Cytokine & Growth Factor Reviews 26 (2015) 615–623

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Mini review

The IL-33/ST2 axis: Role in health and disease

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ARTICLE INFO

Article history:
Received 7 July 2015
Accepted 17 July 2015
Available online 28 July 2015

Keywords:
IL-33
ST2
Autoimmunity
Inflammatory bowel diseases
Table of contents

ABSTRACT

IL-33, an IL-1 family member, is expressed by many cell types and can regulate gene transcription. IL-33 is released upon cell necrosis and the precursor form is enzymatically processed, and then drives inflammation as a damage-associated molecular pattern. The IL-33 receptor ST2, encoded by IL1RL1, is expressed as both a membrane-anchored receptor (ST2L) activated by IL-33, and as a soluble variant (sST2) that exhibits anti-inflammatory properties. The IL-33/ST2 axis is involved in the pathogenesis of atopic and autoimmune diseases, cancer, and central nervous system disorders. Here, we review recent findings on the role of the IL-33/ST2 axis in health and disease.

1. Introduction

Interleukin-33 (IL-33), a member of the IL1 cytokine family, is mainly associated with the induction of T-helper type 2 (Th2) immune response through its receptor, ST2 [1]. Several immune cell types express IL-33, such as macrophages and dendritic cells, as do non-immune cells, such as endothelial cells, epithelial cells and fibroblasts [1–4]. IL33 was initially described as a nuclear repressor factor, and later identified as an extracellular ligand for ST2 [1,2]. The ST2 receptor, encoded by the *IL1RL1* gene, is expressed as a ST2L membrane-anchored receptor variant activated by IL-33, and as the soluble variant sST2, which acts as a decoy receptor and has anti-inflammatory properties [5,6].

The IL-33/ST2 axis has been implicated in numerous disease states, including asthma, rheumatoid arthritis and inflammatory bowel diseases [6–8] and, more recently, in cancer and Alzheimer's disease [9,10].

Here, we review the role of IL-33/ST2 system in innate and adaptive immunity and discuss its impact on inflammatory disorders.

2. The dual role of IL-33: a damage-associated molecular pattern (DAMP) and a cytokine

IL-33 was identified in 2003 as a nuclear protein highly expressed in high endothelial venules (HEV) and initially named nuclear factor from HEV (NF-HEV) [2]. Full-length human IL-33 protein has 270 amino acids and contains a homeodomain-like helix-turn-helix in its N-terminus, important for nuclear localization, heterochromatin association and transcriptional repressor activities [2,11]. On the other hand, full-length IL-33 can, through its N-terminal domain (amino acids 66–109), can interact with nuclear factor κB (NF-κB) transcription factor [12] (Fig. 1A). IL-1β enhances the full-length IL-33 binding to the NF-κB p65 subunit in the cytosol and nucleus, thus decreasing transcription factor binding to DNA-response elements and transactivation of target genes, such as tumor necrosis factor-α (TNF-α) and IκBα [12]. Moreover, IL-33-deficient human endothelial cells show altered expression of NF-κB-dependent genes, such as IL-6, and down-regulation of the chemokines RANTES and Fractalkine [13]. Expression of an IL-33 mutant lacking the N-terminal domain needed for nuclear localization demonstrates its role in immune homeostasis *in vivo*, because mice heterozygous for the mutant protein exhibit poor survival, high serum IL-33 levels, and a marked inflammatory and eosinophilic infiltration into various organs [14]. Consistent with these observations, patients with idiopathic pulmonary arterial hypertension (IPAH), characterized by increased circulating levels of cytokines, have lower nuclear IL-33 content in lung endothelial cells than control subjects [13]. Together, these data suggest that nuclear full-length ($IL\text{-}33_{1-270}$) plays a role in homeostasis by

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http://dx.doi.org/10.1016/j.cytogfr.2015.07.017
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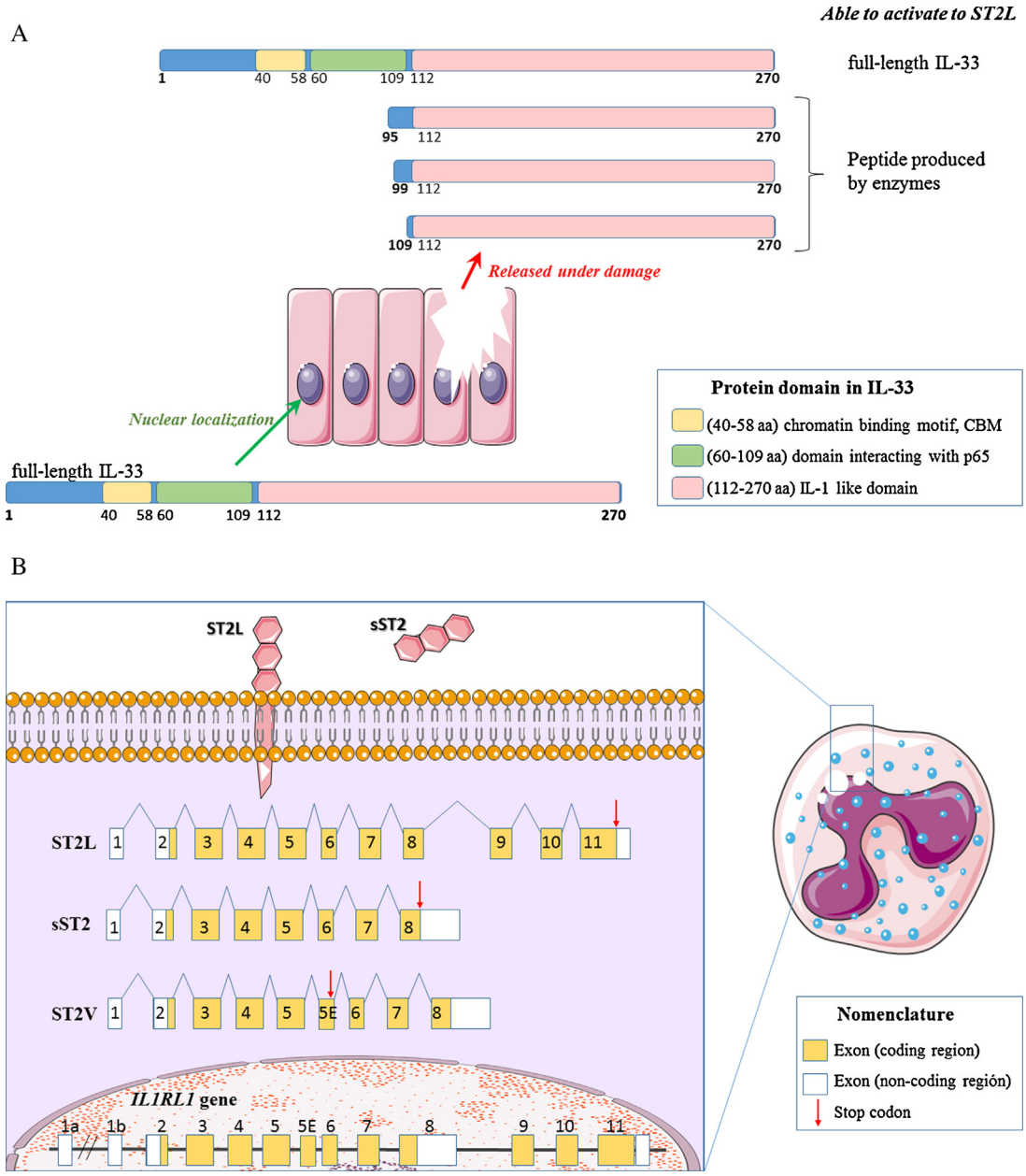

Fig. 1. Variants of IL-33 and its receptor ST2: (A) the full length IL-33 is constitutively expressed and stored in the nucleus of endothelial and epithelial cells. The amino region contains a chromatin binding motif and a domain interacting with p65, while the carboxyl region have an IL-1 like domain. During a cell damage as necrosis, full length IL-33 is released and induce ST2 signaling. Some enzymes associated to neutrophils cleave the IL-33 generating products able to active ST2. (B) ST2 is encoding by the *IL1RL1* gene. In human were identified 3 splicing variants to ST2: ST2L, sST2 and ST2V, but only it was identified in human cell the proteins ST2L and sST2.

modulating cytokine gene expression, although the mechanisms await further investigation.

Initially, experiments using the *in vitro* full-length IL-33 protein suggested that the 30 kDa generated protein is cleaved by caspase-1 leading to a fragment of 18 kDa. Due to this finding, IL-33 was proposed to be expressed as an inactive pro-form (270 amino acids) and, after caspase-1 processing, secreted as a mature-peptide ($IL\text{-}33_{112–270}$) that activates the ST2 receptor [1,15]. Afterwards another group identified a potential caspase-1 cleavage site (DGVD178G) and demonstrated through *in vitro* translation of full-length IL-33 and the mutant $IL\text{-}33_{D178A}$ that the cytokine is processed after residue 178 generating a peptide unable to activate ST2 [16]. In contrast, full-length IL-33 can activate the receptor and proteolysis by caspase-1 may inactivate the cytokine [16]. Altogether, cleavage of IL-33 by caspase-1 *in vitro* could not be reproduced in THP-1 human monocytic cell line [17], suggesting that caspase-1 is not involved in IL-33 processing and further activation. Since full-length IL-33 clearly activates ST2 [17], it has been also proposed to act as an "alarmin", released upon necrotic cellular damage to trigger an inflammatory response similar to that of IL-1α and the high-mobility group box-1 protein (HMGB1) [18]. Indeed, $IL\text{-}33_{1–270}$ was shown to undergo proteolytic cleavage by neutrophil-derived cathepsin G and elastase, and the resulting peptides ($IL\text{-}33_{95–270}$, $IL\text{-}33_{99–270}$ and $IL\text{-}33_{109–270}$) had greater biological activity than did the pro-form $IL\text{-}33_{1–270}$ [19] (Fig. 1A). Overall, the data indicate that IL-33 is a nuclear factor with intracrine functions, where the extracellular form provides a damage-associated signal to the alert the immune system (Table 1).

Table 1
Variants of IL-33 and ST2 in human cells.

Variants	Origin	Function	References
Cytokine/alarmin			
IL-33$_{1-270}$	Pro-form, un-processed	Constitutively expressed and located in the nucleus of endothelial and epithelial cells Associated to heterochromatin, modulating cytokine gene expression Released during necrosis and able to activate ST2L	[13,18,108]
IL-33$_{178-270}$	Cleaved by caspase 1	Peptide generated in vitro, unable to activate ST2 signaling Cleaved and inactivated by caspases in cells undergoing apoptosis	[16]
IL-33$_{95-270}$ IL-33$_{99-270}$ IL-33$_{109-270}$	Processed by neutrophil enzymes (elastase and cathepsin G)	Released IL-33 processed by elastase and cathepsin, amplifying IL-33 bioactivity	[19]
Receptor			
ST2L	Alternative splicing	The membrane-anchored receptor, heterodimerizing with IL-1RAcP in response to IL-33 signaling	[21]
sST2	Alternative splicing	Identical to the ST2L extracellular domain, but with five additional amino acids. Acts as decoy receptor, decreasing IL-33 signaling Serum levels can be considered prognostic markers in diseases	[23,78,109]
ST2V	Alternative splicing	Similar to sST2 but lacking the third extracellular immunoglobulin domain Detected at the mRNA level in human tissues	[24,34]

3. Expression of ST2 isoforms

The ST2 receptor is a type-1 transmembrane protein encoded by the *IL1RL1* gene [5]. ST2 was considered an "orphan" receptor for many years, lacking a specific ligand, until its association with IL-33 was demonstrated [1].

Four ST2 isoforms are generated by alternative splicing (Table 1) (Fig. 1B). These comprise ST2L, corresponding to a membrane-anchored receptor, which is highly homologous to IL-1 type-1 receptors, with extracellular, transmembrane and cytoplasmic domains [20,21]; sST2, a soluble secreted isoform with an extracellular domain identical to ST2L, with 9 and 5 additional amino acids in mice and human, respectively [20,22,23]; ST2V, an isoform similar to sST2 but lacking the third extracellular immunoglobulin domain [24]; and ST2VL, with no transmembrane domain [25]. ST2L is expressed on fibroblasts, mast cells, eosinophils, Th2 lymphocytes, dendritic cells and can be induced in macrophages [23,26–31], while sST2 is expressed by mast cells and fibroblasts [23,32], and is induced by cytokines such as TNF-α in endothelial cells [33]. ST2V mRNA is mainly found in the gut, and its overexpression in cell lines results in a restricted membrane localization [34]. ST2LV has been described in *Gallus gallus* [25] but not yet in humans.

IL1RL1 gene expression is regulated by a distal and proximal promoter that govern ST2L and sST2 variant expression in human cells [35]. GATA1/2 and estrogen-response elements have been identified in the promoter and can modulate ST2 variant expression [23,36]. Different polymorphisms in the promoter region have been associated with inflammatory disorders, for example, −226999G/A single nucleotide polymorphism (SNP) in atopic dermatitis [37].

4. IL-33/ST2 signaling

IL-33 can induce different inflammatory responses depending on the cell type (Fig. 2). Unlike Th1 cells, Th2 cells express ST2L, and exposure to IL-33 induces IL-5 and IL-13 secretion [1,38]. Mast cells treated with IL-33 produce IL-4, IL-5 and IL-6 [39], while primary

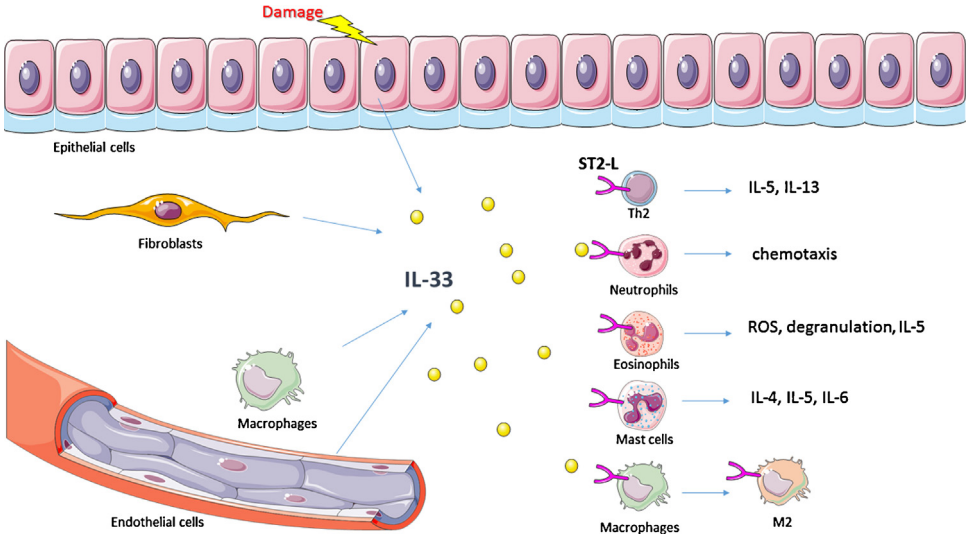

Fig. 2. Role of IL-33 signaling in the mucosa immune response. Tissue damage leads to the release of IL-33 from epithelial cells, fibroblasts, macrophages and/or endothelial cells. IL-33 can induce T helper 2 (Th2) cell activation, cytokine production, and promotes neutrophil migration in an ST2-dependent manner. IL-33 induces reactive oxygen species (ROS) production, degranulation and IL-5 secretion. In mast cells, IL-33 promotes the release of IL-4, IL-5 and IL-6, while macrophages develop an alternatively activated phenotype in response to IL-33.

keratinocytes exposed to IL-33 secrete pro-inflammatory cytokines, such as IL-6 and TNF-α [40]. IL-33 recognition by ST2L promotes receptor dimerization with the IL-1 receptor-accessory protein (IL-1RAcP) which is required as a co-receptor for ligand-induced signaling activation, since IL-1RAcP-deficient mice-derived cells cannot be activated by IL-33 [41].

Different signaling pathways activated by IL-33 have been described (Fig. 3), involving recruitment of MyD88, IL-1R-associated kinase 4 (IRAK4) and TRAF6 to ST2L [1,42]. In mouse embryonic fibroblasts (MEFs), IL-33 induced responses are mediated by p38-, c-Jun N-terminal kinases (JNK) and NF-κB, as well as Erk, in TRAF6-dependent and independent pathways, respectively [42]. Similarly, IL-33 can activate janus kinase 2 (JAK2), which plays an important role in regulating IL-33-induced NF-κB activation, but not p38 and c-JNK activation in murine peritoneal macrophages [43]. Members of the mTOR pathway, such as phosphoinositide-3 kinase (PI3K), can also be activated by IL-33 in Th2 cells, macrophages or eosinophils [44].

IL-33/ST2 signaling is regulated by several mechanisms. One of the most well-studied involves the ability of the sST2 soluble isoform to act as a decoy receptor, sequestering IL-33 and blocking the IL-33-induced pro-inflammatory response in *in vitro* and *in vivo* models [6]. Indeed, in a murine model of allergic inflammation, allergen exposure induced inflammation and high sST2 levels in serum, whereas sST2-pretreated mice showed reduced lung inflammation [45]. Increased sST2 serum levels have been described in several chronic diseases, such as inflammatory bowel diseases, asthma, and chronic heart failure [8,46,47].

An alternative splice transcript of the co-receptor IL-1RAcP encoding a smaller and soluble protein (sIL-1RAcP) lacking the membrane and intracellular domains, has been described [48,49]. The recombinant chimeric sIL-1RAcP-Fc protein decreased the secretion of IL-6 in mast cells exposed to IL-33, and co-incubation with sST2-Fc and sIL-1RAcP-Fc synergistically inhibited IL-33 activity [41], suggesting that sIL-1RAcP also plays a role in modulating IL-33 biological activity.

Another molecule involved in IL-33/ST2 signaling activity is the single Ig IL-1R-related molecule (SIGIRR), a member of the IL-1R-like (ILR) family which is involved in the regulation of IL-18, IL-1 and IL-33 receptor signaling [50]. In Th2 cells exposed to IL-33, SIGIRR dimerization with ST2L negatively regulated IL-33/ST2 signaling [51], through a mechanism that may involve its direct interaction with intermediates of IL-1R family signaling [52], such as assembly of IL-1R and IL1RAcP through its extracellular domain, or by its interaction with MyD88, IRAK and TRAF6, interfering with downstream signaling, or both [52,53].

ST2L signaling in mast cells involves the tyrosine kinase receptor c-Kit which positively regulates IL-33-induced responses [54,55]. Stem cell factor (SCF) is the classical c-Kit ligand and is critical for mast cell growth, maturation and survival [56]. Stimulation of mast cells with SCF is necessary for IL-33-induced IL-6 production through the direct interaction between c-Kit and ST2L [55].

5. Role of the IL-33/ST2 axis in disease

5.1. Airway disorders: asthma and allergy

IL-33 is basally expressed in mouse lung tissue and human small airway epithelial cells, lung fibroblast or bronchial smooth muscle cells [1,28]. There is evidence for higher levels of IL-33 in epithelial cells, airway smooth muscle cells and serum of patients with asthma or allergy compared with healthy controls [57–59].

Mice treated intranasally with IL-33 alone show airway hyper responsiveness, characterized by elevated eosinophil and monocyte numbers in bronchoalveolar lavage fluid, high mRNA levels of IL-4, IL-5 and IL-13 and goblet cell hyperplasia in lungs through an IL-13 dependent mechanism [60]. On the other hand, IL-33 enhances the polarization of alveolar macrophages to an alternatively activated phenotype associated with expression of the mannose receptor (CD206), expression of IL-4Rα and production of high levels of CCL24 and CCL17 in an IL-13-dependent manner *in vitro* and *in vivo* mouse given IL-33 intranasally [28]. On the other hand, IL-33 promotes fibrosis by polarization of alternatively activated macrophages as demonstrated in mice with bleomycin-induced lung fibrosis [61].

Moreover, in a mouse model of acute allergic lung inflammation induced by OVA, mRNA levels of IL-33, ST2L and sST2 are

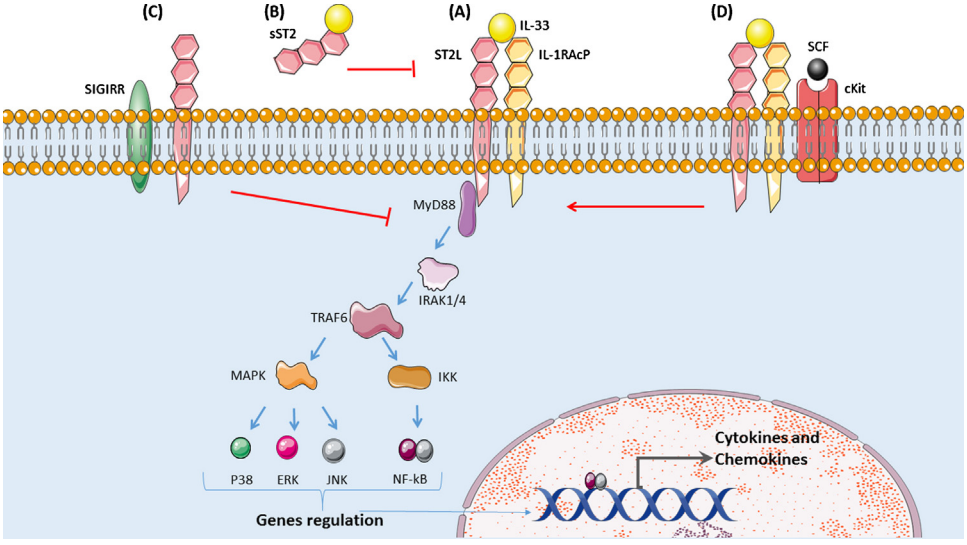

Fig. 3. IL-33/ST2 signaling (A) IL-33 binds to the heterodimer receptor complex consisting of ST2L and IL-1RAcP. This binding leads to recruitment of MyD88 through its TIR domain and to downstream activation of TRAF6, thus further activating NF-κB and mitogen-activated protein kinases p38, ERK, and JNK, all of which are strong inducers of pro-inflammatory cytokine and chemokine secretion. (B) The sST2 variant comprises the extracellular domain of ST2L and has the same ability to bind IL-33, decreasing the molecule availability for ST2L activation. (C) SIGIRR can dimerize with ST2L to negatively regulate the IL33/ST2 signaling pathway. (D) In mast cells, the tyrosine kinase receptor c-Kit acts as a positive regulator of IL33-induced signaling.

significantly increased in the lung [62], along with Th2 cytokines, such as IL-5 and IL-13, and strong eosinophil infiltration, and IL-33-deficiency results in milder lung pathology and decreased levels of Th2 cytokines [62].

Similarly, pretreatment of mice with sST2 reduced the production of pro-inflammatory cytokines in the OVA model of allergic airway disease [6,45].

Furthermore, in mice sensitized by intranasal co-administration of *Alternaria alternata* extracts and OVA, there is a rapid innate immune response reflected by eosinophilia, activation of type 2 innate lymphoid cells (ILC2s), early IL-33 production and a late Th2 response upon re-administration of OVA alone [63]. Interestingly, soluble excretory/secretory products of the nematode *Heligmosomoides polygyrus* (HES), which typically inhibit Th2-related allergy as well as colitis and autoimmunity, potently suppressed inflammation induced by *Alternaria*/OVA, including the high levels of IL-33 secretion [63]. However, the administration of recombinant IL-33 at sensitization together with *Alternaria*/OVA/HES abrogated HES suppression of OVA-specific responses, suggesting a central role of IL-33 in allergy [63].

These antecedents demonstrate that IL-33 promotes a Th2-type response in inflammatory processes in lung pathologies.

5.2. Inflammatory bowel diseases

The inflammatory bowel diseases (IBD), comprising mainly ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory pathologies that affect the gastrointestinal tract. The etiology of both IBD is associated with a diversity of genetic, environmental and immunologic factors [64]. Although some years ago it was considered that Crohn's disease (CD) was a Th1 disease and ulcerative colitis (UC) was an atypical Th2 disease [65], today this paradigm have been questioned, identifying similar high levels of IFN-γ and IL-17 and lower levels of IL-13 in UC and CD [66,67]. High IL-33 and ST2L/sST2 levels have been found in intestinal samples and serum from UC patients compared to controls and CD patients [8,68]. Biological therapy with infliximab decreased circulating IL-33 and increased sST2 in UC patients [68], suggesting that modulation of the IL-33/ST2 system involves TNF-α signaling. Immunohistochemical analyses of intestinal tissue from UC patients showed that a major source of IL-33 was ulceration-associated myofibroblasts, which are typically associated with wound healing [4]. Similar to that observed in patients, the IL-33 expression is elevated in colon of murine colitis model using irritant agents such as trinitrobenzene sulphonic acid (TNBS) and dextran sodium sulphate (DSS) [69].

DSS-induced colitis in IL-33$^{-/-}$ mice showed significantly decreased mortality, inflammation, and myeloperoxidase activity until day 8 of colitis compared to wild-type (WT) animals. However, after 12 days of colitis, inflammation is similar in IL-33$^{-/-}$ and WT mice, suggesting that the IL-33/ST2 is involved in the induction of early stage of inflammation in this model [70]. In the same way, ST2-deficient mice showed reduced signs of intestinal inflammation in TNBS- and DSS-induced colitis compared to WT animals [69]. Experiments with bone-marrow chimaera mice demonstrated that ST2 deficiency in non-hematopoietic cells is sufficient to decrease the signs of colitis, suggesting that the reduced inflammation in ST2 deficient mice might reflect sustained intestinal barrier function [69].

Two murine colitis models, one induced by DSS treatment or the IL-10 deficient mice, showed increased colonic IL-33 levels that correlate with colitis score and induction of GATA-3, a master regulator gene of Th2 differentiation, in T cells from intestinal tissue [71].

Expression of ST2 was recently documented in FOXP$_3^+$-regulatory T cells (Tregs) from colonic tissue of mice, but not in cells from spleen or mesenteric lymph node. Moreover IL-33 regulates GATA3-mediated proliferation and induction of *Foxp3* in Tregs [72]. In C57BL/6 *Rag1*$^{-/-}$ mice injected with naive T cells from ST2-deficient mice showed reduced Treg numbers compared to those from WT mice [72]. Furthermore, IL-23, a cytokine associated with pro-inflammatory responses in IBD, inhibited ST2 expression in Tregs and its IL-33-mediated regulatory response [72].

All these data demonstrate that the role of IL-33/ST2 in IBD is still unclear. Studies with animal models showed a participation of innate and adaptive immunity. Moreover, this pathway has been implicated not only in inflammation, but also in intestinal homeostasis. On the other hand, mouse models of colitis are confounded by the fact thatb they are usually acute and do not reflect the chronic inflammation seen in IBD patients [73].

5.3. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a multifactorial condition characterized by synovial inflammation, with infiltration of inflammatory cells into the joint and hyperplasia of synovial fibroblasts [74]. Interestingly, the CC genotype of rs7044343 in IL-33 has been associated with lower serum IL-33 levels and a decreased disease risk [75]. Evidence that IL-33 contributes to RA is suggested by higher IL-33 levels in synovial fluid of patients with RA than in those with osteoarthritis, and an association of IL-33 levels in synovial fluid with disease activity [76].

The mouse model of RA, based on the injection into the knee joint of methylated-bovine serum albumin, induces neutrophil migration that is inhibited by pre-treatment with intra-peritoneal and intra-articular sST2 injection [7]. IL-33 injection into the knee can mimic the neutrophil migration observed in this RA model, mediated by the induction of cytokines and chemokines, such as TNF-α, CXCL1 or CCL3. Furthermore, IL-33 can directly attract neutrophils expressing ST2L [7]. IL-33 added to synovial fibroblasts from patients with rheumatoid arthritis enhances TNF-α-induced synthesis of the pro-inflammatory molecules IL-6 and IL-8, and of matrix metalloproteinase-3 [77]. In collagen-induced arthritis in mice, administration of anti-ST2 neutralizing antibody at the onset of disease reduces joint destruction and decreases levels of pro-inflammatory cytokines such as IFN-γ and IL-17 [78]. The activation of the ST2/IL-33 axis contributes to the development and severity of rheumatoid arthritis, recruitment of inflammatory cells to the joint and induction of an inflammatory circle.

5.4. Cancer

There is abundant evidence indicates that cytokines contribute to carcinogenesis, and have pro- or anti-tumor roles depending on the balance of different inflammatory mediators and the stage of tumor development [79]. High ST2 and IL-33 mRNA levels have been identified in colonic adenomas and carcinomas compared to normal tissue [9], and higher expression has been described in poorly differentiated human colorectal carcinoma cells [80]. In addition, high IL-33 serum levels have been identified in patients with lung, gastric and hepatocellular carcinoma [81,82], and high sST2 serum levels have been detected in patients with breast cancer and hepatocellular carcinoma [83,84]. There may be an association between IL-33 serum levels and progression or stage of a number of cancers [82], suggesting that IL-33 and ST2 may be used as prognostic marker of disease.

The role of the IL-33/ST2 signaling pathway has been also evaluated in animal models of cancer. In the mouse 4T1 model of breast cancer, intraperitoneal administration of IL-33 increased lung and liver metastases and was associated with increased intra-tumor accumulation of myeloid-derived suppressor cells

expressing TGFβ, increased FOXP3$^+$ Treg and fewer natural killer (NK) cells [85]. Using ST2-deficient mice, a reduction was shown in tumor progression and metastasis as compared to WT mice was accompanied by increased numbers of intra-tumor CD4$^+$, CD8$^+$ T lymphocytes and NK cells [86]. Similarly, inhibition of IL-33 using a lentivirus-mediated gene knockdown in a rat model of glioma attenuated tumor progression [87]. On the other hand, IL-33 may be involved in promoting the epithelial-mesenchymal transition which drives tumor invasion and migration [88]. Overall, the data suggest a pro-tumorigenic role for IL-33/ST2 signaling, associated to maintenance of an immunosuppressive tumor microenvironment and promoting a metastatic phenotype.

5.5. Skin disorders: atopic dermatitis, psoriasis and vitiligo

IL-33 is expressed in healthy skin, predominantly as the full-length precursor [89,90], and skin cells exposed to inflammatory cytokines, infectious agents such as *Staphylococcus aureus,* or UVB radiation, produce high levels of IL-33 mRNA [89,91]. In a *S. aureus* infection model in mouse skin, high levels of IL-33 were produced by macrophages that subsequently induced an antimicrobial state through nitric oxide generation [89]. On the other hand, in human skin explants exposed to UVB radiation there was induction of IL-33 expression by keratinocytes and fibroblasts, suggesting that IL-33-producing fibroblasts may promote an innate immune response by recruitment of neutrophils and mast cells [91].

The IL-33/ST2 signaling pathway has also been associated with chronic skin diseases pathologies, such as atopic dermatitis (AD), psoriasis and vitiligo. Atopic dermatitis is a chronic inflammatory skin disease characterized by eczema, pruritus, relapsing and frequently predates the development of allergic rhinitis or asthma [92,93]. Patients with AD show a Th2 response to allergens with elevated IgE and eosinophilia in the skin lesions and blood [92,93]. Two SNPs in the distal *IL1RL1* promoter, rs6543115(C) and rs6543116(A), are associated with high risk of AD. Patients with these polymorphisms have higher serum sST2 levels compared to controls [37]. Skin lesions from AD patients contain higher IL-33 and ST2 transcripts than healthy skin [94]. Serum IL-33 levels in AD patients are significantly higher than in healthy individuals or in patients with other skin disorders, such as urticaria or psoriasis; IL-33 levels also correlated with excoriation and xerosis scores in AD [95].

Psoriasis is an immune-mediated disorder characterized by squamous skin lesions [96]. Unlike AD, psoriasis shows a predominance of Th1 and Th17 family cytokines, such as IFN-γ and IL-17 and IL-22 in psoriatic plaques [96,97]. Psoriatic skin shows increased expression of IL-33 mRNA and protein, and IL-33 secreted by keratinocytes reportedly increases substance P-induced vascular endothelial growth factor (VEGF) secretion by mast cells in psoriasis [98]. Although local lesions reveal an increase in IL-33, no alterations in the blood have been seen [95].

An alteration in the IL-33/ST2 system was recently described in vitiligo [40], a skin pigmentation disorder characterized by progressive disappearance of melanocytes and increased pro-inflammatory cytokines [99]. Immunofluorescence of skin sections from vitiligo patients reveals increased expression of IL-33 and ST2 in lesional skin, with IL-33 localized only in the cytoplasmic and not in the nucleus, as is seen in normal skin [40].

Thus, studies to date demonstrate the involvement of IL-33/ST2 in skin immunity and in chronic skin pathologies of different etiology. A better understanding of the role of this pathway in different disorders is needed to evaluate its potential for targeted therapy.

5.6. Central nervous system inflammation

IL-33 and ST2 are expressed ubiquitously in nerves, including in brain tissue [1,100]. A search for the role of the IL-33/ST2 system in the central nervous system (CNS) in murine CNS-derived cells showed that endothelial cells and astrocytes express IL-33, while microglia and astrocytes express ST2L and IL-1RAcP, and endothelial cells, microglia and astrocytes express sST2 [101]. Glial cells, the non-neuronal cells in CNS which includes astrocytes, oligodendrocytes and microglia, when exposed to IL-33, express arginase-I, eotaxin-1, TNF-α and IL-6 [102]. Microglia, a CNS immune cell similar to peripheral macrophages, respond to IL-33 with high production of pro-inflammatory cytokines, chemokines and oxidative stress molecules [101].

The IL-33/ST2 system reportedly plays an important role in CNS disorders such as Alzheimer's disease or multiple sclerosis [103,104]. Alzheimer's disease is the most common form of dementia characterized by extracellular deposits known as amyloid plaques (APs) and by intracellular tau-based neurofibrillary tangles (NFTs) [105]. Three SNPs with minor allele frequency in the IL-33 gene have been associated with a reduced risk of AD and have defined an protective haplotype among non-*APOE*ε4 carriers [10]. Moreover, this work described a reduction of IL-33 in the brain of AD patients that was related to a protective role of IL-33 in the disease pathogenesis. However, a later study shown elevated expression of IL-33 and ST2 in the vicinity of APs and NFTs and the exposure of mouse primary astrocytes to β-amyloid peptide induced IL-33 expression [103], suggesting a role for IL-33/ST2 in AD pathogenesis. All these data made necessary to deepen in the role of IL-33 in the AD pathogenesis.

Multiple sclerosis is the most common inflammatory demyelinating disease of the CNS, in which auto-reactive T lymphocytes appear to be crucial in the development of demyelinating lesions [106]. Relapsing–remitting multiple sclerosis patients have elevated levels of IL-33 in plasma and brain compared to controls [104]. In experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis, ST2 expression is greatly increased in the spinal cords compared to control mice [107]. Moreover, EAE mice treated with exogenous IL-33 developed milder disease, which is consistent with the exacerbation of EAE in ST2-deficient mice compared to WT mice [107]. The protective effect of IL-33 is related to decreased IL-17 levels, predominance of Th2 cytokines and polarization of anti-inflammatory M2 macrophages in spleen and lymph nodes [107].

The immune response in brain disorders as AD and multiple sclerosis is an area of study that needs be reinforced. In particular, the studies of IL-33/ST2 axis suggest that this pathway as an attractive therapeutic target.

6. Conclusions

The IL-33/ST2 signaling has emerged as a pathway with a central role in processes of the immune response, homeostasis and tissue injury/repair. IL-33 exerts different functions depending on subcellular localization, proteolytic cleavage and cell target. Furthermore, the IL-33/ST2 system has been linked with various immune-associated disorders, including inflammatory diseases with a Th-1 or Th-2 profile, cardiovascular diseases and cancer. Eventually, it must to be emphasized that all the information on inhibition of ST2 or IL-33 for the treatment of inflammation derive from animal models or *in vitro* cell culture have to be clarified in man because the mechanisms involved in experimental inflammation are not necessarily the same as in human inflammatory processes. However, in many inflammatory disorders such as IBD, rheumatoid arthritis or AD, the altered levels of IL33 and ST2 variants in periphery and tissue related encourage us to deep

in the role of this inflammatory system in these processes. Moreover, the need to find a tool to specifically counteract the main ST2 variants will shed light on the role of the IL-33/ST2 signaling pathway in chronic inflammatory diseases.

Acknowledgments

CONICYT130037,FONDECYT1120577 (MH), FONDECYT3150328 (MKDLF). The figures were produced using Servier Medical Art from www.servier.com.

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