gastrointestinal disorders

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Review

Role of IL-33/ST2 Pathway in Inflammatory Bowel Disease: An Overview and Future Perspectives

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Abstract: Inflammatory bowel disease (IBD) represents a heterogenous and complex group of idiopathic chronic inflammatory conditions affecting the gastrointestinal tract and other extraintestinal systems with rising global incidences. The interplay of genetic predisposition and environmental factors contributes to its pathogenesis. Among the key cytokines implicated in IBD molecular alterations, IL-33 stands out for its multifaceted roles in both pathogenesis and repair mechanisms. IL-33, known for its action in initiating immune responses, is closely associated with Th2 immunity and is considered a potent inflammatory factor with dual functions, acting both as a pro-inflammatory cytokine and a transcriptional regulator. Primarily expressed by non-hematopoietic cells in the gastrointestinal tract, IL-33 interacts with its receptor, ST2, to modulate immune responses. In IBD, dysregulated IL-33 expression exacerbates mucosal inflammation, compromising barrier integrity and promoting tissue damage and fibrosis. Additionally, IL-33 plays a complex role in IBD-related colorectal cancer (CRC), affecting tumor progression and angiogenesis. This review summarizes the multifaceted roles of IL-33 in gastrointestinal health and disease, emphasizing its significance in the pathogenesis of IBD and CRC. Moreover, we thought it of interest to provide new insights into potential therapeutic avenues targeting IL-33 signaling for the management of these debilitating conditions.

Keywords: inflammatory bowel disease; interleukin-33; fibrosis; colorectal cancer; immune regulation

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1. Introduction

Inflammatory bowel disease (IBD) includes various idiopathic chronic inflammatory conditions, which are clinically characterized by periods of remission and relapse that affect the gastrointestinal tract and other extraintestinal systems [1,2]. IBD affects young adults but it can manifest at any age, with a quarter of cases occurring before the age of 20 years. Global incidences, particularly in childhood, are increasing, with certain regions witnessing a significant rise in cases of very early onset IBD [3]. Initially, IBD was mainly concentrated in industrialized regions such as Western Europe, North America, Australia, and New Zealand, with a significant surge in cases taking place during the 20th century [3]. Although IBD incidence has stabilized in these areas, childhood IBD is on the rise [3]. Conversely, since the late 20th century, newly industrialized and developing countries in Asia, Latin America, South America, and Africa have experienced notable increases in IBD cases [3].

Consequently, these conventional geographic barriers have largely dissolved, leading to the global spread of IBD [3]. The global rise in IBD highlights the significant impacts of genetics and environment on its development. Environmental factors can influence the microbiome, resulting in persistent inflammation and compromised integrity of the intestinal barrier. This compromised barrier triggers an uncontrolled immune response, exacerbating mucosal inflammation [4]. Thus, the interplay of genetics, environment, intestinal barrier integrity, and immune response shapes the complex pathology of IBD [4–8].

IBD includes conditions such as ulcerative colitis (UC), Crohn's Disease (CD), and the less commonly diagnosed IBD-unclassified (IBD-U), which presents with an ambiguous clinical scenario; this latter form can develop into either UC or CD as symptoms worsen in severity [2,9].

Ulcerative Colitis (UC) typically presents as persistent inflammation confined to the colon, originating in the rectum and spreading to adjacent segments, predominantly targeting the inner epithelial layer [9,10]. It predominantly afflicts adults aged 30–40 years, although childhood onset UC can severely compromise the quality of life of children [9,11]. In contrast, Crohn's Disease (CD) can affect any segment of the gastrointestinal tract extending from the oral cavity to the anus, and it is more prevalent among individuals aged 15 to 30 years. CD is characterized by non-continuous inflammation and can involve all layers of the intestinal wall [9,12]. In CD, histological examination reveals a thickened submucosa, transmural inflammation, fissuring ulceration, and granulomas [12]. On the other hand, UC is characterized by inflammation limited to the mucosa and submucosa, typically presenting with superficial mucosa erosions, cryptitis, and crypt abscesses [13–15]. Although some therapeutic drugs may be effective for both UC and CD, patients with these conditions often undergo different clinical treatment approaches and vary as to optimal timing for surgical intervention as well as respective complications. Therefore, it is absolutely crucial to distinguish between UC and CD in patients [9].

The initial treatment approach for IBD involves anti-inflammatory therapies, including 5-aminosalicylates (5-ASA) and corticosteroids [16]. 5-ASA has shown effectiveness in IBD treatment by activating γ-form peroxisome proliferator-activated receptors (PPAR-γ) [17–19]. As 5-ASA is effective in treating active CD, a cohort of 5-ASA-treated unselected patients experienced a quiescent disease course without need of additional treatment during follow-up [16]. However, 5-ASA are thought to act topically, which may explain their higher efficacy in UC compared to CD; in fact, for UC, 5-ASA is effective in inducing and maintaining remission in mild to moderate cases [16]. Corticosteroids such as prednisone, methylprednisolone, hydrocortisone, and budesonide produce anti-inflammatory effects by binding to the intracellular glucocorticoid receptor [20,21]. Immunosuppressive agents like 6-mercaptopurine (6-MP), azathioprine (AZA), methotrexate (MTX), and cyclosporine (CSA) have been utilized when patients are un-responsive to 5-ASA and steroids; consequently, the use of conventional immunomodulators should be restricted to patients with a milder course of disease in the absence of risk factors, whereas patients with an aggressive disease course and risk factors should be treated early with biologic therapies [22]. These agents inhibit lymphocyte proliferation or suppress inflammatory-cytokine production [22]. Moreover, during recent decades, therapeutic goals in IBD have evolved toward endoscopic remission and mucosal healing, creating the need for early administration of disease-modifying agents (DMAs). DMAs include conventional immunosuppressants (thiopurines and methotrexate), biologic drugs (anti-TNF, anti-integrin, and anti-IL-12/23 monoclonal antibodies), and small molecules (JAK inhibitors and S1P receptor modulators) [22]. In detail, tumor necrosis factor-alpha (TNF-α) inhibitors, known as biologics, neutralize TNF-α to block pro-inflammatory signaling mechanisms. TNF-α inhibitors like infliximab, adalimumab, and certolizumab pegol are administered to treat IBD [9,22,23]. Additionally, emerging therapies such as melatonin and metabolites from commensal microbiota are being explored for their potential anti-inflammatory effects in IBD [9,24–26].

Given the importance of immune response in IBD, it is crucial to explore the role of specific cytokines in disease pathogenesis. The intricate interactions within the immune system are orchestrated by the activity of various cytokines. Any alteration in this complex cytokine network can lead to a persistence of the inflammatory process [27,28]. Among the most significant cytokines in this context is the interleukin 1 family, which comprises 11 pro-inflammatory and anti-inflammatory cytokines [27,28]. Among the pro-inflammatory cytokines, IL-33 plays a key role in causing tissue damage. Dysregulation of IL-33, along with its receptor, is implicated in several inflammatory pathological conditions, including IBD [27,29–31].

The purpose of the present review is to analyze in depth the role of IL-33 in IBD, mainly focusing on both its pathological and reparative aspects, which may represent additional future therapeutic approaches. Through a critical exploration of the available scientific evidence, we aim to clarify the involvement of IL-33 in the pathogenesis and progression of IBD in comparison to its role in the normal gastrointestinal microenvironment as well as in eventually arising IBD-related colorectal cancer (CRC).

2. IL-33 Structure and Biological Function

IL-33 is a fundamental member of the IL-1 family, expressed in the nucleus of endothelial and epithelial cells of barrier tissues, which is mainly involved in the immune activation response by T-helper lymphocytes, particularly T-helper type 2 cells (Th2), thus inducing the production of IL-5 and IL-13 [32]. IL-33 is a 30 kDa protein composed of 270 amino acids whose coding gene is located on human chromosome 9p24. IL-33 is involved in many other functions, such as the maintenance of tissue homeostasis and repair; inflammation induced by allergic factors, nonallergic factors, and viral infections; and in the pathogenesis of malignant tumors [33,34].

Besides its function as a cytokine, IL-33 also acts as a transcriptional regulator [34]. Although some studies have suggested a nuclear role for IL-33, currently available experimental evidence does not support this hypothesis [35,36]. Instead, it appears that the primary role of IL-33 occurs through extracellular and intercellular mechanisms rather than through the direct regulation of gene or protein expression within cells [35,36].

Structurally, IL-33 is characterized by three main domains: an N-terminal nuclear localization domain, a central protease-sensing domain, and a C-terminal cytokine domain (Figure 1) [36].

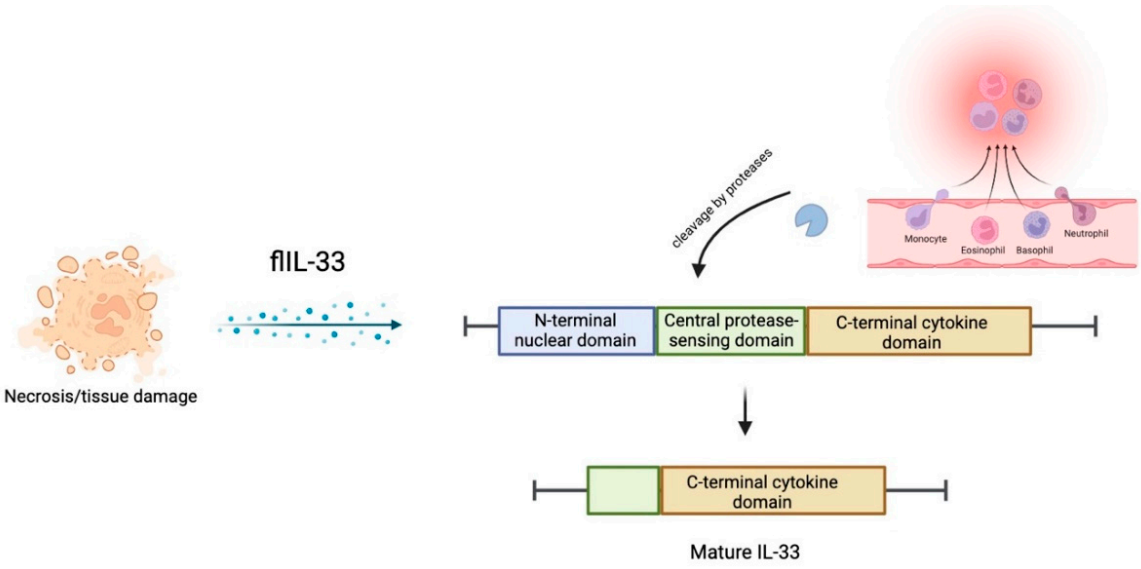

Figure 1. Schematic representation of the IL-33 maturation process and structural composition of the cytokine. This figure was created with BioRender (https://biorender.com (accessed on 21 March 2024)). flIL-33, Full-length interleukin-33; Mature IL-33, Mature interleukin-33.

Unlike other members of the IL-1 family such as IL-18 and IL-1β, IL-33 is not released via the endoplasmic reticulum or Golgi apparatus but is passively released as full-length IL-33 (flIL-33) following cell necrosis or tissue damage-induced cell death [37]. The protease-sensing domain of IL-33 can undergo cleavage by various proteases such as caspase-1, neutrophil elastase, cathepsin G, mast cell chymase, and tryptase. This cleavage produces a shorter mature form of 18 kDa, known as mature IL-33, which exhibits a biological activity approximately 30- to 60-fold higher than that of flIL-33 [36,38]. In contrast, the literature has shown that apoptotic caspases also have an impact on flIL-33 [38]. Intriguingly, the resultant cleavage products from these caspases fail to trigger substantial ST2-dependent responses, unlike IL-33FL itself [38]. This observation implies that caspase-mediated cleavage effectively renders IL-33 inactive during apoptosis [38]. This evolutionarily conserved mechanism of IL-33 regulation is probably crucial in preventing undue activation of the immune system after physiological programmed cell death as opposed to instances of pathological unprogrammed cell death [36]. Furthermore, intracellular flIL-33 can also bind to chromatin through a DNA-binding domain in its N-terminal nuclear localization region, and it is precisely from this interaction that IL-33 can also act as a transcriptional regulator [38].

In normal conditions, IL-33 is mainly expressed by non-hematopoietic cells, particularly intestinal epithelial cells, as well as by myofibroblasts and endothelial cells; it is also expressed in mast cells, Th2 cells, eosinophils, natural killer (NK) cells, and other cell types [39–41]. Several studies have also confirmed that, during acute inflammation, IL-33 is mainly expressed by colonic fibroblasts and that this is independent of the IL-1β pathway [42]. IL-33 can activate many cells such as Th2 cells, mast cells, eosinophils, Treg cells, ILC2, NK cells, Th1 cells, dendritic cells (DCs), and macrophages [43,44]. Unlike other members of the IL-1 family that mainly promote type 1 immune responses, IL-33 generally induces type 2 immune responses and is involved in allergic disorders, parasitic infection and inflammation [45]. IL-33 can exert its biological activity through the interaction with its receptor, suppression of tumorigenicity 2 (ST2), which is also known as IL-1 receptor-like 1 (IL1RL1) and belongs to the Toll-IL-1 receptor (TIR) superfamily [46]. This receptor exists in two different forms, both of which lead to the synthesis of two proteins that have completely different functions. The first of these proteins is ST2L (ST2 long isoform), an important transmembrane receptor that activates downstream signaling once recognized by IL-33, whereas the second protein, sST2 (soluble ST2), is a soluble molecule that acts as a decoy receptor by binding to IL-33 and consequently making it unavailable for binding with the signaling receptor, ST2L [47]. Furthermore, to activate the cellular signaling cascade downstream of IL-33, which binds to the extracellular domain of the receptor, the ST2L receptor also needs a very important coreceptor belonging to the TIR superfamily that is known as IL-1 receptor accessory protein (IL1RAcP) to create a heterodimeric transmembrane receptor complex [47,48]. The IL-1RAcP coreceptor consists of a transmembrane domain and an intercellular domain, called the Toll/IL-1 receptor (TIR), of approximately 160 amino acids [49]. Once IL-33, ST2L, and IL-1RAP form the heterodimeric complex, dimerization of the TIR domain occurs, resulting in activation and subsequent interaction with the adapter protein MyD88 (Myeloid differentiation primary response 88) [44]. MyD88, along with interleukin receptor-associated-kinase (IRAK) 1 and 4 and tumor necrosis factor receptor-associated factor 6 (TRAF6), determines the activation status of various transcription factors such as NF-kB (Nuclear Factor kappa B) and AP-1 (Activator Protein 1) which, also through the MAPK (Mitogen-Activated Protein Kinase) signaling pathway, results in the release of various pro-inflammatory mediators [44,46]. At the same time, c-Jun N-terminal kinase (JNK) and extracellular signal regulated kinases 1/2 (ERK 1/2) are also activated, promoting the activation of interferon regulatory factor 1 (IRF1), which, in turn, inhibits the expression of the forkhead box p3 (Foxp3) and GATA3 (GATA-binding protein 3) transcription factors (Figure 2) [34,50].

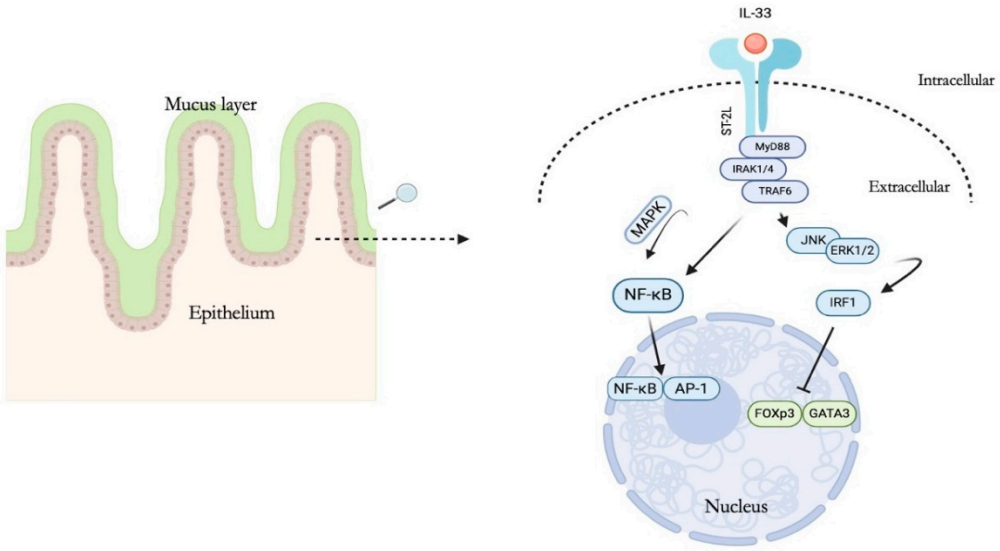

Figure 2. Representation of ST2L/IL-33 signaling. IL-33, interleukin-33; ST2L, suppression of tumorigenicity 2 ligand; IL-1RAcP, IL-1 receptor accessory protein; MyD88, myeloid differentiation primary response 88; IRAK1/4, interleukin receptor-associated kinase; TRAF6, tumor necrosis factor receptor-associated factor 6; MAPK, mitogen-activated protein kinases; NF-kB, Nuclear Factor kB; AP-1, activator protein; JNK, c-Jun N-terminal kinase; ERK1/2, extracellular signal regulated kinases ½; IRF1, interferon regulatory factor 1; Foxp3, forkhead box p3; GATA3, GATA-binding protein 3. This figure was created with BioRender (https://biorender.com (accessed on 21 March 2024)).

Another coreceptor of the IL-1 family is the "single molecule Ig-related IL-1R" (SIGIRR), also simply known as Tir8. This coreceptor can dimerize with ST2 to act as a negative regulator of the IL-33/ST2 signaling pathway, reducing the biological effects of IL-33 [51]. However, there is still only little information regarding the biological and pathophysiological aspects of IL-33 isoform/splice variants, ST2 splice variants, and alternative ST2/SIGIRR signaling. It is evident that the IL-33/ST2 interaction plays a fundamental and primary role in numerous autoimmune and inflammatory diseases; in fact, unlike other interleukins such as IL-1 and IL-18 that mainly promote Th1-type responses, the activation of the heterodimeric complex IL-33/ST2 mainly induces the release of Th2 cytokines and can amplify both Th1/Th17 and Th2 type responses [52]. For all of these reasons, it is necessary to carry out more in-depth research to fully understand the mechanisms of action of the IL-33/ST2 axis to develop targeted interventions.

3. IL-33 and IBD

The development of IBD is intricate and is characterized by an aberrant immune reaction to the normal gut microbiota in individuals with a genetic predisposition for IBD [53]. Environmental factors have the potential to alter the microbiome composition, leading to prolonged inflammation and compromised intestinal barrier function; consequently, this compromised barrier triggers an uncontrolled immune response, exacerbating mucosal inflammation [4–8]. In IBD, the innate immune system is the first responder to Pathogen-Associated Molecular Patterns (PAMPs) and to molecules released from damaged or dying cells (DAMPs). DAMPs and PAMPs activate the innate immune system by interacting with pattern recognition receptors (PRRs) [8]. These patterns can be sensed by several components of the innate immune system, including granulocytes, neutrophils, monocytes, myeloid-derived suppressor cells, macrophages, and dendritic cells (DCs). In addition, these patterns can also be recognized by non-immune cells such as intestinal epithelial cells (IECs) and myofibroblasts. Innate immune cells (IICs) respond to these signals, temporarily enhancing the epithelial barrier and cleaning up the effects of inflammation [8]. The maintenance of intestinal homeostasis is secured by proper functioning of the intestinal barrier and

by tolerogenic immune responses against commensal and beneficial microbes. Impaired barrier function and exaggerated immune responses to bacteria are critical contributing factors to IBD immunopathogenesis [8]. A breakdown in intestinal barrier integrity and subsequent intestinal bacteria translocation lead to the activation of antigen-presenting cells (APCs), including dendritic cells (DCs) and macrophages, which consequently results in pro-inflammatory-cytokine production [8].

In the GI tract, IICs like macrophages, DCs, and epithelial cells respond to microbe-associated molecular patterns (MAMPs) via pattern recognition receptors, notably Toll-like receptors (TLRs) and NOD-like receptors (NLRs), which play pivotal roles in sensing MAMPs [54,55]. This stimulation triggers the production of pro-inflammatory cytokines and chemokines [54,55]. In a healthy patient (Figure 3a), upon tissue damage, IL-33 acts as an alarmin in response to cellular stress from a mucosal breach, promoting epithelial proliferation and aiding in barrier repair and wound healing [27]. It induces Paneth cells to release the antimicrobial peptide REG3γ (Regenerating islet-derived protein 3-gamma), which is crucial for maintaining intestinal flora [56]. Additionally, it stimulates goblet cells involved in mucus production, which is essential for mucosal protection [57]. IL-33 also binds to ST2 receptors on ILC2 (Innate Lymphoid Cells type 2) cells, triggering the production of various molecules: IL-13, which stimulates goblet cell activity [58,59]; AREG (Amphiregulin), which binds to EGFR (Epidermal Growth Factor Receptor) on epithelial cells and promotes tissue repair [60]; and IL-5, which plays a protective role against pathogens by inducing IgA production [61]. Furthermore, if the damage is caused by pathogens, IL-33 polarizes the immune response towards a Th1 (T-helper cell type 1) response, leading to TNF and IFN-γ (interferon-γ) production, which is crucial for inflammation resolution [44]. In cases where damage is caused by parasites or allergens, the response is polarized towards a Th2 (T-helper cell type 2) response involving ILC2 activity. IL-33 also facilitates the expansion of regulatory T lymphocytes (Treg) that contribute to a balanced immune response [37].

IBD patients (Figure 3b) experience heightened exposure of their intestinal epithelium to pathogens due to compromised mucus layer function, leading to an unbalanced immune response in individuals with IBD [62]. This altered immune response may manifest through excessive activation of TLRs and NLRs, which further contribute to the epithelial damage and chronic inflammation associated with IBD [63]. Epithelial injury prompts IL-33 release, initiating an inflammatory response [62]. The activation of antigen-presenting cells (APCs) via Toll-like receptors (TLRs) results in the secretion of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1, thus exacerbating epithelial damage [63]. These pro-inflammatory stimuli upregulate intracellular IL-33 expression, stimulating ST2-expressing cells to amplify pro-inflammatory activity [27]. IL-33 expression polarizes immune responses towards Th2 responses and leads to eosinophil activation, inducing IL-13 secretion and compromising epithelial barrier integrity and permeability [27]. Myofibroblasts in intestinal tissue serve as an IL-33 source in IBD, and mast cell-mediated inflammation may drive fibroblast proliferation towards fibrogenesis [27]. However, the presence of sST2 can mitigate IL-33's effects. Biologically active IL-33 can be cleaved by intestinal mucosa proteases, alleviating its pro-inflammatory effects [27]. The signaling pathways involving IL-33 and TLRs depend on MyD88 as a crucial molecule for activating downstream transcription factors [44,54,55]. When IL-33 and MAMPs bind to ST2 and TLRs, respectively, they converge at MyD88, leading to the activation of NF-κB and MAPK [44,54]. Consequently, IL-33 and TLRs likely cooperate in inducing pro-inflammatory-cytokine responses, disrupting tolerogenic responses to gut bacteria. For this reason, IL-33 is increasingly recognized as a pathogenic cytokine implicated in the development of IBD [64].

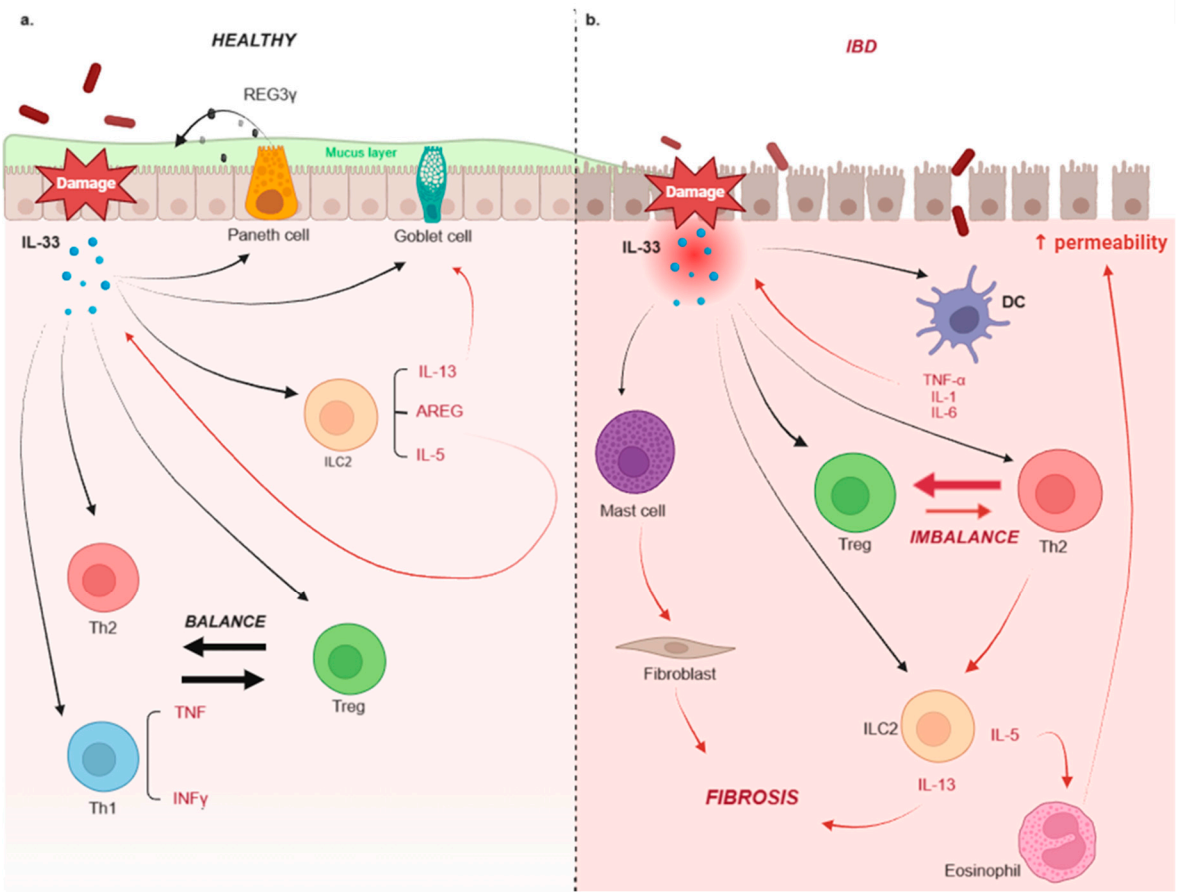

Figure 3. Role of IL-33 in normal gut mucosa (**a**) and in IBD-affected mucosa (**b**). IL-33, interleukin-33; REG3γ, regenerating islet-derived protein; IL-13, interleukin-13; IL-5, interleukin-5; ILC2, innate lymphoid cell type 2; TNF, tumor necrosis factor; INF-γ, Interferon-gamma; Th2, T-helper cell type 2; Th1, T-helper cell type 1; Treg, regulatory T cell; DC, dendritic cell; IL-1, interleukin-1; IL-6, interleukin-1. This figure was created with BioRender (https://biorender.com (accessed on 21 March 2024)).

3.1. Ulcerative Colitis

In UC-affected tissue, there is a significant increase in levels of the mucosal bioactive form of IL-33, particularly in the intestinal epithelium, infiltrating macrophages, and B cells in the lamina propria of active UC patients. However, in serum samples only the cleaved form of IL-33 has been detected [65,66]. Studies indicate the upregulation of IL-33 transcripts and protein in inflamed mucosal tissues of UC patients, with expression observed in ulceration-associated myofibroblasts [30,65–67]. Similarly, ST2, the IL-33 receptor, is elevated in both the colon wall and serum of IBD patients [30]. Despite reduced epithelial ST2 expression in IBD, there is increased infiltration of ST2-expressing APCs and T cells in the lamina propria in IBD patients [67,68]. Pro-inflammatory cytokines and signals from Pathogen-Associated Molecular Patterns (PAMPs) stimulate heightened IL-33 expression in epithelial cells. Upon epithelial injury, IL-33 release stimulates immune responses via ST2-expressing cells, potentially reducing inflammation severity [31,69]. However, in certain situations this pathway can exacerbate inflammation. In fact, in UC patients increased IL-33 production can lead to the activation and production of other inflammatory molecules like IL-5 and IL-13, thus worsening colon inflammation [44,62]. Therefore, IL-33 secretion compromises intestinal barrier integrity, tissue repair, and immunological function. In a UC-like mouse model, IL-33 expression in the intestinal epithelium correlated with disease, and inhibition of the IL-33/ST2 axis has yielded positive outcomes [27,31].

IL-33's role in IBD, particularly in colitis, is complex. Mice lacking IL-33 are more susceptible to colitis and colorectal cancer (CRC), suggesting a protective function of IL-33

in intestinal immunity [70]. Active UC patients often exhibit low IL-33 expression levels in biopsies, indicating a potential negative correlation between IL-33 levels and UC severity [71]. The investigation into IL-33's role in IBD involves studying immunological mechanisms using murine colitis models like dextran sodium sulfate (DSS)-induced colitis and 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis [27]. DSS-induced colitis, driven mainly by chemical damage, represents a T-cell-independent immune response [27]. However, administering IL-33 at disease onset might worsen colitis severity, although it can improve the condition during the chronic or recovery phase. IL-33 potentially promotes the expansion of regulatory T lymphocytes and polarization of macrophages towards an M2-like phenotype, thus offering a protective mechanism [72,73]. In TNBS-induced colitis, which relies on a Th1 immune response, IL-33 administration reduces disease development [27]. It promotes macrophage polarization towards an M2-like phenotype and stimulates Th2 and Treg immune responses, with Foxp3 expression playing a role in IL-33-mediated colitis improvement [74,75]. It has been reported that, in IBD patients, Treg cells are enriched for IL-17$^+$ Treg cells, which represent an "inflammatory" Treg cell population, although these IL-17$^+$Foxp3$^+$CD4$^+$ T cells can suppress proliferation and cytokine production comparably to IL-17$^-$Foxp3$^+$ T cells. In fact, circulating IL-17$^+$Foxp3$^+$CD4$^+$ T cells are increased in patients with CD and UC compared to healthy controls [74,75]. However, there is increasing evidence that IL-33 also has a tissue-protective role in experimental IBD through the expansion of gut-associated Tregs expressing Foxp3. In addition, it has been shown that the administration of IL-33 ameliorated TNBS colitis through the downregulation and upregulation of Th1 and Foxp3$^+$ Treg responses, respectively [75].

IL-33 may have different roles in different disease UC stages. Elevated IL-33 levels in active IBD compared to in remission suggests its involvement during active phases [31]. In the chronic phase, IL-33 shows a protective role, improving chronic colitis through amphiregulin/EGFR signaling [60]. Additionally, it enhances neutrophil infiltration during both acute and chronic phases but reduces the harmful translocation of bacteria during the chronic phase [27,60]. In summary, IL-33 plays a multifaceted role in IBD/UC, offering both protective and harmful effects that vary depending on the immunological context and disease phase.

3.2. Crohn's Disease

In CD, chronic inflammation is driven by pro-inflammatory cytokines like IL-12, IL-23, and TNF-α, which are secreted by macrophages and DCs and promote Th1 and Th17 (T-helper cell type 17) immune responses [27]. This chronic inflammation is further fueled by IL-33 release from myofibroblasts and intestinal epithelial cells, triggering Th1 responses that are typically associated with CD [31,76,77]. IL-33 and IL-12 synergistically amplify these pathogenic Th1 responses [62]. When exposed to commensal antigens and TLRs, Th1 cells prompt IL-33 release by macrophages and DCs [44]. In CD patients, IL-12 secretion by DCs and macrophages in submucosal tissue upregulates ST2 expression through the activation of signal transducer and activator of transcription 4 (STAT4) [77]. Therefore, IL-33 plays a crucial role in driving pathogenic Th1 responses when antigens penetrate the compromised intestinal epithelial tissue in CD patients. The increased IL-33 expression associated with CD activity highlights its potential contribution to disease progression [31,39].

One of the most common complications in patients with Crohn's disease is intestinal fibrosis that is characterized by narrowed intestinal segments, structural impairment, and functional limitations [78,79]. Therefore, it has been suggested that IL-33 plays a pivotal role in activating key cell populations involved in fibrotic processes, including ILC2 and Th2 cells, which subsequently release factors promoting fibrosis and sub-stenosis [44]. Th2-derived cytokines contribute to pathological changes such as increased mucous secretion, eosinophil infiltration, and tissue fibrosis [80]. Similarly, ILC2 cells contribute to fibrosis by secreting type 2 cytokines via antigen presentation-independent mechanisms [81]. Animal models support these observations, demonstrating IL-33's induction of profibrotic Th2 responses and the expansion of ILC2 cell populations, leading to IL-5 and IL-13 production

and subsequent fibrosis [76]. Moreover, in IBD/CD patient myofibroblasts, elevated IL-13 levels induced by IL-33 exacerbate collagen accumulation by inhibiting matrix metalloproteinases synthesis [82]. Additionally, IL-33 can directly stimulate human myofibroblasts proliferation [83]. These findings highlight the intricate interplay between IL-33, ILC2 cells, Th2 cells, and myofibroblasts, underscoring IL-33's multifaceted role in driving intestinal fibrosis.

4. IL-33 and IBD-Related CRC

IBD-related cancer, the CRC subtype that is associated with inflammatory bowel disease (IBD), is difficult to recognize and treat, thus showing high mortality. Patients affected by IBD present with a 60% higher risk of CRC compared to the general population, and it has been shown that CRC risk in IBD patients rises from 1% to 5% as disease duration increases from 10 years to more than 20 years [84]. Specifically, in the context of IBD-related CRC, the IL-33/ST2 axis is highly active in the intestinal colonic mucosa, where IL-33 assumes a crucial function by triggering the activation of subepithelial myofibroblasts (SEMFs) and mast cells before the onset of carcinoma [37,85]. This activation induces the release of Th2 cytokines, thus supporting tumor progression. Specifically, higher levels of IL-33 and ST2 expression are observed in IBD-related CRC tissues than in adjacent normal tissues; moreover, overexpression of both IL-33 and ST2 have been reported in intestinal adenomas and adenocarcinomas, which are more advanced stages of CRC [84,86]. The increased expression of this cytokine and its receptor suggests that the IL-33/ST2 axis might play a crucial role in CRC development [86]. On the other hand, CRC localization may also influence the immune response, as the expression of IL-33 was observed to be increased in left-sided CRC patients compared to right-sided patients, with IL-33 reaching even higher levels in CRC patients with lymph node (LN) metastasis [84–87]. Furthermore, it has been reported that increased IL-33/ST2 signaling promoted CRC metastasis, whereas attenuated IL-33/ST2 signaling decreased CRC metastasis in humans as well as in nude mice [88]. Taking into consideration the crucial role of IL-33/ST2 signaling for metastatic development, increases in the expression of IL-6, CXCR4, MMP2, and MMP9 have also been observed [88].

Moreover, IL-33 contributes to tumorigenesis by prompting the secretion of diverse growth factors and pro-angiogenic agents like FGF (Fibroblast Growth Factor), AREG, and VEGF-C (Vascular Endothelial Growth Factor C) [37]. Furthermore, it activates tumor-associated macrophages and DCs, leading to the release of Th2 cytokines like IL-10, IL-4, and IL-13, which are crucial for inhibiting immune responses and hampering tumor control [37]. For this reason, inhibiting the IL-33/ST2 axis may represent a promising target for a specific therapy to hinder tumor progression [89].

However, increased IL-33 expression in CRC cells triggers PPARγ (Peroxisome Proliferator-Activated Receptor-γ) expression in ILC2 cells, which, in turn, leads to the release of IL-13, thus promoting tumor migration [37,89]. Blocking PPARy could potentially suppress the pro-metastatic effects of ILC2 cells, making it an intriguing potential candidate for cancer specific therapy [90]. On the other hand, IL-33 leads to reduced Treg activity, facilitating tumor progression [37]; in fact, IL-33 is able to directly foster CRC by interacting with its receptor, triggering the NF-KB pathway, and amplifying COX2 (Cyclooxygenase-2) expression alongside PGE2 (Prostaglandin E2) production, finally leading to tumor growth [91]. In IBD-associated CRC, it has been revealed that Nuclear factor erythroid 2-related factor 3 (NFE2L3), which acts as a transcription factor able to enhance cell proliferation by alleviating DUX4-mediated inhibition of CDK1 (Cyclin-Dependent Kinase 1), plays a role in promoting CRC growth and metastasis by upregulating IL-33 expression and mitigating the inhibitory effects of Tregs [92]. In addition, IL-33 has been recognized as a cytokine with significant pro-angiogenic properties due to high ST2 expression in the endothelial cells of micro-vessels [93,94]. In fact, IL-33 can stimulate the production of pro-angiogenic factors like vascular endothelial growth factor (VEGF) and IL-8, which are both considered well-established pro-angiogenic factors in human cancers, including in CRC [94].

In contrast, it has been suggested that IL-33 may effect a potential protective role against CRC, by recruiting anti-tumor macrophages or expressing cytokines affecting the tumor environment [95]. These contradictory hypothesized functions further stress the complex role of IL-33 in colorectal cancer, where its effects can either promote or inhibit tumor growth.

5. Perspectives

Future research efforts should focus on elucidating the specific pathways and interactions through which IL-33 modulates immune responses and tissue homeostasis in IBD and CRC. By unraveling the complexities of IL-33 signaling, novel therapeutic strategies could be developed to effectively mitigate disease activity and progression, thus improving patient outcomes. However, the pleiotropic nature of IL-33 is related to the extracellular and intracellular functions of the IL-33/ST2 heterodimeric complex that blocks or induces IL-33 activity.

Differences in the profiles of miRNAs have been considered to represent a useful tool in the diagnosis of UC and CD and as prognostic markers in both diseases [96]. Several studies have been conducted with the aim of characterizing alterations in the expression of miRNAs in IBD; in fact, miRNA alterations in IBD patients have revealed 11 miRNAs that are differentially expressed in patients with UC vs. controls. Levels of the miRNAs miR-16, miR-21, miR-23a, miR-24, miR-29a, miR-126, miR-195, and let-7f were increased in UC patients, whereas levels of miR-192, miR-375, and miR-422b were reduced. Consequently, some of these miRNAs have been suggested as potential biomarkers for CD or UC in colonic tissues [96–98]. However, it has been argued that microRNA 378a-3p (miR-378a-3p) induces a novel mechanism of IL-33 modulation in the intestinal colon epithelium during the inflammatory process [21]. Inflammation-mediated suppression of miR-378a-3p results in metabolic dysfunction in inflamed intestinal mucosal tissue due to an increased level of IL-33 protein in the intestinal epithelium [21].

Additionally, the role of miRNAs in the interaction with the host and its microbiota has been increasingly explored, presenting new opportunities to diagnose and treat IBD. Moreover, the use of diet supplemented with prebiotics or probiotics, which may modulate the intestinal microbiota and regulate the expression of miRNAs, could probably improve the intestinal inflammatory process in patients with IBD, although further studies and research in this new field are required. Further intriguing therapeutic prospects may be found on the interaction of IL-33 and the gut microbiome, as IL-33 has been shown to interact with commensal microbiota and their metabolites, suggesting that it may play a role in shaping the gut microbiome.

6. Conclusions

In the gastrointestinal tract, this cytokine basically guarantees the correct functioning of the intestinal barrier, highlighting its multifaceted role in IBD pathogenesis and progression. In detail, elevated IL-33 levels exacerbate inflammation in UC, compromising intestinal barrier integrity and promoting tissue damage. In CD, IL-33 contributes to chronic inflammation and drives pathogenic Th1 responses. Finally, IL-33's involvement in intestinal fibrosis underscores its significance in disease complications. In CRC, IL-33 is involved in promoting tumor progression through various mechanisms, such as the activation of subepithelial myofibroblasts, the induction of pro-angiogenic factors, and modulation of the tumor microenvironment. In contrast, IL-33 also plays a potentially protective role in the intestinal mucosa, highlighting the complexity of its involvement in IBD-related CRC.

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Abbreviations

IBD—inflammatory bowel disease; GI—gastrointestinal; CD—Crohn's disease; UC—ulcerative colitis; IBD-U—IBD-unclassified; 5-ASA—5-aminosalicylates; PPAR-γ—γ-form peroxisome proliferator-activated receptors; 6-MP—6-mercaptopurine; AZA—azathioprine; MTX—methotrexate; CSA—cyclosporine; TNF—tumor necrosis factor; IL—interleukin; flIL-33—full-length interleukin-33; NK—natural killer; DC—dendritic cell; ST2—suppression of tumorigenicity 2; IL1RL1—interleukin-1 receptor-like 1; TIR—Toll-interleukin-1 superfamily receptor; ST2L—suppression of tumorigenicity 2 long isoform; sST2—soluble ST2 isoform; IL1RAcP—interleukin-1 receptor accessory protein; MyD88—myeloid differentiation primary response 88; IRAK—interleukin receptor-associated-kinase; TRAF—tumor necrosis factor receptor-associated factor; NF-kB—Nuclear Factor kappa B; AP-1—Activator Protein 1; MAPK—Mitogen-Activated Protein Kinase; JNK—Jun N-terminal kinase; ERK—extracellular signal regulated kinases; IRF—interferon regulatory factor; Foxp3—forkhead box p3; GATA3—GATA-binding protein 3; SIGIRR—single molecule Ig-related IL-1R; MAMPs—microbe-associated molecular patterns; TLR—toll-like receptor; NLR—NOD-like receptor; REG3γ—Regenerating islet-derived protein 3-gamma; ILC2—Innate Lymphoid Cells type 2; AREG—amphiregulin; EGFR—Epidermal Growth Factor Receptor; Th1—T-helper cell type 1; IFN—interferon; Th2—T-helper cell type 2; Treg—regulatory T lymphocytes; APC—antigen-presenting cell; PAMP—Pathogen-Associated Molecular Patterns; CRC—colorectal cancer; DSS—dextran sodium sulfate; TNBS, 2,4,6-trinitrobenzenesulfonic acid; Th17—T-helper cell type 17; STAT4—signal transducer and activator of transcription 4; SEMFs—subepithelial myofibroblasts; FGF—Fibroblast Growth Factor; VEGF-C—Vascular Endothelial Growth Factor C; PPAR—Peroxisome Proliferator-Activated Receptor; COX—cyclooxygenase; PGE2—Prostaglandin E2; NFE2L3—Nuclear factor erythroid 2-related factor 3; CDK1—Cyclin-Dependent Kinase 1; VEGF—vascular endothelial growth factor.

References

1. Borowitz, S.M. The epidemiology of inflammatory bowel disease: Clues to pathogenesis? *Front. Pediatr.* **2023**, *10*, 1103713. [CrossRef] [PubMed]
2. Kofla-Dłubacz, A.; Pytrus, T.; Akutko, K.; Sputa-Grzegrzółka, P.; Piotrowska, A.; Dzięgiel, P. Etiology of IBD—Is It Still a Mystery? *Int. J. Mol. Sci.* **2022**, *23*, 12445. [CrossRef]
3. Caviglia, G.P.; Garrone, A.; Bertolino, C.; Vanni, R.; Bretto, E.; Poshnjari, A.; Tribocco, E.; Frara, S.; Armandi, A.; Astegiano, M.; et al. Epidemiology of Inflammatory Bowel Diseases: A Population Study in a Healthcare District of North-West Italy. *J. Clin. Med.* **2023**, *12*, 641. [CrossRef] [PubMed]
4. Ramos, G.P.; Papadakis, K.A. Mechanisms of Disease: Inflammatory Bowel Diseases. *Mayo Clin. Proc.* **2019**, *94*, 155–165. [CrossRef]
5. Shouval, D.S.; Rufo, P.A. The Role of Environmental Factors in the Pathogenesis of Inflammatory Bowel Diseases: A Review. *JAMA Pediatr.* **2017**, *171*, 999–1005. [CrossRef] [PubMed]
6. Nishida, A.; Inoue, R.; Inatomi, O.; Bamba, S.; Naito, Y.; Andoh, A. Gut Microbiota in the Pathogenesis of Inflammatory Bowel Disease. *Clin. J. Gastroenterol.* **2018**, *11*, 1–10. [CrossRef] [PubMed]
7. Chang, J.T. Pathophysiology of Inflammatory Bowel Diseases. *N. Engl. J. Med.* **2020**, *383*, 2652–2664. [CrossRef] [PubMed]
8. Saez, A.; Herrero-Fernandez, B.; Gomez-Bris, R.; Sánchez-Martinez, H.; Gonzalez-Granado, J.M. Pathophysiology of Inflammatory Bowel Disease: Innate Immune System. *Int. J. Mol. Sci.* **2023**, *24*, 1526. [CrossRef] [PubMed]
9. Liu, D.; Saikam, V.; Skrada, K.A.; Merlin, D.; Iyer, S.S. Inflammatory Bowel Disease Biomarkers. *Med. Res. Rev.* **2022**, *42*, 1856–1887. [CrossRef]
10. Ungaro, R.; Mehandru, S.; Allen, P.B.; Peyrin-Biroulet, L.; Colombel, J.-F. Ulcerative Colitis. *Lancet* **2017**, *389*, 1756–1770. [CrossRef]
11. Høivik, M.L.; Moum, B.; Solberg, I.C.; Henriksen, M.; Cvancarova, M.; Bernklev, T.; IBSEN Group. Work Disability in Inflammatory Bowel Disease Patients 10 Years after Disease Onset: Results from the IBSEN Study. *Gut* **2013**, *62*, 368–375. [CrossRef]
12. Baumgart, D.C.; Sandborn, W.J. Crohn's Disease. *Lancet* **2012**, *380*, 1590–1605. [CrossRef]

13. Paudel, D.; Nair, D.V.T.; Joseph, G.; Castro, R.; Tiwari, A.K.; Singh, V. Gastrointestinal microbiota-directed nutritional and therapeutic interventions for inflammatory bowel disease: Opportunities and challenges. *Gastroenterol. Rep.* **2024**, *12*, goae033. [CrossRef]
14. Vebr, M.; Pomahačová, R.; Sýkora, J.; Schwarz, J. A Narrative Review of Cytokine Networks: Pathophysiological and Therapeutic Implications for Inflammatory Bowel Disease Pathogenesis. *Biomedicines* **2023**, *11*, 3229. [CrossRef]
15. Gajendran, M.; Loganathan, P.; Catinella, A.P.; Hashash, J.G. A Comprehensive Review and Update on Crohn's Disease. *Dis. Mon.* **2018**, *64*, 20–57. [CrossRef]
16. Burisch, J.; Bergemalm, D.; Halfvarson, J.; Domislovic, V.; Krznaric, Z.; Goldis, A.; Dahlerup, J.F.; Oksanen, P.; Collin, P.; Epi-IBD Group. The use of 5-aminosalicylate for patients with Crohn's disease in a prospective European inception cohort with 5 years follow-up—An Epi-IBD study. *United Eur. Gastroenterol. J.* **2020**, *8*, 949–960. [CrossRef]
17. Rousseaux, C.; Lefebvre, B.; Dubuquoy, L.; Lefebvre, P.; Romano, O.; Auwerx, J.; Metzger, D.; Wahli, W.; Desvergne, B.; Naccari, G.C.; et al. Intestinal Antiinflammatory Effect of 5-Aminosalicylic Acid Is Dependent on Peroxisome Proliferator–Activated Receptor-γ. *J. Exp. Med.* **2005**, *201*, 1205–1215. [CrossRef]
18. Desreumaux, P.; Ghosh, S. Review Article: Mode of Action and Delivery of 5-Aminosalicylic Acid—New Evidence. *Aliment. Pharmacol. Ther.* **2006**, *24*, 2–9. [CrossRef]
19. Bertin, B.; Dubuquoy, L.; Colombel, J.-F.; Desreumaux, P. PPAR-Gamma in Ulcerative Colitis: A Novel Target for Intervention. *Curr. Drug Targets* **2013**, *14*, 1501–1507. [CrossRef]
20. Ramamoorthy, S.; Cidlowski, J.A. Corticosteroids: Mechanisms of Action in Health and Disease. *Rheum. Dis. Clin. N. Am.* **2016**, *42*, 15–31. [CrossRef]
21. Dubois-Camacho, K.; Ottum, P.A.; Franco-Muñoz, D.; De la Fuente, M.; Torres-Riquelme, A.; Díaz-Jiménez, D.; Olivares-Morales, M.; Astudillo, G.; Quera, R.; Hermoso, M.A. Glucocorticosteroid Therapy in Inflammatory Bowel Diseases: From Clinical Practice to Molecular Biology. *World J. Gastroenterol.* **2017**, *23*, 6628–6638. [CrossRef] [PubMed]
22. Sokic-Milutinovic, A.; Milosavljevic, T. IBD: From conventional immunosuppression to biological therapy. *Dig. Dis.* **2023**, 1–11. [CrossRef]
23. Guo, Y.; Lu, N.; Bai, A. Clinical Use and Mechanisms of Infliximab Treatment on Inflammatory Bowel Disease: A Recent Update. *Biomed. Res. Int.* **2013**, *2013*, 581631. [CrossRef]
24. Krishnan, S.; Ding, Y.; Saedi, N.; Choi, M.; Sridharan, G.V.; Sherr, D.H.; Yarmush, M.L.; Alaniz, R.C.; Jayaraman, A.; Lee, K. Gut Microbiota-Derived Tryptophan Metabolites Modulate Inflammatory Response in Hepatocytes and Macrophages. *Cell Rep.* **2018**, *23*, 1099–1111. [CrossRef]
25. Zhang, J.; Zhu, S.; Ma, N.; Johnston, L.J.; Wu, C.; Ma, X. Metabolites of Microbiota Response to Tryptophan and Intestinal Mucosal Immunity: A Therapeutic Target to Control Intestinal Inflammation. *Med. Res. Rev.* **2021**, *41*, 1061–1088. [CrossRef]
26. Ma, N.; Zhang, J.; Reiter, R.J.; Ma, X. Melatonin Mediates Mucosal Immune Cells, Microbial Metabolism, and Rhythm Crosstalk: A Therapeutic Target to Reduce Intestinal Inflammation. *Med. Res. Rev.* **2020**, *40*, 606–632. [CrossRef]
27. Aggeletopoulou, I.; Tsounis, E.P.; Triantos, C. Molecular Mechanisms Underlying IL-33-Mediated Inflammation in Inflammatory Bowel Disease. *Int. J. Mol. Sci.* **2023**, *24*, 623. [CrossRef]
28. Garlanda, C.; Dinarello, C.A.; Mantovani, A. The Interleukin-1 Family: Back to the Future. *Immunity* **2013**, *39*, 1003–1018. [CrossRef]
29. Andoh, A.; Nishida, A. Pro- and Anti-Inflammatory Roles of Interleukin (IL)-33, IL-36, and IL-38 in Inflammatory Bowel Disease. *J. Gastroenterol.* **2023**, *58*, 69–78. [CrossRef]
30. Chen, J.; He, Y.; Tu, L.; Duan, L. Dual immune functions of IL-33 in inflammatory bowel disease. *Histol. Histopathol.* **2020**, *35*, 137–146.
31. Pastorelli, L.; Garg, R.R.; Hoang, S.B.; Spina, L.; Mattioli, B.; Scarpa, M.; Fiocchi, C.; Vecchi, M.; Pizarro, T.T. Epithelial-Derived IL-33 and Its Receptor ST2 Are Dysregulated in Ulcerative Colitis and in Experimental Th1/Th2 Driven Enteritis. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 8017–8022. [CrossRef] [PubMed]
32. Liew, F.Y.; Girard, J.P.; Turnquist, H.R. Interleukin-33 in health and disease. *Nat. Rev. Immunol.* **2016**, *16*, 676–689. [CrossRef]
33. Cayrol, C.; Girard, J.P. Interleukin-33 (IL-33): A nuclear cytokine from the IL-1 family. *Immunol. Rev.* **2018**, *281*, 154–168. [CrossRef] [PubMed]
34. Murdaca, G.; Greco, M.; Tonacci, A. IL-33/IL-31 Axis in Immune-Mediated and Allergic Diseases. *Int. J. Mol. Sci.* **2019**, *20*, 5856. [CrossRef] [PubMed]
35. Baekkevold, E.S.; Roussigne, M.; Yamanaka, T.; Johansen, F.E.; Jahnsen, F.L.; Amalric, F.; Brandtzaeg, P.; Erard, M.; Haraldsen, G.; Girard, J.P. Molecular characterization of NF-HEV, a nuclear factor preferentially expressed in human high endothelial venules. *Am. J. Pathol.* **2003**, *163*, 69–79. [CrossRef]
36. Cayrol, C.; Girard, J.-P. Interleukin-33 (IL-33): A Critical Review of Its Biology and the Mechanisms Involved in Its Release as a Potent Extracellular Cytokine. *Cytokine* **2022**, *156*, 155891. [CrossRef] [PubMed]
37. Wang, Y.; He, C.; Xin, S.; Liu, X.; Zhang, S.; Qiao, B.; Shang, H.; Gao, L.; Xu, J. A Deep View of the Biological Property of Interleukin-33 and Its Dysfunction in the Gut. *Int. J. Mol. Sci.* **2023**, *24*, 13504. [CrossRef] [PubMed]
38. Lefrancais, E.; Roga, S.; Gautier, V.; Gonzalez-de-Peredo, A.; Monsarrat, B.; Girard, J.P.; Cayrol, C. IL-33 is processed into mature bioactive forms by neutrophil elastase and cathepsin G. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 1673–1678. [CrossRef] [PubMed]

39. Sedhom, M.A.K.; Pichery, M.; Murdoch, J.R.; Foligné, B.; Ortega, N.; Normand, S.; Mertz, K.; Sanmugalingam, D.; Brault, L.; Grandjean, T.; et al. Neutralisation of the Interleukin-33/ST2 Pathway Ameliorates Experimental Colitis through Enhancement of Mucosal Healing in Mice. *Gut* **2013**, *62*, 1714–1723. [CrossRef]
40. Lopez-Casado, M.A.; Lorite, P.; Palomeque, T.; Torres, M.I. Potential role of the IL-33/ST2 axis in celiac disease. *Cell. Mol. Immunol.* **2017**, *14*, 285–292. [CrossRef]
41. Cayrol, C.; Girard, J.P. The IL-1-like cytokine IL-33 is inactivated after maturation by caspase-1. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 9021–9026. [CrossRef]
42. Waddell, A.; Vallance, J.E.; Fox, S.; Rosen, M.J. IL-33 is produced by colon fibroblasts and differentially regulated in acute and chronic murine colitis. *Sci. Rep.* **2021**, *11*, 9575. [CrossRef] [PubMed]
43. Cayrol, C. IL-33, an Alarmin of the IL-1 Family Involved in Allergic and Non Allergic Inflammation: Focus on the Mechanisms of Regulation of Its Activity. *Cells* **2021**, *11*, 107. [CrossRef] [PubMed]
44. Yi, X.M.; Lian, H.; Li, S. Signaling and functions of interleukin-33 in immune regulation and diseases. *Cell Insight.* **2022**, *1*, 100042. [CrossRef] [PubMed]
45. Seidelin, J.B.; Rogler, G.; Nielsen, O.H. A role for interleukin-33 in T_H2-polarized intestinal inflammation? *Mucosal Immunol.* **2011**, *4*, 496–502. [CrossRef]
46. Schmitz, J.; Owyang, A.; Oldham, E.; Song, Y.; Murphy, E.; McClanahan, T.K.; Zurawski, G.; Moshrefi, M.; Qin, J.; Li, X.; et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity* **2005**, *23*, 479–490. [CrossRef]
47. Fagundes, C.T.; Amaral, F.A.; Souza, A.L.S.; Vieira, A.T.; Xu, D.; Liew, F.Y.; Souza, D.G.; Teixeira, M.M. ST2, an IL-1R Family Member, Attenuates Inflammation and Lethality after Intestinal Ischemia and Reperfusion. *J. Leukoc. Biol.* **2007**, *81*, 492–499. [CrossRef]
48. Palmer, G.; Lipsky, B.P.; Smithgall, M.D.; Meininger, D.; Siu, S.; Talabot-Ayer, D.; Gabay, C.; Smith, D.E. The IL-1 Receptor Accessory Protein (AcP) Is Required for IL-33 Signaling and Soluble AcP Enhances the Ability of Soluble ST2 to Inhibit IL-33. *Cytokine* **2008**, *42*, 358–364. [CrossRef]
49. Griesenauer, B.; Paczesny, S. The ST2/IL-33 Axis in Immune Cells during Inflammatory Diseases. *Front. Immunol.* **2017**, *8*, 475. [CrossRef]
50. Chen, Q.; Carroll, H.P.; Gadina, M. The Newest Interleukins: Recent Additions to the Ever-Growing Cytokine Family. *Vitam. Horm.* **2006**, *74*, 207–228.
51. Bulek, K.; Swaidani, S.; Qin, J.; Lu, Y.; Gulen, M.F.; Herjan, T.; Min, B.; Kastelein, R.A.; Aronica, M.; Kosz-Vnenchak, M.; et al. The Essential Role of Single Ig IL-1 Receptor-Related Molecule/Toll IL-1R8 in Regulation of Th2 Immune Response. *J. Immunol.* **2009**, *182*, 2601–2609. [CrossRef] [PubMed]
52. Bonanno, A.; Gangemi, S.; La Grutta, S.; Malizia, V.; Riccobono, L.; Colombo, P.; Cibella, F.; Profita, M. 25-Hydroxyvitamin D, IL-31, and IL-33 in Children with Allergic Disease of the Airways. *Mediat. Inflamm.* **2014**, *2014*, 520241. [CrossRef] [PubMed]
53. Kaur, H.; Kaur, G.; Ali, S.A. IL-33's role in the gut immune system: A comprehensive review of its crosstalk and regulation. *Life Sci.* **2023**, *327*, 121868. [CrossRef] [PubMed]
54. Oboki, K.; Ohno, T.; Kajiwara, N.; Arae, K.; Morita, H.; Ishii, A.; Nambu, A.; Abe, T.; Kiyonari, H.; Matsumoto, K.; et al. IL-33 is a crucial amplifier of innate rather than acquired immunity. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 18581–18586. [CrossRef] [PubMed]
55. Lamhamedi-Cherradi, S.E.; Zheng, S.J.; Maguschak, K.A.; Peschon, J.; Chen, Y.H. Defective thymocyte apoptosis and accelerated autoimmune diseases in $TRAIL^{-/-}$ mice. *Nat. Immunol.* **2003**, *4*, 255–260. [CrossRef]
56. Xiao, Y.; Huang, X.; Zhao, Y.; Chen, F.; Sun, M.; Yang, W.; Chen, L.; Yao, S.; Peniche, A.; Dann, S.M.; et al. Interleukin-33 Promotes REG3γ Expression in Intestinal Epithelial Cells and Regulates Gut Microbiota. *Cell Mol. Gastroenterol. Hepatol.* **2019**, *8*, 21–36. [CrossRef] [PubMed]
57. Seo, D.H.; Che, X.; Kwak, M.S.; Kim, S.; Kim, J.H.; Ma, H.W.; Kim, D.H.; Kim, T.I.; Kim, W.H.; Kim, S.W.; et al. Interleukin-33 Regulates Intestinal Inflammation by Modulating Macrophages in Inflammatory Bowel Disease. *Sci. Rep.* **2017**, *7*, 851. [CrossRef] [PubMed]
58. Kondo, Y.; Yoshimoto, T.; Yasuda, K.; Futatsugi-Yumikura, S.; Morimoto, M.; Hayashi, N.; Hoshino, T.; Fujimoto, J.; Nakanishi, K. Administration of IL-33 Induces Airway Hyperresponsiveness and Goblet Cell Hyperplasia in the Lungs in the Absence of Adaptive Immune System. *Int. Immunol.* **2008**, *20*, 791–800. [CrossRef] [PubMed]
59. Schumacher, M.A.; Hsieh, J.J.; Liu, C.Y.; Appel, K.L.; Waddell, A.; Almohazey, D.; Katada, K.; Bernard, J.K.; Bucar, E.B.; Gadeock, S.; et al. Sprouty2 Limits Intestinal Tuft and Goblet Cell Numbers through GSK3β-Mediated Restriction of Epithelial IL-33. *Nat. Commun.* **2021**, *12*, 836. [CrossRef]
60. Monticelli, L.A.; Osborne, L.C.; Noti, M.; Tran, S.V.; Zaiss, D.M.W.; Artis, D. IL-33 Promotes an Innate Immune Pathway of Intestinal Tissue Protection Dependent on Amphiregulin-EGFR Interactions. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 10762–10767. [CrossRef]
61. Satoh-Takayama, N.; Kato, T.; Motomura, Y.; Kageyama, T.; Taguchi-Atarashi, N.; Kinoshita-Daitoku, R.; Kuroda, E.; Di Santo, J.P.; Mimuro, H.; Moro, K.; et al. Bacteria-Induced Group 2 Innate Lymphoid Cells in the Stomach Provide Immune Protection through Induction of IgA. *Immunity* **2020**, *52*, 635–649.e4. [CrossRef] [PubMed]
62. Strober, W.; Fuss, I.J. Proinflammatory Cytokines in the Pathogenesis of Inflammatory Bowel Diseases. *Gastroenterology* **2011**, *140*, 1756–1767. [CrossRef] [PubMed]

63. Watanabe, T.; Minaga, K.; Kamata, K.; Sakurai, T.; Komeda, Y.; Nagai, T.; Kitani, A.; Tajima, M.; Fuss, I.J.; Kudo, M.; et al. RICK/RIP2 Is a NOD2-Independent Nodal Point of Gut Inflammation. *Int. Immunol.* **2019**, *31*, 669–683. [CrossRef] [PubMed]
64. Kurimoto, M.; Watanabe, T.; Kamata, K.; Minaga, K.; Kudo, M. IL-33 as a Critical Cytokine for Inflammation and Fibrosis in Inflammatory Bowel Diseases and Pancreatitis. *Front. Physiol.* **2021**, *12*, 781012. [CrossRef] [PubMed]
65. Sponheim, J.; Pollheimer, J.; Olsen, T.; Balogh, J.; Hammarström, C.; Loos, T.; Kasprzycka, M.; Sørensen, D.R.; Nilsen, H.R.; Küchler, A.M.; et al. Inflammatory Bowel Disease-Associated Interleukin-33 Is Preferentially Expressed in Ulceration-Associated Myofibroblasts. *Am. J. Pathol.* **2010**, *177*, 2804–2815. [CrossRef] [PubMed]
66. Gundersen, M.D.; Goll, R.; Hol, J.; Olsen, T.; Rismo, R.; Sørbye, S.W.; Sundnes, O.; Haraldsen, G.; Florholmen, J. Loss of Interleukin 33 Expression in Colonic Crypts—A Potential Marker for Disease Remission in Ulcerative Colitis. *Sci. Rep.* **2016**, *6*, 35403. [CrossRef] [PubMed]
67. Kobori, A.; Yagi, Y.; Imaeda, H.; Ban, H.; Bamba, S.; Tsujikawa, T.; Saito, Y.; Fujiyama, Y.; Andoh, A. Interleukin-33 Expression Is Specifically Enhanced in Inflamed Mucosa of Ulcerative Colitis. *J. Gastroenterol.* **2010**, *45*, 999–1007. [CrossRef] [PubMed]
68. Pastorelli, L.; De Salvo, C.; Cominelli, M.A.; Vecchi, M.; Pizarro, T.T. Novel Cytokine Signaling Pathways in Inflammatory Bowel Disease: Insight into the Dichotomous Functions of IL-33 during Chronic Intestinal Inflammation. *Ther. Adv. Gastroenterol.* **2011**, *4*, 311–323. [CrossRef]
69. Artis, D. Epithelial-Cell Recognition of Commensal Bacteria and Maintenance of Immune Homeostasis in the Gut. *Nat. Rev. Immunol.* **2008**, *8*, 411–420. [CrossRef]
70. Malik, A.; Sharma, D.; Zhu, Q.; Karki, R.; Guy, C.S.; Vogel, P.; Kanneganti, T.-D. IL-33 Regulates the IgA-Microbiota Axis to Restrain IL-1α–Dependent Colitis and Tumorigenesis. *J. Clin. Investig.* **2016**, *126*, 4469–4481. [CrossRef]
71. Tahaghoghi-Hajghorbani, S.; Ajami, A.; Ghorbanalipoor, S.; Hosseini-Khah, Z.; Taghiloo, S.; Khaje-Enayati, P.; Hosseini, V. Protective Effect of TSLP and IL-33 Cytokines in Ulcerative Colitis. *Autoimmun. Highlights* **2019**, *10*, 1. [CrossRef] [PubMed]
72. Groβ, P.; Doser, K.; Falk, W.; Obermeier, F.; Hofmann, C. IL-33 Attenuates Development and Perpetuation of Chronic Intestinal Inflammation. *Inflamm. Bowel Dis.* **2012**, *18*, 1900–1909. [CrossRef]
73. Ngo Thi Phuong, N.; Palmieri, V.; Adamczyk, A.; Klopfleisch, R.; Langhorst, J.; Hansen, W.; Westendorf, A.M.; Pastille, E. IL-33 Drives Expansion of Type 2 Innate Lymphoid Cells and Regulatory T Cells and Protects Mice From Severe, Acute Colitis. *Front. Immunol.* **2021**, *12*, 669787. [CrossRef]
74. Tu, L.; Chen, J.; Xu, D.; Xie, Z.; Yu, B.; Tao, Y.; Shi, G.; Duan, L. IL-33-Induced Alternatively Activated Macrophage Attenuates the Development of TNBS-Induced Colitis. *Oncotarget* **2017**, *8*, 27704–27714. [CrossRef] [PubMed]
75. Duan, L.; Chen, J.; Zhang, H.; Yang, H.; Zhu, P.; Xiong, A.; Xia, Q.; Zheng, F.; Tan, Z.; Gong, F.; et al. Interleukin-33 Ameliorates Experimental Colitis through Promoting Th2/Foxp3^{+} Regulatory T-Cell Responses in Mice. *Mol. Med.* **2012**, *18*, 753–761. [CrossRef]
76. De Salvo, C.; Buela, K.-A.; Creyns, B.; Corridoni, D.; Rana, N.; Wargo, H.L.; Cominelli, C.L.; Delaney, P.G.; Rodriguez-Palacios, A.; Cominelli, F.; et al. NOD2 Drives Early IL-33-Dependent Expansion of Group 2 Innate Lymphoid Cells during Crohn's Disease-like Ileitis. *J. Clin. Investig.* **2021**, *131*, e140624. [CrossRef]
77. Baumann, C.; Bonilla, W.V.; Fröhlich, A.; Helmstetter, C.; Peine, M.; Hegazy, A.N.; Pinschewer, D.D.; Löhning, M. T-Bet- and STAT4-Dependent IL-33 Receptor Expression Directly Promotes Antiviral Th1 Cell Responses. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 4056–4061. [CrossRef]
78. Bouma, G.; Strober, W. The Immunological and Genetic Basis of Inflammatory Bowel Disease. *Nat. Rev. Immunol.* **2003**, *3*, 521–533. [CrossRef] [PubMed]
79. Hirai, F.; Andoh, A.; Ueno, F.; Watanabe, K.; Ohmiya, N.; Nakase, H.; Kato, S.; Esaki, M.; Endo, Y.; Yamamoto, H.; et al. Efficacy of Endoscopic Balloon Dilation for Small Bowel Strictures in Patients With Crohn's Disease: A Nationwide, Multi-Centre, Open-Label, Prospective Cohort Study. *J. Crohn's Colitis* **2018**, *12*, 394–401. [CrossRef]
80. Nakayama, T.; Hirahara, K.; Onodera, A.; Endo, Y.; Hosokawa, H.; Shinoda, K.; Tumes, D.J.; Okamoto, Y. Th2 Cells in Health and Disease. *Annu. Rev. Immunol.* **2017**, *35*, 53–84. [CrossRef]
81. Eberl, G.; Colonna, M.; Di Santo, J.P.; McKenzie, A.N.J. Innate Lymphoid Cells. Innate Lymphoid Cells: A New Paradigm in Immunology. *Science* **2015**, *348*, aaa6566. [CrossRef]
82. Bailey, J.R.; Bland, P.W.; Tarlton, J.F.; Peters, I.; Moorghen, M.; Sylvester, P.A.; Probert, C.S.J.; Whiting, C.V. IL-13 Promotes Collagen Accumulation in Crohn's Disease Fibrosis by down-Regulation of Fibroblast MMP Synthesis: A Role for Innate Lymphoid Cells? *PLoS ONE* **2012**, *7*, e52332. [CrossRef] [PubMed]
83. Nishida, A.; Andoh, A.; Imaeda, H.; Inatomi, O.; Shiomi, H.; Fujiyama, Y. Expression of Interleukin 1-like Cytokine Interleukin 33 and Its Receptor Complex (ST2L and IL1RAcP) in Human Pancreatic Myofibroblasts. *Gut* **2010**, *59*, 531–541. [CrossRef] [PubMed]
84. Pisani, L.F.; Teani, I.; Vecchi, M.; Pastorelli, L. Interleukin-33: Friend or Foe in Gastrointestinal Tract Cancers? *Cells* **2023**, *12*, 1481. [CrossRef] [PubMed]
85. Eissmann, M.F.; Dijkstra, C.; Wouters, M.A.; Baloyan, D.; Mouradov, D.; Nguyen, P.M.; Davalos-Salas, M.; Putoczki, T.L.; Sieber, O.M.; Mariadason, J.M.; et al. Interleukin 33 Signaling Restrains Sporadic Colon Cancer in an Interferon-γ-Dependent Manner. *Cancer Immunol. Res.* **2018**, *6*, 409–421. [CrossRef]
86. Pastille, E.; Wasmer, M.H.; Adamczyk, A.; Vu, V.P.; Mager, L.F.; Phuong, N.N.T.; Palmieri, V.; Simillion, C.; Hansen, W.; Kasper, S.; et al. The IL-33/ST2 pathway shapes the regulatory T cell phenotype to promote intestinal cancer. *Mucosal Immunol.* **2019**, *12*, 990–1003. [CrossRef]

87. Akimoto, M.; Takenaga, K. Role of the IL-33/ST2L axis in colorectal cancer progression. *Cell Immunol.* **2019**, *343*, 103740. [CrossRef]
88. Liu, X.; Zhu, L.; Lu, X.; Bian, H.; Wu, X.; Yang, W.; Qin, Q. IL-33/ST2 pathway contributes to metastasis of human colorectal cancer. *Biochem. Biophys. Res. Commun.* **2014**, *453*, 486–492. [CrossRef]
89. Van der Jeught, K.; Sun, Y.; Fang, Y.; Zhou, Z.; Jiang, H.; Yu, T.; Yang, J.; Kamocka, M.M.; So, K.M.; Li, Y.; et al. ST2 as Checkpoint Target for Colorectal Cancer Immunotherapy. *JCI Insight* **2020**, *5*, e136073. [CrossRef]
90. Ercolano, G.; Gomez-Cadena, A.; Dumauthioz, N.; Vanoni, G.; Kreutzfeldt, M.; Wyss, T.; Michalik, L.; Loyon, R.; Ianaro, A.; Ho, P.-C.; et al. PPARγ Drives IL-33-Dependent ILC2 pro-Tumoral Functions. *Nat. Commun.* **2021**, *12*, 2538. [CrossRef]
91. Li, Y.; Shi, J.; Qi, S.; Zhang, J.; Peng, D.; Chen, Z.; Wang, G.; Wang, Z.; Wang, L. IL-33 Facilitates Proliferation of Colorectal Cancer Dependent on COX2/PGE2. *J. Exp. Clin. Cancer Res.* **2018**, *37*, 196. [CrossRef] [PubMed]
92. Saliba, J.; Coutaud, B.; Makhani, K.; Epstein Roth, N.; Jackson, J.; Park, J.Y.; Gagnon, N.; Costa, P.; Jeyakumar, T.; Bury, M.; et al. Loss of NFE2L3 Protects against Inflammation-Induced Colorectal Cancer through Modulation of the Tumor Microenvironment. *Oncogene* **2022**, *41*, 1563–1575. [CrossRef]
93. Zhang, Y.; Davis, C.; Shah, S.; Hughes, D.; Ryan, J.C.; Altomare, D.; Peña, M.M.O. IL-33 Promotes Growth and Liver Metastasis of Colorectal Cancer in Mice by Remodeling the Tumor Microenvironment and Inducing Angiogenesis. *Mol. Carcinog.* **2017**, *56*, 272–287. [CrossRef] [PubMed]
94. Cui, G.; Yuan, A.; Pang, Z.; Zheng, W.; Li, Z.; Goll, R. Contribution of IL-33 to the Pathogenesis of Colorectal Cancer. *Front. Oncol.* **2018**, *8*, 561. [CrossRef]
95. O'Donnell, C.; Mahmoud, A.; Keane, J.; Murphy, C.; White, D.; Carey, S.; O'Riordain, M.; Bennett, M.W.; Brint, E.; Houston, A. An Antitumorigenic Role for the IL-33 Receptor, ST2L, in Colon Cancer. *Br. J. Cancer* **2016**, *114*, 37–43. [CrossRef] [PubMed]
96. Oliveira, E.C.S.; Quaglio, A.E.V.; Magro, D.O.; Di Stasi, L.C.; Sassaki, L.Y. Intestinal Microbiota and miRNA in IBD: A Narrative Review about Discoveries and Perspectives for the Future. *Int. J. Mol. Sci.* **2023**, *24*, 7176. [CrossRef] [PubMed]
97. Suri, K.; Bubier, J.A.; Wiles, M.V.; Shultz, L.D.; Amiji, M.M.; Hosur, V. Role of microRNA in inflammatory bowel disease: Clinical evidence and the development of preclinical animal models. *Cells* **2021**, *10*, 2204. [CrossRef] [PubMed]
98. Masi, L.; Capobianco, I.; Magrì, C.; Marafini, I.; Petito, V.; Scaldaferri, F. MicroRNAs as Innovative Biomarkers for Inflammatory Bowel Disease and Prediction of Colorectal Cancer. *Int. J. Mol. Sci.* **2022**, *23*, 7991. [CrossRef]