine model of asthma, ST2^{-/-} mice have less airway inflammation than their wild type counterparts. Consistently, exogenous IL-33 treatment exacerbates airway inflammation in wild type mice, resulting in induction of IL-5-producing T cells and alternatively activated macrophages (Kurowska-Stolarska et al., 2008, 2009; Kearley et al., 2009). Subsequent studies have further demonstrated that IL-33 exerts its activity on mast cells, eosinophils, and basophils in the development of asthma, leading to airway epithelium dysfunction (Drake and Kita, 2017). However, it has been shown that intestine environment

with a spectrum of protective cytokines was orchestrated by MC-dependent IL-33/ST2 signaling (He et al., 2018). In addition, it is worth noting that IL-33 can increase mucus production, epithelial cell hyperplasia, and hypertrophy in the gastrointestinal tract (Schmitz et al., 2005). IL-33 levels are increased in the serum and the inflamed colonic mucosa of IBD patients, particularly in the epithelial cells (Beltran et al., 2010; Kobori et al., 2010; Pastorelli et al., 2010). TNF α is a crucial inflammatory cytokine that is implicated in the pathological progression of IBD, and inhibition of TNF α activity has been widely used as a clinical treatment for IBD (Argollo et al., 2017). Treatment of IBD patients with an anti-TNF α antibody markedly decreases the serum level of IL-33. These findings are confirmed in SAMP mice, which develop a spontaneous chronic intestinal inflammation resulting from a mixed Th1/Th2 immune response (Pastorelli et al., 2010). Concordant with these results, another study found that up-regulated IL-33 expression is also positively correlated with the disease severity score and Th2-specific transcription factor GATA-3 levels in UC patients and piroxicam-accelerated colitis in IL-10^{-/-} mice. In contrast, the correlation between IL-33 and expression of the Th1-specific transcription factor T-bet was not significant (Seidelin et al., 2015). Furthermore, IL-33 treatment augments the production of inflammatory cytokines IL-5, IL-6, and IL-17 from mesenteric lymph node (MLN) cells of SAMP mice and IL-10^{-/-} mice *ex vivo* (Pastorelli et al., 2010; Seidelin et al., 2015). However, in these experiments, exogenous IL-33 administration was not performed and ST2^{-/-} mice were not used. Consequently, it cannot be said for certain that IL-33/ST2 signaling was necessary for the development of colitis in these experiments.

Subsequently, it has been demonstrated that IL-33 promotes colonic inflammation in DSS-induced acute colitis in BALB/c mice. Although exogenous IL-33 treatment prevents goblet cell depletion but exacerbates body weight loss and disease activity index, the investigators suggested that the actions of IL-33 are more detrimental than protective (Imaeda et al., 2011). Pushparaj et al. also observed increased IL-33 expression in the colonic tissues after DSS treatment. Accordingly, colonic inflammation and diarrhea were more severe when the mice were treated with exogenous recombinant IL-33, while this effect is impaired in ST2^{-/-} mice. These findings were also seen in mice with a BALB/c background. Consistent with the Th2-type immunity induced by IL-33 in previous reports, they also found that the disease-exacerbating effect of IL-33 depends on the IL-4 pathway (Pushparaj et al., 2013). Furthermore, blockade of the IL-33/ST2 signaling pathway using an anti-ST2 antibody decreases disease severity and decreases the Th2-type immune response in SAMP mice, while IL-33 administration elicits Th2-type cytokine production and eosinophil infiltration in the ilea of uninflamed control mice (De Salvo et al., 2016). These studies indicate that Th2-type responses induced

by IL-33 may be crucial for the pathogenesis of IBD.

IL-33 in innate immunity

IL-33 has emerged as an important player in both adaptive and innate immune responses. However, hyperglycemia and transaminase levels in IL-33^{-/-} and wild type mice are not significantly different in mice with streptozotocin-induced diabetes and concanavalin A (ConA)-induced hepatitis, respectively (Oboki et al., 2010); and T cells or NKT cells are crucial for the progression of these diseases (Seino et al., 1997; Lamhamedi-Cherradi et al., 2003). These findings suggest that IL-33 is not essential for the development of T or NKT cell-mediated tissue injury. Additionally, body weight loss and mortality during the onset of disease are decreased in IL-33^{-/-} mice with DSS-induced colitis, where T and B cells are dispensable for disease development (Oboki et al., 2010). Therefore, IL-33 may regulate the innate immune response during the onset of DSS-induced colitis. However, IL-33 and Rag double KO mice should be used to confirm this.

The Non-hematopoietic function of IL-33

Numerous studies show that ST2 is expressed in epithelial cells, especially in inflamed colonic tissue (Beltran et al., 2010; Pastorelli et al., 2010). Although IL-33 seems to be a crucial amplifier of innate rather than acquired immunity as described above (Oboki et al., 2010), the decreased disease activity and body weight loss in IL-33^{-/-} mice with DSS-induced colitis may be due to a non-hematopoietic function of IL-33. Intestinal epithelial cells form protective barriers and participate in host defenses, and they are essential for maintaining intestinal homeostasis by regulating immune cell function (Peterson and Artis, 2014). Previous studies have shown that the dysfunction of the epithelium has a crucial role in the pathogenesis of IBD, including impaired differentiation of tolerogenic CD103⁺ dendritic cells (DC) (Rescigno and Di Sabatino, 2009; Strauch et al., 2010; Mak'Anyengo et al., 2018). Sedhom et al. observed that exogenous IL-33 treatment considerably augments the morbidity of DSS-induced colitis. Furthermore, in TNBS-induced colitis or DSS-induced colitis, ST2^{-/-} mice have less intestinal inflammation and decreased disease activity index scores compared to wild type mice. However, unlike the hematopoietic function of IL-33 shown in previous studies, using bone marrow chimera experiments, they demonstrated that the ST2 signaling pathway in non-hematopoietic cells promotes colonic tissue injury, and that IL-33 negatively regulates epithelial barrier function in the colon (Sedhom et al., 2013). Consistently, a mesenchymal population in the epithelial crypts expressing IL-33 might impair epithelial proliferation (Kinchen et al., 2018). However, the normal function of endogenous IL-33 is protection during acute resolving colitis, and the lack of either IL-33 or ST2 impedes the overall recovery process.

Mechanistically, IL-33/ST2 plays a crucial role in gut mucosal healing by inducing epithelial-derived miR-320 (Lopetuso et al., 2018). These mechanisms can be confirmed using ST2 epithelial-specific KO mice in future studies.

IL-33 as a homeostatic cytokine

The protective function of Th2-type immune induction by IL-33

It is well documented that Th2-type cytokines suppress cell-mediated immune responses and inhibit Th1/Th17 type immune responses, which play a critical role in the pathogenesis of IBD (Neurath, 2014). Given this knowledge, it seems likely that IL-33 may play a protective role in Th1/Th17 mediated diseases. In a model of experimental cardiac allogeneic transplantation, recipient mice given exogenous IL-33 showed significantly enhanced allograft survival, which was associated with a Th2-type immune bias (Yin et al., 2010). Consistently, IL-33 profoundly reduced plaque development in ApoE^{-/-} mice fed a high-fat diet. Atherosclerosis and allograft rejection are mainly mediated by Th1 and Th17 responses. Therefore, it is likely that a Th1-to-Th2 switch accounted for the decreased lesion size (Miller et al., 2008). Consistently, most studies have demonstrated that promoting Th2 immune responses can reduce the pathological progression of Th1/Th17-mediated colitis (Hunter and McKay, 2004; Daniel et al., 2008); and our previous study also showed that the alleviation of TNBS-induced colitis by IL-33 was partly due to the induction of a Th2-type immune response. IL-33 treatment resulted in markedly increased Th2-type cytokine production and decreased expression of the Th1-type cytokine IFN- γ in mice with TNBS inoculation. In addition, ST2⁺ CD4⁺ T cells, which are thought to play an important role in the generation of Th2-type cytokines, were also enriched in the lamina propria mononuclear cells (LPMCs) and MLN of mice treated with IL-33 (Duan et al., 2012). Similar findings were observed in DSS-induced chronic colitis (Zhu et al., 2015). Likewise, the Th2-associated cytokines TSLP and IL-25 also exhibit immunoregulatory properties during the development of colonic inflammation (Caruso et al., 2009; Taylor et al., 2009). Therefore, increased expression of IL-33 during colonic inflammation may serve a regulatory function that impedes the development of colitis.

IL-33 regulates Treg function

An imbalance of Th1/Th17 cells and Tregs has been shown to play a critical role in IBD (Bai et al., 2009; Rovedatti et al., 2009). Tregs are immunosuppressive and generally they suppress induction and proliferation of effector T cells. Studies in mouse models have suggested that modulation of Treg function can be used to treat autoimmune disease (Miyara et al., 2014). It has

been shown that Treg function is impaired in ST2^{-/-} mice, suggesting that IL-33/ST2 signaling might be involved in the development and function of Tregs (Zdravkovic et al., 2009). In heart transplantation, IL-33 administration prolongs transplant survival by increasing ST2⁺ Tregs in mice, and increased Foxp3⁺ cells in the allograft of IL-33-treated recipients were observed (Turnquist et al., 2011). Consistent with these findings, our previous study showed an increase of Foxp3⁺ Tregs in IL-33-treated mice with TNBS-induced colitis. Although IL-33 facilitates Th2 and Treg expansion, Treg depletion with anti-CD25 antibody treatment abolished the protective role of IL-33 when compared with the IgG control group, whereas anti-IL-4 antibody treatment only partly reversed the protective effect of IL-33. Thus, IL-33 alleviates TNBS-induced colonic inflammation mainly through regulation of Tregs (Duan et al., 2012). A subsequent study showed that ST2 expression is markedly upregulated in colonic Tregs when compared with spleen or MLN, and ST2 expression was mainly restricted to colonic Foxp3⁺ GATA3⁺ Tregs (Schiering et al., 2014). Consistent with TNBS-induced acute colitis, IL-33 also promotes Tregs in chronic colitis (Schiering et al., 2014; Zhu et al., 2017). The adoptive transfer of ST2^{-/-} Tregs does not prevent colonic inflammation and cellular infiltration, which suggests that IL-33 acts directly on Tregs to promote their proliferation and accumulation (Schiering et al., 2014). Aside from the direct action on Tregs, IL-33 also indirectly induces Tregs by promoting CD103⁺ IDO⁺ tolerogenic DCs and stimulating the DCs to secrete IL-2, which plays a critical role in Treg expansion (Duan et al., 2012; Matta et al., 2014).

IL-33 regulates B cell function

The role of IL-33 was also explored in spontaneous colitis in IL-10-deficient mice, which has been widely used as an animal model of IBD. Although IL-33 administration exacerbates the development of colonic inflammation in IL-10^{-/-} mice, IL-33-mediated mucosal inflammation was not observed in IL-10^{+/+} wild type mice. Unexpectedly, no significant change in the frequency of Tregs in the IL-10^{-/-} mice was seen with IL-33 treatment, while increased regulatory B cells (CD19⁺ CD25⁺ CD23⁻) were observed in both IL-10^{-/-} knockout and IL-10^{+/+} wild type mice (Sattler et al., 2014). Regulatory B cells (Bregs), a relatively newly discovered population of B cells, have gained attention for their role in restraining inflammation. Bregs can suppress Th1 and Th17 immune responses and facilitate Treg propagation. Bregs have been shown to inhibit immune responses via the production of IL-10, IL-35, and TGF- β (Mauri and Menon, 2017). It has been reported that Breg function is impaired during the development of human autoimmune diseases such as rheumatoid arthritis (RA) (Banko et al., 2017), multiple sclerosis (MS) (Staun-Ram and Miller, 2017), and systemic lupus erythematosus (SLE) (Shipman, 2016).

In keeping with these findings, IL-10^{-/-} mice given IL-33-induced Bregs by adoptive transfer showed reduced disease activity, and leukocyte infiltration into the colon was also decreased. Therefore, in addition to the regulation of Tregs, IL-33 also induces a subset of IL-10-producing Bregs. Malik et al. also showed that IL-33^{-/-} mice inoculated with DSS develop a dysbiotic microbiota and serious colitis. They further demonstrated that IL-33 is important for maintaining microbial homeostasis in the intestine through the promotion of IgA production from B cells (Malik et al., 2016).

The regulation of IL-33 in innate immunity

It has been reported that exaggerated activation of CD4⁺ T cells leads to intestinal tissue damage and the development of IBD, while innate immune cells are involved in the suppression of colonic inflammation (Uhlir and Powrie, 2018). Macrophages are critical in initiating the innate immune response and modulating the adaptive immune response, and their dysfunction can lead to an abnormal immune response, resulting in tissue injury in many diseases. Indeed, a crucial role in the limitation of inflammation and promotion of tissue repair by macrophages has been described in IBD (Mantovani et al., 2013; Gren and Grip, 2016). Typically, macrophages are divided into two categories: classically-activated macrophages (CAM, M1) and alternatively-activated macrophages (AAM, M2). Exposure of naïve monocytes or recruited macrophages to Th1-related cytokines (IFN- γ , TNF- α) or lipopolysaccharide (LPS) favors CAM polarization, which plays an essential role in anti-microbial activities and Th1-type responses, while Th2-related cytokines (IL-4 and IL-13) are closely linked with AAM polarization (Mills, 2015). In contrast to CAM, AAM produce fewer pro-inflammatory cytokines and participate in tissue remodeling and resolution of inflammation (Gordon and Martinez, 2010). Therefore, during the inflammatory response in diseases such as IBD, macrophages may exert a complex role by either exacerbating or resolving inflammation. Excessive production of inflammatory cytokines TNF- α and IFN- γ in IBD has been described in many reports (Gren and Grip, 2016). However, it has been reported that the Th2-type cytokine IL-25 can ameliorate intestinal inflammation induced by TNBS by promoting AAM polarization (Rizzo et al., 2012). Worm infection has been proposed as a treatment of colitis, as worm infection can cause a Th2-type immune response and may promote AAM polarization. Indeed, a reduced severity of dinitrobenzene sulfonic acid (DNBS)-induced colitis was observed in mice infected with the worm *Hymenolepis diminuta*, and the intestinal number of AAM was increased in the worm-infected mice (Hunter et al., 2010). In our published study, IL-33 administration increased the expression of AAM markers, such as arginase-1 and FIZZ1 in mice with

colitis (Tu et al., 2017), which was also demonstrated in EAE and allergic mice treated with IL-33 (Kurowska-Stolarska et al., 2009; Jiang et al., 2012). We provided clear evidence that IL-33 primes macrophages into AAM, which play a protective role in TNBS-induced colitis. Another study also showed that IL-33 treatment was sufficient to ameliorate TNBS and DSS-induced acute colitis by facilitating macrophage switching from the CAM to the AMM phenotype and restoring goblet cell numbers (Seo et al., 2017).

Neutrophils are generally thought to play an important role in the pathogenesis of IBD (Wera et al., 2016). Depletion of neutrophils or blocking of neutrophil migration exacerbates TNBS and DNBS-induced colitis in rats and transfer colitis in mice (Kuhl et al., 2007). Similar results are also observed in DSS-induced colitis when mice are treated with anti-Ly6G (clone1A8) or anti-Gr-1 (clone RB6-8C5), leading to neutrophil depletion (Conway et al., 2012; Zindl et al., 2013). These data indicate a protective role for neutrophils during colitis. As shown in IL-33^{-/-} mice, the body weight was markedly decreased in DSS-induced acute experimental colitis in the recovery phase of inflammation. The delayed resolution of tissue damage might be due to decreased expression of neutrophil-chemoattractant factors KC and MIP-2 in IL-33^{-/-} mice (Oboki et al., 2010). The protective effects of IL-33 in inducing neutrophil influx during chronic inflammation were also investigated in DSS-induced chronic colitis (Grobeta et al., 2012). IL-33 reduces the mortality associated with cecal ligation and puncture experimental sepsis (CLP) in mice by promoting the influx of neutrophils into the site of infection, which results from the prevention of CXCR2 down-regulation induced by TLR activation (Alves-Filho et al., 2010).

ILCs, a recently discovered group of innate immune

cells, have important roles in IBD (Peters et al., 2016). ILC2 cells are a subset of ILCs that secrete large amounts of IL-5 and IL-13 in response to IL-33 stimulation (Yasuda et al., 2012). In addition to Th2-type cytokine induction, IL-33 also promotes ILC2 to produce the epidermal growth family member amphiregulin, which has been shown to be important for lung epithelial repair and remodeling (Monticelli et al., 2011). In a similar paradigm, ILC2-intrinsic amphiregulin contributes to the regulation of intestinal inflammation. In DSS-induced acute colitis, exogenous IL-33 administration orchestrates intestinal tissue protection by inducing ILC2 to produce amphiregulin, which markedly enhances Treg immune suppressive function by binding EGFR (Monticelli et al., 2015). Therefore, IL-33 may induce crosstalk between ILC2 and Tregs, which plays a tissue-protective role in the colonic intestinal mucosa during disease.

Conclusion

Although numerous studies of IL-33 in the pathogenesis of experimental disease models have occurred, the roles and mechanisms of IL-33 remain contradictory. In this review, we have comprehensively summarized the contribution of IL-33-mediated immune regulation to the resolution or progression of IBD (Table 1). Moreover, we focused on elucidating the complex results of the IL-33/ST2 function in colonic inflammation. At the beginning of intestinal inflammation, the increased intracellular IL-33 expression might be spontaneous feedback in order to suppress excessive inflammation via inhibiting the NF- κ B signals (Lee et al., 2008). However, the inhibitory effect of intracellular IL-33 will be dampened by the strong activation of NF- κ B in the persistent

Table 1. Summary of pathogenic and protective functions of IL-33 in experimental colitis.

Function	Mice and gene background	Experimental Models	Mechanisms
Pathogenic role	SAMP mice (Pastorelli et al., 2010; De Salvo et al., 2016), IL-10 ^{-/-} (C57BL/6) (Seidelin et al., 2015)	Spontaneous chronic colitis	Th2-type immune response induction
	ST2 ^{-/-} (BALB/c) (Pushparaj et al., 2013)	DSS-induced acute colitis	
	ST2 ^{-/-} (C57BL/6) (Sedhom et al., 2013)	DSS-induced acute colitis, TNBS-induced acute colitis	Non-hematopoietic function of IL-33
Protective role	BALB/c	TNBS-induced acute colitis	Regulation of Tregs/Th2 (Duan et al., 2012) and AAM (Tu et al., 2017) function
		TNBS-induced acute colitis	Promotes AAM polarization (Seo et al., 2017)
	C57BL/6	DSS-induced acute colitis	Regulation of Tregs/Bregs (Zhu et al., 2017), neutrophils (Oboki et al., 2010), AAM (Seo et al., 2017), and ILC2 (Monticelli et al., 2015) function
		DSS-induced chronic colitis	Th2-type immune response (Zhu et al., 2015) and neutrophil influx induction (Grobeta et al., 2012)
	ST2 ^{-/-} (C57BL/6)	T cell transfer colitis	Regulation of IL-33 on Treg function (Schiering et al., 2014)
	IL-10 ^{-/-} (C57BL/6) (Sattler et al., 2014)	Spontaneous chronic colitis	
	IL-33 ^{-/-} (C57BL/6) (Malik et al., 2016)	DSS-induced acute and chronic colitis	Regulation of IL-33 on B cell function

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inflammatory stimulation, which will lead to upregulation of inflammatory mediators and tissue damage. Subsequently, releasing intracellular IL-33 into the extracellular space from activated cells and/or damaged cells can bind to its ST2 receptor in which it can subsequently regulate the functions of Th2, ILC2s, Tregs, macrophage, neutrophils, DCs as well as eosinophils. In this respect, IL-33 can induce excessive Th2-type immune response that exacerbates the Th2-mediated intestine inflammation (Pastorelli et al., 2010; Seidelin et al., 2015; De Salvo et al., 2016). Additionally, IL-33 can play a protective role in T cell transfer colitis, DSS and TNBS-induced colitis, where Th1/Th17 immune response is a key pathological factor. However, an opposite result was observed by using the ST2 KO and IL-33 KO mice (Grobeta et al., 2012; Pushparaj et al., 2013). These suggest that IL-33 might not be the only ligand for ST2. Indeed, membrane ST2 can cross-activate another IL-33-independent signaling pathways (Kamradt and Drube, 2013). Furthermore, ST2 has another two isoforms ST2V and STV2L generated by different alternative splicing, which might also play a role in the pathogenesis of IBD. Thus, results obtained from ST2 KO mice may not be able to draw conclusions about the role of IL-33 in the development of IBD. Besides, ST2 might have different effects on hematopoietic and non-hematopoietic cells, for instance ST2 expression on non-hematopoietic cells is sufficient for IL-33 to induce intestinal inflammation (Sedhom et al., 2013). Recently, the microbiota has been shown to play a key role in intestinal homeostasis, and differences in gut microbiota caused by different laboratory environments may be another important factor. Similar contradictions can also be seen in studies of other molecules, such as NLRP3 (Bauer et al., 2010; Zaki et al., 2010). Therefore, further studies, including clinical studies, are required to fully understand the pathophysiological function of IL-33 in IBD, which will help to develop immunomodulatory therapeutics against intestinal inflammation.

Conflict of Interest Statement. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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