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Research paper

Role of the IL-33/ST2L axis in colorectal cancer progression

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ABSTRACT

Interleukin-33 (IL-33) has been identified as a natural ligand of ST2L. IL-33 primarily acts as a key regulator of Th2 responses through binding to ST2L, which is antagonized by soluble ST2 (sST2). The IL-33/ST2L axis is involved in various inflammatory pathologies, including ulcerative colitis (UC). Several recent investigations have also suggested that the IL-33/ST2L axis plays a role in colorectal cancer (CRC) progression. In CRC, tumor- and stroma-derived IL-33 may activate ST2L on various cell types in an autocrine and paracrine manner. Although several findings support the hypothesis that the IL-33/ST2L axis positively regulates CRC progression, other reports do not; hence, this hypothesis remains controversial. At any rate, recent studies have provided overwhelming evidence that the IL-33/ST2L axis plays important roles in CRC progression. This review summarizes the role of the IL-33/ST2L axis in the UC and CRC microenvironments.

1. Introduction

Colorectal cancer (CRC) is one of the most common cancer types and causes of death globally [1]. CRC development involves a multistep adenoma-carcinoma sequence resulting from the accumulation of numerous genetic aberrations in key oncogenes and tumor suppressor genes. Somatic mutations or polymorphisms that are frequently found in CRC affect the various signaling pathways, including the Wnt/β-catenin, KRAS, MYC, mitogen-activated protein kinase (MAPK), and transforming growth factor (TGF)-β/bone morphogenetic protein (BMP) signaling [2,3]. In addition, CRC progression is closely related to chronic inflammation [4]; patients with an inflammatory bowel disease (IBD) such as ulcerative colitis (UC) are at high risk of developing CRC [5–7]. As many studies have suggested that various cytokines are associated with or accelerate CRC progression [2], inflammatory cytokines are important components of the CRC microenvironment [8,9].

Interleukin-33 (IL-33), a member of the interleukin-1 (IL-1) family, has been identified as a natural ligand for ST2L. The IL-33/ST2L axis is primarily associated with the induction of T-helper type 2 (Th2) immune responses [10] and has been implicated in numerous inflammatory and allergic diseases, including asthma [11], rheumatoid arthritis [12], cardiovascular disease [13], atopic dermatitis [14], and IBD [15]. In addition, the IL-33 signaling pathway has been reported to be associated with colitis-associated cancer (CAC) [16]. More recent studies have shown a relationship between the IL-33/ST2L axis and the progression of various cancers, including CRC [17–21]. Therefore, the IL-33/ST2L axis has recently received attention for its contribution to UC and CRC. Here, we review the role of the IL-33/ST2L axis in the progression of UC and CRC and discuss the therapeutic application of inhibiting IL-33/ST2L signaling for the treatment of metastatic CRC.

2. IL-33/ST2L axis

2.1. The molecular characteristics of IL-33

IL-33 was originally discovered as a nuclear repressor factor and was named 'nuclear factor from HEV (NF-HEV)' because it is highly expressed in high endothelial venules (HEV) [22]. IL-33 protein is initially synthesized as a 30 kDa pro-protein containing an N-terminal domain, which is necessary for nuclear localization, association with heterochromatin and targeting to mitotic chromosomes, and a C-terminal IL-1-like cytokine domain [10,23]. Full length IL-33 exerts dual functions as a nuclear factor that modulates gene expression and as a cytokine stimulated by damage-associated molecular patterns (DAMPs) [24,25]. After synthesis, IL-33 translocates into the nucleus, where it binds to chromatin and modulates gene expression [23]. In fact, nuclear-localized IL-33 acts as a transcriptional repressor of nuclear factor κB (NF-κB); the N-terminal part of IL-33 binds to the N-terminal Rel homology domain of NF-κB p65, thereby decreasing NF-κB-induced gene expression and consequently pro-inflammatory signaling [25]. After its extracellular release in response to necrotic cellular damage, full-length IL-33 binds to the transmembrane receptor ST2L via its C-terminal IL-1-like cytokine domain [10], thereby acting as an "alarmin" triggering an inflammatory response, similarly to the

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actions of IL-1α and high-mobility group box-1 protein (HMGB1) [26]. Thus, intracellular full-length IL-33 modulates cytokine gene expression as a nuclear factor, whereas the extracellular full-length IL-33 serves as a damage-associated signal that alerts the immune system.

Similarly to that of other alarmins, the bioactivity of IL-33 is strictly controlled to prevent excessive damage-inducing inflammation. Full-length IL-33 was initially assumed to undergo proteolytic maturation by caspase-1, like typical IL-1 family members such as IL-1β and IL-18; however, more recent studies have demonstrated that IL-33 is not a substrate for caspase-1 [27–29]. Instead, IL-33 has been found to be processed within its C-terminal domain and inactivated by pro-apoptotic caspases (caspases 3 and 7), not by inflammation-associated caspases (caspases 1, 4, and 5) [28,29]. These findings suggest that IL-33 bioactivity is attenuated by caspase-mediated proteolysis in apoptotic cells [28,29] and that the mechanism might ensure immune tolerance during apoptosis by inhibiting the release of active IL-33. Under inflammatory conditions, full-length IL-33 released from inflammatory cells and damaged cells is enzymatically processed by neutrophil-derived serine proteases (i.e., cathepsin G and elastase) [30] and mast cell-derived serine proteases (i.e., chymase, tryptase and granzyme-B) [31,32]. In contrast to apoptosis-induced caspases, these serine proteases cleave full-length IL-33 at its central domain, generating hyperactive mature IL-33 isoforms with 10- to 30-fold increased bioactivity compared with that of full-length IL-33 [30–33]. Mature IL-33 protein lacking the N-terminal domain acts as an IL-1-like cytokine through its C-terminal IL-1-like cytokine domain.

2.2. The molecular characteristics of ST2

ST2, an IL-33 receptor encoded by the *IL1RL1* gene, is a member of the IL-1 receptor family that was originally identified as a responsive gene in serum- or oncogene-stimulated mouse fibroblasts [34,35]. At least four ST2 isoforms are produced from the *IL1RL1* gene via alternative splicing: ST2L, sST2, ST2V and ST2LV. ST2L is a membrane-anchored receptor that is highly homologous to IL-1 type-1 receptors and comprises an extracellular region of three Ig-like domains, a transmembrane region, and an intracellular Toll-like/IL-1 receptor domain [36–38]. sST2 is secreted as a glycosylated protein containing an extracellular domain identical to that of ST2L with an additional short amino acid sequence [37,39]. ST2V is similar to sST2 but gains a hydrophobic tail instead of losing the third immunoglobulin-like domain [40,41]. ST2LV is a soluble and N-glycosylated variant that lacks the transmembrane domain within ST2L [42]. Although the two major isoforms, ST2L and sST2, have been well studied, little is known about the biological function of ST2V and ST2LV. ST2L forms a transmembrane heterodimeric receptor with IL-1 receptor accessory protein (IL-1RAcP), an essential co-receptor for IL-33 binding and activity [10], while sST2 acts as a decoy receptor by sequestering IL-33 [39,43]. Recent studies have revealed that *IL1RL1* gene expression is controlled by GATA1/2 and estrogen-response elements (EREs) within distal and proximal promoters that regulate both ST2L and sST2 variant expression [39,44,45].

2.3. IL-33 and ST2L expression in normal cells

Several immune cell types express IL-33, including mast cells [46], dendritic cells [47], macrophages [48] and monocytes [49], as do non-immune cells such as epithelial cells of mucosal sites [50], fibroblasts [51], keratinocytes [52], smooth muscle cells [53], adipocytes [54], and endothelial cells [55]. ST2L is expressed on the surfaces of fibroblasts [39], mast cells [56], eosinophils [57], Th2 lymphocytes [58,59], dendritic cells [60], basophils, iNKT cells [61], and macrophages [62], whereas sST2 is predominantly produced by fibroblasts [43] and epithelial cells [63].

2.4. Regulation of IL-33/ST2L signaling

2.4.1. Regulation by decoy receptors

IL-33/ST2 signaling is regulated by several mechanisms. One of the most studied molecular regulators is sST2, which acts as a decoy receptor by sequestering IL-33 [39,43]. Similarly to sST2, an alternative splice transcript of IL-1RAcP encodes a smaller soluble protein (sIL-1RAcP) lacking the transmembrane and intracellular domains that can also act as a decoy receptor for IL-33 [64,65]. Therefore, sST2 and sIL-1RAcP abrogate IL-33/ST2L signaling by antagonizing IL-33 biological activity. Indeed, treatment of mice with sST2 before induction of allergic asthma has been found to ameliorate severe lung inflammation by inhibiting IL-33-induced NF-κB activity and the Th2 response [11]. In addition, co-incubation with recombinant chimeric sST2-Fc and sIL-1RAcP-Fc synergistically inhibits IL-33-induced IL-6 production in mast cells [66].

2.4.2. Regulation by oxidation of IL-33

IL-33/ST2L signaling is also regulated by conformational changes in IL-33. A recent report has proposed that IL-33 bioactivity is rapidly inactivated by oxidation, owing to the formation of two disulfide bridges, thus resulting in an extensive conformational change that distorts the ST2 binding site. Oxidized, inactive IL-33 has been detected in the lungs of mice challenged with a fungal allergen and in sputum from patients with asthma. Disruption of this inactivation mechanism *in vivo* markedly enhances lung inflammation [67].

2.4.3. Regulation at the transcriptional level

IL-33 and ST2L expression is controlled at the transcriptional level by several cytokines, such as tumor necrosis factor-α (TNF-α) [68] and epidermal growth factor (EGF) [69]. In epithelial cells from patients with active UC, full-length IL-33 expression is increased, whereas ST2L expression is decreased [68]. Anti-TNF-α therapy (infliximab) increases sST2 levels and decreases circulating IL-33 in patients with UC [68]. In support of these findings, TNF-α modulates intestinal epithelial cell-derived full-length IL-33 and sST2 *in vitro* [68]. EGF may also regulate the expression of IL-33 and ST2 in intestinal epithelial cells at the transcriptional level, because administration of gefitinib, an EGFR inhibitor, downregulates the expressions of IL-33 and ST2 in mouse colitis [69], and, conversely, EGF treatment enhances their expression levels in the IEC-6 rat intestinal epithelial cell line. Additionally, IL-1β and IL-33 have also been shown to increase IL-33 expression in lung carcinoma cells [70].

Interestingly, a recent report has shown that HIF-1α enhances IL-33 production by activating certain signaling pathways, particularly the p38 and ERK pathways. IL-33, in turn, induces HIF-1α expression, thereby forming a HIF-1α/IL-33 positive feedback loop [71]. Moreover, TNF-α promotes HIF-1α expression by both activating NF-κB signaling and regulating IL-33 expression in a HIF-1α-dependent manner. Therefore, TNF-α facilitates HIF-1α-dependent IL-33 expression [72]. More recently, a functional binding site for HIF-1α has been identified in the IL-33 promoter region, thus suggesting that *IL-33* gene transcription may be directly regulated by HIF-1 [72]. Although the mechanisms are still not clear, these findings suggest that IL-33 may be upregulated in hypoxic tumor microenvironments.

2.5. Biological activity of IL-33/ST2L signaling

Extracellular IL-33 binds to a receptor complex composed of ST2L and IL-1RAcP through its C-terminal IL-1-like cytokine domain. Subsequently, the IL-33 signal is transduced by the recruitment of myeloid differentiation primary response gene 88 (MyD88), IL-1 receptor-associated kinases (IRAK-1 and IRAK-4) and TNF receptor-associated factor 6 (TRAF6) to the intracellular domain of the receptor complex [10,73]. The IL-33/ST2L axis triggers the production and secretion of Th2 cytokines, such as IL-4, IL-5 and IL-13 [10,74,75], via

activation of the NF-κB, MAPK or phosphoinositide-3 kinase (PI3K) pathway [23,76,77]. Consequently, the released Th2 cytokines enhance the accumulation and activation of innate lymphoid cells type 2 (ILC2) [78], Th2 cells and M2-polarized macrophages [62], thereby leading to type-2 immune responses, such as Th2 differentiation, Th1 to Th2 skewing [79,80] and M2 polarization [62]. Excessive stimulation of the IL-33/ST2L axis promotes rheumatic and airway inflammatory diseases, and inflammatory and fibrotic disorders of the gastrointestinal tract [81–84]. Therefore, blockade of the IL-33/ST2L axis may effectively ameliorate IL-33-related disorders; in fact, in a murine model of allergic inflammation, lung inflammation has been found to be alleviated by pretreatment with sST2 [43].

Although IL-33 has generally been considered a key regulator of Th2 responses, a recent *in vitro* study has demonstrated that IL-33 and other pro-inflammatory cytokines collaboratively amplify both Th1- and Th2-oriented immune responses via interactions with basophils, Th2 cells, iNKT cells and NK cells [61]. In support of this finding, administration of anti-ST2 antibodies in a mouse model of arthritis decreases interferon-γ (IFN-γ) and IL-17, thus suggesting that IL-33 induces non-Th2 cytokines such as other IL-1 cytokine family members [85]. Moreover, even within the same cell, IL-33/ST2L signaling can be transduced via different pathways and can induce expression of various cytokines, depending on the extracellular and intracellular conditions. For instance, in mouse embryonic fibroblasts (MEFs), IL-33 activates NF-κB through TRAF6-dependent p38 and c-Jun N-terminal kinase (JNK) pathways, thus inducing monocyte chemoattractant protein 1 (MCP-1), MCP-3 and IL-6 expression [73]. In contrast, IL-33 can activate NF-κB via an alternative Janus kinase 2 (JAK2)-dependent pathway, thereby leading increasing expression of IL-6, C−C motif chemokine ligand 2 (CCL2)/MCP-1 and C-X-C chemokine ligand 1 (CXCL1)/KC [86]. Beyond the conventional functions, recent studies have demonstrated that IL-33/ST2L signaling in intestinal FOXP3$^+$-regulatory T cells (Tregs) promotes GATA3-mediated proliferation and increases production of Foxp3, thereby amplifying Tregs [87].

Interestingly, IL-33 has been reported to be a pro-angiogenic factor that promotes both angiogenesis and vascular permeability [55]. Recombinant IL-33 protein induces pro-angiogenic properties, including the proliferation, migration, and morphologic differentiation of human umbilical vein endothelial cells (HUVECs), in an ST2L-dependent manner. IL-33 also increases endothelial permeability by decreasing vascular endothelial cadherin-facilitated cell–cell junctions, thus resulting in vascular leakage. Mechanistically, the binding of IL-33 to ST2L on endothelial cells rapidly increases endothelial nitric oxide (NO) production through TRAF6- mediated activation of phosphoinositide-3-kinase, Akt, and endothelial NO synthase (eNOS). Thus, the IL-33/ST2L axis may induce angiogenesis and vascular leakage via the TRAF6-Akt-eNOS signaling pathway in endothelial cells. Therefore, these findings suggest that defects in the IL-33/ST2L axis may be involved in the development of inflammatory vascular diseases such as atherosclerosis, rheumatoid arthritis, and various types of cancer [55]. Collectively, IL-33/ST2L signaling elicits diverse biological effects.

2.6. The roles of IL-33/ST2L signaling in tumor immunity

The roles of IL-33/ST2L signaling in tumor immunity have been studied in various types of cancer. Genetic depletion of ST2L in a 4T1 breast cancer model suppressed metastasis, which is associated with enhanced cytotoxic activity of NK cells and increased systemic Th1 and Th17 cytokines [88], suggesting that the IL-33/ST2L axis may promote cancer progression in this model. In fact, intraperitoneal administration of recombinant IL-33 (rIL-33) promoted 4T1 tumor growth and lung and liver metastases by suppressing antitumor immunity and by enhancing tumor angiogenesis [89]. Mechanistically, IL-33 expands IL-13-producing ILCs to amplify the immunosuppressive activities of myeloid-derived suppressor cells (MDSCs) and subsequently induces CD4$^+$ Foxp3$^+$ IL-10$^+$ Tregs that promote the generation of immature tolerogenic DCs, resulting in reduced NK cell cytotoxicity [89]. IL-33 can also act directly on MDSCs to induce arginase-1 expression and activates NF-κB and MAPK signaling, thereby facilitating the immunosuppressive and pro-tumorigenic capacity of MDSCs [90]. Moreover, IL-33 promotes GM-CSF secretion from MDSCs, which forms an autocrine amplification loop to promote the survival and accumulation of MDSCs.

In contrast, overexpression of IL-33 in B16 melanoma cells and Lewis lung carcinoma (LLC) cells suppressed tumor growth and metastasis by promoting antitumor immunity [91,92]. In these cases, IL-33 accelerated the cytotoxic activity of tumor antigen-specific CD8$^+$ T cells and NK cells through NF-κB signaling, leading to increased tumor-eradicating type 1 immune responses [92]. Similarly, Dominguez et al. demonstrated that systemic administration of rIL-33 inhibited established and *de novo* B16 melanoma tumor growth [93]. In addition to CD8$^+$ T cell expansion and IFN-γ production, IL-33 can also activate myeloid dendritic cells (mDCs) via the IL-33–ST2L–MyD88–STAT1 axis, restoring antitumor T cell activity and increasing Ag cross-presentation within the tumor microenvironment [93]. IL-33 may also contribute to immune surveillance, which is attenuated during metastatic progression that facilitates immune escape [94]. Low expression levels of IL-33 in metastatic murine prostate and lung carcinomas are associated with decreased expression levels of major histocompatibility complex class I (MHC-I) antigen-processing machinery (APM) components, including beta-2-microglobulin (β2m) and human leukocyte antigens (HLA-A, HLA-B and HLA-C). Reconstitution of IL-33 expression in metastatic tumors improves the expression levels of APM components and the functionality of MHC-I, resulting in reduced tumor growth and circulating tumor cells (CTCs).

Collectively, several investigations have demonstrated opposing effects of IL-33/ST2L in tumor immunity. Notably, systemic injection of low levels of IL-33 increased tumor metastasis in 4T1 tumor-bearing mice [89]. In contrast, overexpression of IL-33 in 4T1 cells promoted antitumor immune responses [92]. Gao et al. attributed the discrepancy in these studies to the differences in the IL-33 concentration and in the primary target cells of IL-33; persistent and high levels of IL-33 in tumor tissues synergize with other cytokines, such as IL-2 and IL-12, to promote type 1 immune responses, whereas low-level and systemic delivery of IL-33 protein into resting or tumor-bearing mice results in immune tolerance [92].

3. The roles of IL-33/ST2L in UC

3.1. Localization of IL-33 and ST2 in UC tissues

IBDs, including UC and Crohn's disease (CD), are chronic inflammatory pathologies that affect the gastrointestinal tract [95]. The risk of developing CRC is higher in patients with IBDs than the general population [96], which may be related to persistent repair of inflammation-induced damage to the epithelial monolayer [97]. Although recent studies have indicated the involvement of IL-33 in UC, there are conflicting reports regarding its role, sources and localization in the colonic mucosa [15]. Higher levels of IL-33 and ST2 have been detected in intestinal lesions and serum from UC patients compared with controls and CD patients, and these levels correlate with disease severity [68,98–107] (Table 1). IL-33 is localized in the nucleus of epithelial cells [102,106], ulceration-associated myofibroblasts [99,101] and lamina propria mononuclear cells (LPMCs) [68,100,105] in intestinal tissue from UC patients. In contrast, ST2 expression is high in normal, non-inflamed intestinal epithelial cells but decreases during chronic inflammation [68]. Instead, ST2-positive hematopoietic cells, such as macrophages and lymphocytes, infiltrate the lamina propria [68,102].

In a dextran sodium sulfate (DSS)-induced colitis mouse model, IL-33 has been observed in the nuclei of myofibroblasts and enterocytes, whereas ST2 primarily localizes in the colonic epithelia [84,102].

Table 1
Expression levels of IL-33 and ST2 in IBD.

Studies	Sample	Methods	Expression level	
Kobori et al. (2010) [99]	Biopsied specimens	qPCR	IL-33	NC, CD < UC
Pastorelli et al. (2010) [68]	Biopsied specimens	qPCR, WB	IL-33	NC, CD < UC (only full-length)
			sST2	NC, CD < UC
	Surgical specimens	IHC	IL-33	NC, CD < UC
			ST2	NC, CD < inflamed UC
	IEC from surgical specimens	qPCR	IL-33	NC, CD < UC
			Total ST2	NC > UC
		WB	ST2L	NC > UC
			sST2	NC < CD, UC
	Serum	ELISA, WB	IL-33	NC < CD, UC (only cleaved form) NC < CD, UC
			sST2	
Seidelin et al. (2010) [100]	IEC from surgical specimens	qPCR	IL-33	NC < inactive UC < active UC
		WB	IL-33	NC=inactive UC < active UC (only full-length)
Sponheim et al. (2010) [101]	Biopsied specimens	qPCR	IL-33	NC < UC
Sedhom et al. (2012) [102]	Surgical specimens	IHC	IL-33	Non-involved IBD < active IBD
Wakahara et al. (2012) [103]	Colonic explant cultures	ELISA	IL-33	NC < UC, CD
Saadah et al. (2015) [104]	Serum	ELISA	IL-33	NC < UC (correlated with disease activity)
Waddel et al. (2015) [105]	Biopsied specimens	qPCR	IL-33	Non-IBD < UC
Gundersen et al. (2016) [106]	Biopsied specimens	IHC	IL-33	NC < UC
Boga et al. (2016) [107]	Serum	ELISA	sST2	NC, IBS < CD, UC
				inactive CD < active CD
				inactive UC < active UC
Hyuk Seo et al. (2017) [117]	Serum	ELISA	IL-33	NC > IBD
			sST2	NC < IBD

NC, normal control; CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IEC, intestinal epithelial cell; qPCR, quantitative PCR; WB, western blotting; ELISA, enzyme-linked immunosorbent assay; IHC, immunohistochemistry.

3.2. The roles of the IL-33/ST2L axis in intestinal immunity

In the intestine, IL-33 is released by epithelial damage [108]. Subsequently, IL-33 stimulates both pathogenic Th2 and Th17 responses, while it also induces wound healing of mucosa damaged during the inflammatory response [84,102,109] by coordinating the activities of ILC2s and Tregs [87,109–115]. Colonic Tregs express ST2L, which promotes Treg function and adaptation. IL-33 acts as a co-factor that enhances TGF-β1-mediated differentiation of Tregs and promotes Treg accumulation and maintenance in inflamed tissues [87]. Interestingly, sST2 was significantly increased during *Helicobacter*-induced murine chronic colitis, as well as in patients with active IBD, suggesting that IL-33 activity is antagonized by sST2 to suppress Treg responses under pathogenic inflammation. In accordance, ST2-deficient Tregs showed a diminished ability to prevent colonic inflammation, and IL-23, a key pathogenic mediator of IBD, restrained Treg responses by inhibition of sST2 expression [87].

3.3. The roles of IL-33/ST2 in mouse colitis models

Genetic ablation of IL-33 [84] or ST2 [102] decreases the symptoms and intestinal inflammation in early phases of DSS-induced colitis. Because experiments with bone-marrow chimera mice have revealed that ST2 depletion in non-hematopoietic cells is sufficient to protect against DSS-induced colitis, the decreased inflammation in ST2-deficient mice might reflect sustained intestinal barrier function [102]. However, these improvements in response to IL-33 depletion are restricted to the early phase of DSS-derived colitis, thus suggesting that the IL-33/ST2 axis is involved in inducing the early stage of inflammation in this model [84]. Treatment of DSS mice with exogenous recombinant IL-33 exaggerates the inflammation by inducing an IL-4-dependent immune response [116]. In addition, IL-33 plays a pathogenic role in SAMP1/YitFc mice, a spontaneous model of IBD with aspects of Th1 and Th2 immunity [68]. Therefore, IL-33 might conceivably worsen colitis by increasing neutrophilia and inflammation after epithelial barrier disruption with DSS. However, several reports have demonstrated that IL-33 enhances epithelial barrier function by stimulating wound healing and goblet cell proliferation during resolution [84,117]. In addition, recent reports have demonstrated that exogenous administration of IL-33 has a protective effect in trinitrobenzene sulfonic acid (TNBS)-induced colitis, a Th1-type immune model that mimics human CD, by promoting a switch from Th1 to Th2 immunity and Treg development [109,118]. Furthermore, IL-33 has recently been shown to induce macrophage switching from pro-inflammatory M1 to anti-inflammatory M2 phenotype in DSS and TNBS model mice, thereby ameliorating colitis [117,119]. These results indicate a protective role of IL-33 in UC. Therefore, the role of the IL-33/ST2 axis in UC is still a matter of debate; it may either promote or inhibit colitis, depending on inflammatory conditions and, in particular Th1/Th2 balance in the lesion.

3.4. sST2 in IBD

Tregs prevent dysregulated inflammatory responses to environmental stimuli and thus contribute to the pathogenesis of IBD [120]. Recent studies have indicated that the IL-33/ST2L axis may be involved in wound repair within the intestine by coordinating the action of ILC2 and Tregs [110,113,121,122]. Colonic Tregs express ST2L, which promotes Treg function and adaptation after binding of IL-33 [87]. IL-33 acts as a co-factor that enhances TGF-β1-mediated Treg differentiation and promotes Treg accumulation and maintenance in inflamed tissues [87]. Serum sST2 levels are elevated in patients with IBD compared with healthy controls and are correlated with IBD severity [107,117]. These results suggest that IL-33 exhibits a protective effect against IBD and that sST2 antagonizes IL-33 activity, thus resulting in the suppression of Treg responses and macrophage M2 polarization under conditions of pathogenic inflammation.

4. The roles of IL-33/ST2L in CRC

4.1. Cells expressing IL-33 and ST2 in CRC tissues

In human and mouse CRC tissue, IL-33 is predominantly expressed in tumor cells, stromal endothelial cells [123–125] and myofibroblasts [125]. In contrast, ST2L is mainly expressed on tumor cells [123,125], myofibroblasts [124] and endothelial cells [125]. Our recent results

Table 2
IL-33 and ST2 levels in patients with CRC.

Studies	Samples	Methods	Expression level		Correlation with tumor grade
Liu et al. (2014) [123]	Tissue	IHC	IL-33	NT < CRC	Positive correlation
	Tissue	IHC	ST2	NT < CRC	Positive correlation
Maywald et al. (2015) [124]	Tissue	IHC	IL-33	NT < CRC	–
	Serum	ELISA	IL-33	HC < CRC patients	–
Cui et al. (2015) [125]	Tissue	IHC	IL-33	NT < CRC < Adenoma	–
	Tissue	IHC	ST2	NT < CRC < Adenoma	Positive correlation with TNM
Zhang et al. (2016) [127]	Tissue	qPCR	IL-33	NT < CRC	Stage I-III > Stage IV
O'Donell (2016) [129]	Tissue	qPCR	IL-33	NT = CRC	–
	Tissue	qPCR	ST2	NT = CRC	–
	Tissue	qPCR	ST2L	NT > CRC	Negative correlation
	Serum	ELISA	IL-33	HC > CRC	–
	Serum	ELISA	sST2	HC = CRC	–
Akimoto et al. (2016) [21]	Serum	ELISA	sST2	–	Negative correlation
Fang et al. (2017) [128]	Serum	ELISA	IL-33	–	Negative correlation with survival in patients with metastatic CRC

NT, normal tissue; HC, healthy control; CRC, colorectal cancer.

have shown that tumor cells also produce sST2 [21].

4.2. IL-33 and ST2 levels in human CRC

There are contradictory data regarding the tissue and serum levels of IL-33 and ST2 and their correlation with tumor grade (Table 2). Higher expression levels of IL-33 and total ST2 (ST2L and sST2) in CRC tissues compared with adjacent normal tissues have been reported in several studies [123–127]. Similarly, serum IL-33 levels are higher in CRC patients than in healthy volunteers [124]. Interestingly, IL-33 and ST2 expression is higher in adenoma and low-grade CRC (Stages I–III) and, to a lesser extent, in higher-grade and more advanced tumors (Stage IV) than in normal tissue [123–127]. Notably, the increased IL-33 and ST2 expression during the colorectal adenoma-carcinoma sequence suggests that the IL-33/ST2L axis might play an important role, especially in early stages of CRC development. In support of this possibility, IL-33 expression is elevated in early stages of adenoma, as a result of induction and activation by pro-inflammatory cytokines, probably IL-6 and IL-1β, derived from the tumor microenvironment [127]. Increased IL-33 expression is observed in poorly differentiated human CRC cells [123], which is associated with poor survival in patients with metastatic colon cancer [128]. In addition, the ST2 expression level is correlated with tumor/node/metastasis (TNM) stage [125]. Therefore, IL-33 and ST2 are potential prognostic markers of CRC. However, one study has shown that IL-33 and total ST2 levels do not differ in CRC tissues and adjacent non-tumor tissues and that a higher tumor grade is associated with lower ST2L expression [129]. Although the reason for the discrepancy is unclear, the difference in serum IL-33 levels may be due to differences in the disease stage or the treatment status of the recruited patients. The difference in tissue ST2 level may be attributable to the ST2 isoforms examined, either total ST2 or ST2L. Nonetheless, further detailed investigations are required.

4.3. The role of IL-33/ST2L in CRC progression in mouse models

4.3.1. AOM/DSS model

Accumulating evidence from mouse models of CAC and CRC indicates the role of the IL-33/ST2 axis in CRC tumorigenesis and progression. In the azoxymethane (AOM)/DSS model, IL-33 expression levels are transiently upregulated in the colon at the peak of acute colitis and immediately return to near background levels after the removal of DSS [84,102]. Therefore, activation of the IL-33/ST2L axis may contribute to tumorigenesis by stimulating or amplifying inflammation in the early stages of the AOM/DSS model. ST2-knockout mice treated with AOM/DSS show delayed CAC development and fewer and smaller intestinal tumors with lower-grade lesions as compared with those in wild-type mice [126]. In this model, IL-33 may not directly affect tumor proliferation but may instead decrease the integrity of the intestinal barrier, which in turn may promote the invasiveness of intestinal bacteria or by-products into normally sterile tissue and trigger the production of pro-tumorigenic IL-6 by immune cells [126]. In contrast, another study has reported that IL-33-deficient mice are highly susceptible to AOM/DSS-induced colitis and CAC, showing augmented secretion of inflammatory cytokines and increased tumor number, size, and grade in model mice compared with wild-type mice [16]. The increased susceptibility of IL-33-deficient mice to CAC is markedly ameliorated by reconstitution of symbiotic microbiota or IL-1α ablation, thus suggesting that IL-33 prevents microbial dysbiosis and IL-1α-dependent inflammation in the intestine by promoting IgA production in B cells [16].

4.3.2. $Apc^{Min/+}$ model

In the $Apc^{Min/+}$ mouse, a model for human familial adenomatous polyposis, IL-33 localizes to tumor epithelial cells, and ST2 is associated with stromal subepithelial myofibroblasts (SEMFs) and mast cells within adenomatous polyps [124]. Abrogation of the IL-33/ST2L axis in the $Apc^{Min/+}$ mouse by knockout of IL-33 [124] or ST2 [126] inhibits proliferation, induces apoptosis, and suppresses angiogenesis in $Apc^{Min/+}$ polyps, thus decreasing both tumor number and size. IL-33 deficiency also decreases mast cell density in $Apc^{Min/+}$ polyps and suppresses the gene expression of mast cell-derived proteases and cytokines (*Il4* and *Il6*) that promote angiogenesis, Treg function and MDSC recruitment within the tumor microenvironment [130–132]. In addition, IL-33 stimulates SEMFs to induce the expression of extracellular matrix components and growth factors involved in intestinal tumor progression [124].

4.4. The role of IL-33/ST2 in CRC progression

4.4.1. Effect of IL-33/ST2 on malignant growth

Overexpression of IL-33 in SW620 human CRC cells enhanced tumor growth and lung metastasis and decreased the survival of recipient nude mice, whereas downregulation of IL-33 had the opposite effects [123]. Similarly, in a subcutaneous xenograft model, overexpression of IL-33 in MC-38 mouse CRC cells that were injected into the cecum in syngeneic mice enhanced tumor growth and liver metastasis [127]. In this orthotopic model of CRC, tumor- rather than recipient-derived IL-33 induced the tumor infiltration of $CD11b^+F4/80^+$ macrophages and $CD11b^+Gr\text{-}1^+$ MDSCs, thereby modulating the tumor microenvironment. A recent study demonstrated that specific sST2 knockdown in NM11 mouse colon cancer cells and SW480 human colon cancer cells with low metastatic potential resulted in increased tumor growth and metastasis. Conversely, overexpression of sST2 in the highly metastatic LuM1 mouse colon cancer cells suppressed tumor growth and

metastasis [21]. Thus, these findings indicate that IL-33/ST2L signaling in CRC tissues enhances the malignant growth of colon cancer cells.

In contrast, knockdown of ST2 in CT26 mouse colon cancer cells enhanced tumor development after injection of the cells into the flanks of syngeneic BALB/c mice [129], indicating that IL-33 has an antitumor effect in CRC. This effect is associated with a decrease in macrophage infiltration into tumors, probably because of a decrease in IL-33-induced CCL2 production by tumor cells with a dampened IL-33/ST2L axis. The findings that IL-33 and ST2 are predominately expressed in adenoma and low-grade CRC and, to a lesser extent, in higher-grade and more advanced-stage CRC [123–127] and the results obtained in the AOM/DSS model [16] support the antitumor role of IL-33 in CRC.

As such, the roles of IL-33/ST2L in CRC remain controversial. As mentioned above, IL-33, ST2L and sST2 are expressed in cancer cells and stromal cells in CRC tissues [123–125]. Therefore, tumor- and stroma-derived IL-33 may stimulate IL-33/ST2L signaling in an autocrine and paracrine manner within the CRC tumor microenvironment, thus complicating the *in vivo* results. The use of immune compromised mice or WNT/apc-activated $Apc^{Min/+}$ mice with expanded MDSCs [123–125,133] and the fact that IL-33 has opposing effects in tumor immunity depending on its concentration [92] further complicate the *in vivo* results. Further experiments should be performed to ascertain the exact role of the IL-33/ST2 axis on tumor immunity.

4.4.2. Effect of IL-33 on the stemness of tumor cells

A recent report has revealed the role of IL-33/ST2 signaling in inducing cancer stem cell-like properties in CRC cells. According to this study, IL-33/ST2L signaling enhances *in vivo* tumor growth, chemoresistance and sphere formation in human and mouse colon cancer cells via c-Jun activation, and subsequent expression of the core stem cell genes NANOG, NOTCH3 and OCT3/4 [128]. Furthermore, IL-33 recruits macrophages into the tumor microenvironment, where they produce prostaglandin E_2, which supports stemness. These data provide a novel mechanism underlying the enhancement of CRC malignancy by IL-33.

4.4.3. Effect of IL-33 on macrophage recruitment

Functional analyses of the IL-33/ST2L axis in CT26 cells have revealed that IL-33 stimulation induces CCL2 expression, which in turn promotes macrophage migration [129]. Tumor-derived IL-33 enhances the recruitment of $F4/80^+$ myeloid cells into the CT26 tumor microenvironment by increasing the expression of mobilizing cytokines [127]. In these studies, the macrophage type (M1 or M2) is unclear. M2 macrophages in the tumor microenvironment are termed tumor-associated macrophages (TAMs) and are known to promote tumor malignancy by enhancing tumor angiogenesis, tumor cell invasion, migration, and intravasation, as well as suppressing anti-tumor immunity [134–138]. TAM accumulation in tumor tissue is associated with malignancy in a variety of human cancers, including CRC. Recently, a study has reported that TAM infiltration is reduced in CRC tissues with high sST2 expression, thus suggesting that sST2 inhibits the IL-33-induced recruitment of monocytes or marginal macrophages into tumor tissues [21]. In accordance with this finding, *in vitro* experiments have revealed that IL-33 enhances the migration of mouse macrophage RAW264.7 cells in an ST2L-dependent manner, and this effect is inhibited by sST2 [21]. In addition, IL-33 has been proposed to stimulate M2, but not M1, polarization by promoting Th2 responses [135–137]. As expected, IL-10-positive M2 populations and the expression of M2a markers, such as CD163, mannose receptor complex-1 (Mrc1) and arginase-1 (Arg1), are significantly upregulated in tumors with low sST2 expression [21]. Thus, IL-33 may enhance monocyte recruitment and infiltration into the tumor microenvironment and induce M2a polarization of infiltrated monocytes, thereby stimulating TAMs to promote tumor angiogenesis and CRC cell invasion and metastasis.

4.4.4. Effect of IL-33 on angiogenesis and invasion

A recent study showed increased microvessel densities in the stroma of IL-33-positive and ST2L-positive CRC tissues [125]. In animal experiments, substantial generation of microvessels has been observed in IL-33-overexpressing mouse colon cancer tissues [21,127]. Tumor angiogenesis in CRC tumors with high sST2 expression is significantly suppressed [21]. As described above, IL-33 itself has pro-angiogenic activities, thereby directly promoting the proliferation, migration, and morphologic differentiation of endothelial cells [55]. Additionally, tumor-derived IL-33 induces the tumor infiltration of $CD11b^+$ $F4/80^+$ macrophages and $CD11b^+$ $Gr\text{-}1^+$ MDSCs and promotes the release of the pro-angiogenic factors VEGF and S100A8/9 from these cell populations [127]. Although intraperitoneal administration of IL-33 in a 4T1 breast cancer model mice enhanced tumor angiogenesis by promoting the intratumoral accumulation of immunosuppressive cells and ILC2s [89], tumor angiogenesis in CRC appears to be independent of innate lymphoid cells because $CD45^+CD3^+$ lymphoid cells were not significantly decreased in sST2-expressing CRC tumors [21].

In addition, *in vitro* experiments revealed that recombinant IL-33 protein directly acts on SW620 cells to increase the gene expression levels of IL-6, C-X-C chemokine receptor type 4 (CXCR4), matrix metalloproteinase 2 (MMP2) and MMP9 in an ST2L-dependent manner, thereby enhancing their invasive potential [123].

Thus, IL-33 may conceivably promote the production of pro-angiogenic factors or synergizes with these factors and promotes CRC progression and metastasis through enhancement of tumor angiogenesis and invasion.

5. IL-33/ST2L axis as a potential target for CRC treatment

Currently, cytokine blockade is applied for the treatment of inflammatory disorders; for example, anti-TNF-α monoclonal antibodies are used to treat UC and CD [69]. However, there is no experimental evidence clearly indicating the suitability of this approach for CRC. Meanwhile, our recent study revealed that sST2 effectively suppresses CRC progression by modulating the inflammatory tumor microenvironment. On the basis of these findings, we further studied the therapeutic effect of sST2-Fc protein against CRC and found that circulating and intratumorally administered sST2-Fc fusion protein decreases tumor growth, metastatic spread and tumor angiogenesis in mice with highly metastatic CRC [21]. Importantly, these findings provide the first experimental evidence that sST2 protein may function as a potent anti-cancer and anti-metastatic agent in CRC following systemic administration.

In addition, blockade of the IL-33/ST2L axis might be used in combination with conventional therapies. IL-33/ST2L inhibition may suppress pro-tumorigenic inflammation in tumor microenvironments, thereby improving the efficacy of conventional cancer therapies. Irinotecan (CPT-11), a topoisomerase I inhibitor, is an anti-proliferative drug used to treat metastatic CRC. However, systemic administration of CPT-11 has serious adverse side effects, including severe mucosal damage, diarrhea, and body weight loss. CPT-11-induced mucositis is mediated by the IL-33/ST2L axis and is markedly attenuated by IL-33 blockade with an anti-IL-33 antibody or sST2 protein [139]. CPT-11 treatment increases neutrophil accumulation in the intestine and promotes neutrophil adhesion to mesenteric veins, partly in an IL-33-dependent manner. Therefore, inhibiting the IL-33/ST2L axis may be a novel approach for ameliorating inflammatory mucosal damage and thus improving the effectiveness of conventional chemotherapy, such as FOLFIRI (folinic acid + 5-fluorouracil + irinotecan). Therefore, sST2 alone or in combination with other therapies is a potential novel, potent therapeutic strategy for CRC. However, we must confirm that inhibition of the IL-33/ST2 axis is effective because previous reports have found antitumor effects of IL-33 on CRC progression. Inadequate inhibition of IL-33 function would lead to accelerated CRC progression. In the future, the effectiveness of targeting IL-33/ST2L for the treatment of CRC with inflammation should be carefully evaluated in humans.

6. Conclusions

To date, clinical and experimental investigations have demonstrated opposing effects of IL-33/ST2L in both UC and CRC. As might be expected, IL-33 expression and bioactivity are controlled by multiple layers of regulation involving various factors, such as the extent of cell damage, other inflammatory cytokines, the balance between ST2L and sST2, the hypoxic state in the microenvironment, different cell types, immunological conditions and disease stages. This complexity may contribute to the conflicting results. At any rate, recent studies have provided overwhelming evidence that the IL-33/ST2L axis plays important roles in CRC progression. Further research should be performed to ascertain the exact role of the IL-33/ST2 axis and to obtain evidence-based knowledge for CRC treatment.

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Conflicts of interest

We declare that we have no conflicts of interest.

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