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Review

ST2 and the ST2/IL-33 signalling pathway–biochemistry and pathophysiology in animal models and humans

Irene Pusceddu[a], Benjamin Dieplinger[b], Thomas Mueller[a,*]

[a] Department of Clinical Pathology, Hospital of Bolzano, Bolzano, Italy
[b] Department of Laboratory Medicine, Konventhospital Barmherzige Brueder Linz, Linz, Austria

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ABSTRACT

ST2 is an interleukin (IL)-1 receptor family member with transmembrane (ST2L) and soluble (sST2) isoforms. Structurally, the ST2 gene products are very similar in mice and humans. In humans and in mice, alternative promoter activation and splicing produce ST2L and sST2. ST2L represents the longest transcript, whereas sST2 is the truncated, soluble isoform. ST2L is the biological receptor for IL-33, a member of the IL-1 family. IL-33 is the functional ligand of ST2L and signals the presence of tissue damage to local immune cells. IL-33/ST2L signalling leads to the production of inflammatory cytokines/chemokines and to the induction of the immune response. Conversely, sST2 functions as a decoy receptor for IL-33, inhibiting the effects of IL-33/ST2L signalling. Animal studies have allowed the investigation of ST2 and the IL-33/ST2L signalling pathway at multiple levels. However, clinical studies have mainly focused on the determination of sST2 in the circulation. In humans, plasma concentrations of sST2 increase in several diseases, such as heart disease, pulmonary disease, burn injury and graft-versus-host disease. Consequently, increased plasma concentrations of sST2 are not specific for a single disorder in humans and are thus of limited value for diagnostic purposes. However, increased plasma concentrations of sST2 have been linked to a worse prognosis in numerous diseases. Nevertheless, the major source of circulating sST2 in healthy and diseased humans is currently not fully established. In addition, whether the downregulation of sST2 can improve the outcome of patients in the clinical setting has not been elucidated. The aim of the present review was to provide an update on the findings regarding the biochemistry and pathophysiology of ST2 and the sST2 signalling pathway in humans and experimental models.

1. Introduction

The protein “interleukin-1 receptor-like 1” (alternative name: protein ST2) is a member of the interleukin (IL)-1 receptor family with transmembrane (ST2L) and soluble (sST2) isoforms [1–3]. As described later in this review, the human ST2 gene is located on chromosome 2, and through alternative promotor splicing, it encodes the different isoforms. In 1989, the protein ST2 was discovered by two independent research groups [1] but remained an orphan receptor until 2005, when Schmitz et al. identified IL-33 as the natural ligand of ST2 [4]. IL-33 is an interleukin-1-like cytokine secreted by living cells in response to cell damage. IL-33 functions as a danger signal or an alarmin by signalling the presence of tissue damage to local immune cells after exposure to pathogens, injury-induced stress, or death by necrosis [3]. Once secreted, IL-33 binds the ST2L receptor, and IL-33/ST2L signalling leads to inflammatory gene transcription and ultimately to the production of inflammatory cytokines/chemokines and an immune response [5,6]. sST2 avidly binds to IL-33 in competition with ST2L and thus functions as a decoy receptor for IL-33. Therefore, the interaction of sST2 with IL-33 blocks the IL-33/ST2L system [7]. These key points are illustrated in Fig. 1 (adopted from reference [7]).

The purpose of this in-depth review was to report the biochemistry of the ST2/IL-33 pathway (including structure, expression and function) in animal models and humans, thereby evaluating the concordance/discordance of the findings in humans and experimental models. Another purpose of this review was to highlight the pathophysiology of sST2 with specific examples. Thus, we described the role of sST2 in heart disease, pulmonary disease, burn injury and graft-

Abbreviations: ERK, extracellular signal-regulated kinase; IL, interleukin; IL-1RAcP, IL-1 receptor accessory protein; IRAK, IL-1R-associated kinase; MAPK, mitogen-activated protein kinase; MyD88, myeloid differentiation primary response protein 88; NF-kB, nuclear factor ‘kappa-light-chain-enhancer’ of activated B-cells; sST2, soluble isoform of ST2; ST2L, transmembrane isoform ST2; ST2V, ST2 variant; TIR, Toll-IL-1 receptor; TNF-α, tumour necrosis factor-α; TRAF-6, TNF receptor-associated factor 6

* Corresponding author at: Department of Clinical Pathology, Hospital of Bolzano, Via Lorenz Boehler 5, 39100 Bolzano, Italy.
E-mail address: thomas.mueller@sabes.it (T. Mueller).

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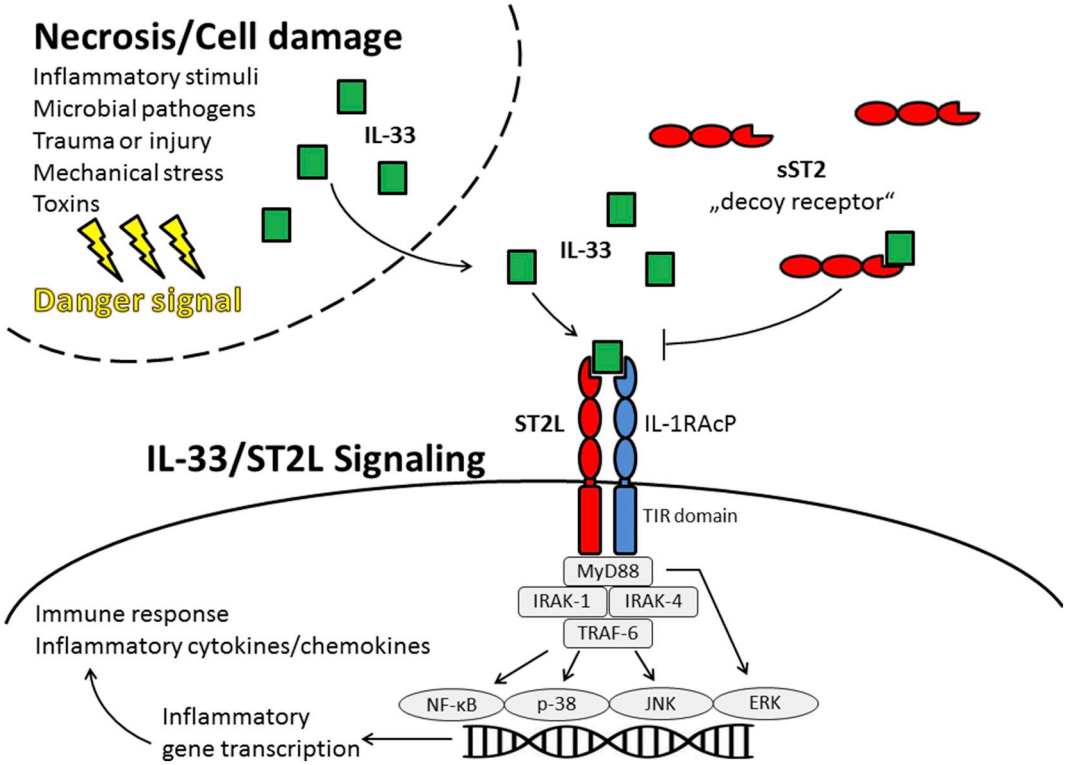

Fig. 1. Interleukin-33/ST2L signalling and the function of sST2.
Damage to stromal cells can induce necrosis and release of full-length IL-33 (active IL-33), which can activate the heterodimeric ST2L/IL-1RAcP complex on a variety of immune cells or can be neutralized by sST2, which acts as a "decoy" receptor for IL-33. Activation of the ST2L/IL-1RAcP complex induces signalling through the Toll-IL-1 receptor domain. Through activation of diverse intracellular kinases and factors, this process leads to inflammatory gene transcription and ultimately to the production of inflammatory cytokines/chemokines and an adequate immune response.
Abbreviations: IL-1RAcP: IL-1 receptor accessory protein; IRAK: IL-1R-associated kinase; JNK: JUN N-terminal kinase; MyD88: Myeloid differentiation primary response protein 88; sST2: Soluble isoform of ST2; ST2L: Transmembrane isoform ST2; TIR: Toll-IL-1 receptor; TRAF-6: TNF receptor-associated factor 6
Adopted with permission from reference [7].

versus-host disease.

2. Biochemistry

2.1. ST2

2.1.1. Structure in animals and humans

2.1.1.1. Studies in animal models. In *Mus musculus,* ST2 is encoded by a gene located on chromosome 1 (Gene ID: 17082, https://www.ncbi.nlm.nih.gov/gene/17082, last access 04/16/2019). Depending on the cell type, the gene produces at least two variants through alternative promoter activation and splicing [8]. Variant 1 represents the longest transcript and encodes the full-length transmembrane isoform of ST2, which is composed of an extracellular domain characterized by three immunoglobulin/like motifs, a transmembrane domain and an intracellular Toll-IL-1 receptor (TIR) domain [9]. The second variant is shorter than variant 1, has a distinct C-terminus, lacks several exons, and encodes the sST2 isoform. The sST2 structure is identical to the extracellular region of the long ST2 isoform except for nine additional amino acids localized at the C-terminus of the molecule [10].

2.1.1.2. Studies in humans. The human ST2 gene is localized on chromosome 2 (Gene ID: 9173, https://www.ncbi.nlm.nih.gov/gene/9173, last access 04/16/2019), and through alternative promotor splicing, it encodes at least three isoforms [3,11]. The transcription of ST2L and sST2 is under the control of two distinct promoters that are 25.4 kb apart from each other (the proximal and distal promoters, respectively), resulting in a 3′ coding region and 3′ untranslated region [12]. Variant 1 (ST2L) represents the longest transcript and encodes the full-length transmembrane isoform. Variant 2 (sST2) is shorter than variant 1, has an alternate 5′ exon, lacks several 3′ terminal exons, and has a distinct C-terminus. Variant 3 (ST2V) has distinct 5′ and 3′ untranslated regions and shorter N- and C-termini. In this isoform, alternative splicing inserts a new exon, resulting in the gain of a new hydrophobic tail and in the lack of the third immunoglobulin-like domain of ST2L [13].

As previously described, the IL1RL1 gene (synonyms: DER4, ST2, T1) for the protein "interleukin-1 receptor-like 1" (alternative name: protein ST2) is found on human chromosome 2 and plays a major role in immune and inflammatory responses. Further details for the protein "interleukin-1 receptor-like 1" and its structure (including the crystal structure of IL-33 in complex with the ectodomain of ST2) can be found on the "Universal Protein Resource" (UniProt, https://www.uniprot.org/uniprot/Q01638, last access 04/16/2019). Of note, this protein ST2 should not be confused with "suppression of tumourigenicity 2" also called ST2 (Gene ID: 6761, https://www.ncbi.nlm.nih.gov/gene/6761, last access 04/16/2019), which is a different gene on chromosome 11, a region that represents a putative locus associated with various forms of cancer.

2.1.2. Expression in animals and humans

2.1.2.1. Studies in animal models. In mice, ST2 gene expression was detected from embryonic day 14 and continued after birth in haematopoietic tissues. In contrast, in non-haematopoietic cells, the expression of the ST2 gene was observed only in the embryo [14]. ST2L is selectively expressed by T helper 2 cells [15] and T regulatory cells [16] but not by T helper 1 cells [17]. This expression is independent of induction by IL-4, IL-5, or IL-10 [16]. In T helper 2 cells [18] and T

regulatory cells [16], ST2L is induced by IL-33 through activation and recruitment of GATA3. ST2L is also expressed by several other cell types, such as neonatal rat cardiac myocytes induced by mechanical strain [2]; mouse left ventricular tissue and thymus after myocardial infarction; and mouse spleen, lung, atrium and liver [2].

2.1.2.2. Studies in humans. In humans, ST2L is expressed by several tissues, including the colon [19], endothelium [20], and a wide variety of haematopoietic cells [21], such as basophiles [22], CD4 lymphocytes [23], eosinophils [24], macrophages [20], and T helper 2 cells [25]. ST2L was also identified after stimulation with IL-33 in keratinocytes [26] and eosinophils [24]. The third variant of the ST2 gene, ST2V, was described in a human leukaemic cell line; in human helper T cell clones [27]; and on the cell surface of the stomach, small intestine and colon [11].

2.1.3. Function in animals and humans (the IL-33/ST2L signalling pathway)

2.1.3.1. Studies in animal models. Once secreted, IL-33 binds the ST2L receptor that forms a heterodimer with the IL-1 receptor accessory protein (IL-1RAcP) [28], leading to the dimerization of the TIR domain. This configuration induces the recruitment of the TIR domain that binds myeloid differentiation primary response protein 88 (MyD88); in turn, MyD88 induces the activation of IL-1R-associated kinase (IRAK), which activates mitogen-activated protein kinase (MAPK) and nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NF-kB) pathways [5,29]. When the MAPK or NF-kB signalling pathways are preferentially activated remains unclear. However, the NF-kB pathway requires the activation of TNF receptor-associated factor 6 (TRAF6), which is not necessary for the extracellular signal-regulated kinase (ERK) signalling pathway [30]. Mice treated for one week with IL-33 developed splenomegaly; anatomical changes in the stomach; histological changes in the lung, oesophagus, small intestine and vascular lumen; increased blood eosinophils and lymphocytes; and higher serum concentrations of immunoglobulin A, immunoglobulin E, IL-5 and IL-13 [5,29].

2.1.3.2. Studies in humans. Nuclear magnetic resonance and small-angle X-ray scattering analyses on purified fusion proteins of recombinant human IL-33 and ST2 revealed that IL-33 binds its primary receptor ST2L in a 1:1 stoichiometry and needs to recruit a second distinct co-receptor to form the bioactive 1:1:1 heterotrimeric complex [31]. IL-1RAcP is the main co-receptor that mainly interacts with Ig repeats D1 and D3 of ST2L [31]. In vitro human mast cells respond to IL-33 signalling by releasing inflammatory cytokines and expressing ST2L and sST2 [32]. The investigation of the IL-33/ST2L signalling pathway in humans is limited to a few studies as ST2L is a cell surface protein that is activated only upon binding with IL-33. The analyses of the molecular downstream effectors of this signalling pathway were investigated in only in vitro studies and not in vivo, probably due to the lower availability of tissue samples in humans. To our knowledge, there is no evidence for a specific role of ST2V. Its expression has been reported on the plasma membrane of the stomach, small intestine, and colon, suggesting a possible role in modification of the ST2L signalling pathways [13].

2.2. sST2

2.2.1. Structure in animals and humans

2.2.1.1. Studies in animal models. The soluble form of ST2 is identical to the extracellular region of the long ST2 isoform except for nine additional amino acids, which are present at the C-terminus of the molecule [9]. More details are reported in Section 2.1.1 in this review.

2.2.1.2. Studies in humans. The soluble form of ST2 is identical to the extracellular region of the long ST2 isoform except for five additional amino acids, which are present at the C-terminus of the molecule [33]. Soluble ST2 is composed of 328 amino acids (UniProt, https://www.uniprot.org/uniprot/Q01638, last access 04/16/2019). More details are reported in Section 2.1.1 in this review.

2.2.2. Expression in animals and humans

2.2.2.1. Studies in animal models. The expression of sST2 is induced by mechanical strain in neonatal rat cardiac myocytes [31]. However, mechanical deformation can also regulate NOS expression as a direct consequence of an inflammatory process [2,34]. sST2 expression is induced by IL-1β but not by other factors, such as angiotensin II, hydrogen peroxide, IL-4 and lipopolysaccharide [2]. Mouse bone marrow-derived mast cells constitutively express sST2 mRNA, which is highly expressed after stimulation with IL-33 [32].

2.2.2.2. Studies in humans. In humans, sST2 can be produced spontaneously in the lung, kidney, heart, and small intestine [35] and after activation with IL-33 in mast cells [32] or with anti-CD3/anti-CD28 in both CD4 and CD8 T cells [36]. The expression of sST2 has mainly been investigated in individuals with diseases rather than in healthy people.

2.2.3. Function in animals and humans

2.2.3.1. Studies in animal models. The function of sST2 was investigated in murine cells cultured in vitro, mouse models treated with sST2 and sST2 transgenic mice models. The in vitro treatment of murine thymoma cells stably expressing ST2L with sST2 impairs the activation of NF-kB as a consequence of the suppression of the IL-33/ST2 signalling pathway [37].

ST2−/− mice, lacking both ST2L and sST2, develop normally, although they are deficient in T helper 2 cytokine responses and are characterized by increased cardiac fibrosis, increased hypertrophy, impaired systolic function, increased left ventricular dilation, increased natriuretic peptide production and higher mortality compared to those in wild-type mice [38]. Treatment of these mice with IL-33 rescued these phenotypes in wild-type mice but not in ST2−/− mice [38].

Compared with control mice, sST2 transgenic mice, which constitutively express sST2 in virtually all tissues, do not exhibit differences in mortality or IL-6 and tumour necrosis factor-α (TNF-α) secretion when treated with lipopolysaccharide [29]. However, when the same transgenic mouse model is induced with pristine, they are not protected from the development of arthritis [29]. These differences could be attributed to activation of different pathways by lipopolysaccharide and pristine. In addition, the administration of IL-33 in these transgenic mice was not accompanied by increased production of typical cytokines (IL-4, IL-5, IL-6, and IL-13) compared to that in wild-type mice [29].

In addition to this canonical action, based on recent research, sST2 may have actions of its own in certain cell types. For example, previous work analysing rat aortic vascular smooth muscle cells determined that the stimulation of these cells with sST2 can increase the expression of collagen type I, fibronectin, and different pro-fibrotic factors, such as transforming growth factor beta and connective tissue growth factor, thus modulating extracellular matrix remodelling and turnover [39].

Taken together, these studies indicate that sST2 acts as a negative regulator of T helper 2 cytokine production through IL-33 signalling. As sST2 modulates the T helper 2 cell-mediated immune responses, sST2 may act as a therapeutic agent. However, whether chronic over-expression of sST2 may cause any harmful effects is unknown.

2.2.3.2. Studies in humans. The molecular function of sST2 was predominantly analysed in animal models, and its role in humans was investigated mainly in clinical settings. In addition to environmental factors and diseases, serum concentrations of sST2 seem to be regulated by genetic factors for up to 40% of inter-individual variability [40]. In a genome-wide association study conducted on 2991 subjects of the Framingham Offspring Cohort study, multiple single nucleotide

polymorphisms within the ST2 gene were associated with sST2 concentrations. For example, the five missense variants (rs6749114, rs4988956, rs10204137, rs10192157, and rs10206753) associated with increased sST2 concentrations were located within the TIR domain of the transmembrane ST2 receptor and are not part of the circulating sST2 protein [40].

2.3. IL-33

2.3.1. Structure in animals and humans

2.3.1.1. Studies in animal models. The murine IL-33 gene is located on chromosome 19 (Gene ID: 77125, https://www.ncbi.nlm.nih.gov/gene/77125, last access 04/16/2019) [38] and encodes a 266 amino acid polypeptide, corresponding to a full-length protein of 29.9 kilodaltons (UniProt, www.uniprot.org/uniprot/Q8BVZ5, last access 04/16/2019) [5]. Unlike other members of the IL-1 family, IL-33 is efficiently cleaved by apoptosis-associated caspases (caspase 3 and 7) but not by inflammatory caspases (caspase 1, 4 and 5). Cleavage by caspases occurs in a motif that is fully conserved between humans and mice. In mice, this site is located after Asp175 [41]. This cleavage is not required for ST2L binding but increases the susceptibility of IL-33 to degradation.

2.3.1.2. Studies in humans. In humans, IL-33 is encoded by a gene located on chromosome 9 (Gene ID: 90865, https://www.ncbi.nlm.nih.gov/gene/90865, last access 04/16/2019) [38]. The full-length protein is composed of 270 amino acids and has a mass of 30.8 kilodaltons (UniProt, www.uniprot.org/uniprot/O95760, last access 04/16/2019) [4]. The inactive form is produced by cleavage by caspase 3 and 7 at the IL-1 cytokine domain located after Asp 178 and induces cell apoptosis [42]. This inactivation by caspases is thought to alleviate the immune response [42]. IL-33 acts as a regulator of transcription. This protein moves into the nucleus due to the presence of a nuclear localization sequence, undergoes ubiquitination and associates with heterochromatin to regulate gene expression. IL-33 can also be cleaved by extracellular proteases, including cathepsin G and elastase, at the activation domain, increasing the biological activity of cleaved IL-33 by 10 to 30 times compared to that of full-length IL-33 [43]. During stress, IL-33 is released in either the full-length or cleaved form.

2.3.2. Expression in animals and humans

2.3.2.1. Studies in animal models. In mice, high concentrations of IL-33 mRNA have been found in the stomach, lung, spinal cord, brain and skin [4]. Lower concentrations were observed in lymph tissue, spleen, pancreas, kidney and heart [4]. Sanada et al. analysed rat neonatal hearts and found that IL-33 was expressed by cardiac fibroblasts and cardiomyocytes after binding to ST2L [38].

2.3.2.2. Studies in humans. Schmitz et al. analysed a panel of human cDNA libraries and identified high concentrations of IL-33 mRNA in smooth muscle cells of various tissues, such as bronchial, pulmonary artery and coronary artery, as well as epithelial cells of mammary tissue, kidney, bronchium and lung airway [4]. IL-33 in humans is also highly expressed by mesangial cells [4]; cardiac fibroblasts and myocytes [44]; and stromal cells such as endothelial cells, epithelial cells, and fibroblasts [45–47]. Lower concentrations were observed in lymph tissue, spleen, pancreas, kidney and heart [4]. In contrast, in primary lung or dermal fibroblasts and keratinocytes, IL-33 gene expression was induced only after activation with TNF-α and IL-1β [4]. The only haematopoietic cells that can express IL-33 at low concentrations in humans are activated dendritic cells and macrophages [4].

2.3.3. Function in animals and humans (independent of ST2)

2.3.3.1. Studies in animal models. The nuclear localization of IL-33 was identified only in mouse 3 T3 fibroblasts [47]. IL-33 is localized to pericentromeric heterochromatin in mouse cells [47]. No other studies have reported the function of IL-33 as a nuclear factor in mice.

2.3.3.2. Studies in humans. In vitro studies performed on HeLa, human HEK293T epithelial cell lines and endothelial cells of human endothelial venules derived from human tonsils, lymph nodes and Payer's patch cells have shown that IL-33 localizes to the nucleus, associates with peri-nucleolar heterochromatin and mitotic chromosomes, and exhibits potent transcriptional-regulation properties [47]. The uncommon functions of this IL-1 family member is mediated by an evolutionarily conserved domain within the IL-33 N-ter, which is necessary and sufficient for IL-33 nuclear localization [47]. For example, in primary human endothelial cells, IL-33 binds promoter-bound homeodomain proteins, such as histone methyltransferases, and suppresses IL-6 and sST2 transcription [48]. In HEK293T cells, IL-33 induces the transcription of the type 2 inflammatory cytokine IL-13 by binding a conserved non-coding sequence before the transcription initiation site [49]. In addition, IL-33 reportedly functions as a transcriptional regulator of NF-kB [50].

3. Pathophysiology

3.1. Heart disease

3.1.1. Studies in experimental models

Based on research in animals, the IL-33/ST2 signalling axis might protect the myocardium against maladaptive hypertrophy, fibrosis, and cardiomyocyte apoptosis, thereby reducing cardiac dysfunction and improving survival [3]. By sequestrating IL-33, sST2 exerts negative effects on the myocardium [2,38]. In vitro studies have shown that cardiomyocytes cultured with IL-33 were protected from hypoxia-induced apoptosis and that this cardio-protection was partially inhibited by sST2 [51]. Further in vivo studies have shown that compared with wild-type mice, ST2−/− or IL-33−/− mice with pressure or mechanical overload induced by transverse aortic constriction were characterized by cardiac fibrosis, hypertrophy, impaired systolic function, increased left ventricular dilation, impaired survival and increased gene expression of atrial and B-type natriuretic peptides [38,52]. All these phenotypic and genotypic alterations were rescued after treatment with IL-33 in wild-type mice but not in ST2−/− mice [52]. In a randomized study of ST2−/− versus wild-type littermate mice subjected to myocardial infarction, 4 weeks after myocardial infarction, IL-33 reduced ventricular dilation and improved contractile function and survival in wild-type mice but not in ST2−/− mice [51]. In addition, the IL-33/ST2 signalling pathway seems to be involved in the mechanism of atherosclerosis as the administration of IL-33 in ApoE−/− mice on a high fat diet was associated with a reduced plaque size in the aortic sinus [53]. Moreover, sST2 concentrations were higher in ApoE−/− mice than in control mice [54].

Only a few studies have analysed the effects of certain drugs on sST2 concentrations in mice affected by myocardial infarction. For example, the treatment of myocardial infarction rats with eplerenone or anakinra improved left ventricular end-diastolic volume, reduced the concentrations of sST2, reduced inflammatory markers and consequently inhibited fibrosis [55]. Although these preliminary results on the drug effects on sST2 myocardial expression are promising, the capacity of these drugs to significantly reduce the plasma concentrations of sST2 remains to be clarified.

3.1.2. Studies in humans

The determination of sST2 has been included in the 2017 ACCF/AHA guideline for additive risk stratification of patients with acute and chronic heart failure [56]. Conversely, in the 2016 heart failure guidelines of the European Society of Cardiology, there is no definitive recommendation to measure sST2 in clinical practice [57].

In published studies, the prognostic value of single sST2

measurements has been consistently demonstrated [56]. These properties were recently confirmed in two meta-analyses conducted on chronic and acute heart failure [58,59]. sST2, together with natriuretic peptides and cardiac troponins, constitutes the triad of biomarkers with predictive value in a bio-clinical risk score [60].

In addition to these observational studies, only a few studies have analysed the utility of sST2 determination in longitudinal settings. For example, a reduction in sST2 concentrations has been observed in heart failure patients treated with sacubitril/valsartan compared to that in those treated with enalapril [61]. However, there was a lack of interaction between sST2 reduction and treatment with respect to outcomes [61]. Moreover, no differences in sST2 were observed between patients treated with valsartan versus LCZ696 at baseline or after 12 or 36 weeks [62]. Although studies suggest a role for sST2 determination in the management of heart failure patients, no study has demonstrated the utility of a different therapeutic approach for patients with increased sST2 concentrations. Recently, a monocentric prospective randomized controlled trial has been proposed (STADE-HF study) in which 300 subjects with heart failure will be randomized to conventional or sST2-guided therapy [63]. On day 4 after randomization, clinicians will be made aware of sST2, and sST2 concentrations will be used to adjust heart failure treatment [63].

In addition to heart failure, the usefulness of sST2 determination has been proposed as a prognostic biomarker of other cardiac diseases, such as atrial fibrillation [64] or myocardial infarction [2,65].

The source of sST2 in heart failure patients remains uncertain. Despite extensive research in preclinical studies, few studies have analysed the cellular origin of sST2 in humans. Increased arterial plasma concentrations of sST2 (obtained from the arterial and coronary sinus during right heart catheterization) were elevated in heart failure patients compared to those in healthy individuals [21]. However, the authors of this study were unable to identify an sST2 gradient in normal or heart failure patients [21]. By contrast, a net trans-cardiac gradient was detected for natriuretic peptides in both healthy individuals and patients with heart failure [21]. More recently, lungs have been suggested as a relevant source of sST2 in heart failure [66]. The lack of a trans-cardiac gradient for sST2 was also reported by other studies performed on patients with myocardial infarction [67,68], and circulating sST2 concentrations were neither associated with myocardial expression of sST2 nor with myocardial fibrosis [67,68]. In addition, whether serum sST2 elevation after myocardial infarction occurs as a response to cell injury or to increased ventricular stress remains unclear. Taken together, these results support the hypothesis of a non-cardiac origin of circulating sST2.

3.2. Pulmonary disease

3.2.1. Studies in experimental models

In a murine model of allergic airway inflammation, a biphasic increase in serum sST2 was immediately identified after allergen exposure, with a maximal increase at 3 h and a slight increase at 36 h post-challenge [69]. Compared to transfection with a non-coding plasmid, in vivo transfection with a lipid-DNA complex coding sST2 resulted in a drastic reduction in the number of eosinophils and in the levels of IL-4 and IL-5 in the broncho-alveolar lavage [69]. In agreement with these findings, in a murine model of asthma, pretreatment with sST2 negatively regulated T helper 2 cytokine production, such as IL-4, IL-5 and IL-13 [37]. The prophylactic neutralization of IL-33 with recombinant sST2 attenuated allergic airway inflammation in mice exposed to traffic-related pollutants [70]. Similarly, an IL-33 subcutaneous vaccination of an airway inflammation mouse model suppressed the accumulation of inflammatory cells in the airways to reduce the number of eosinophils in broncho-alveolar lavage as well as the expression of IL-25, IL-17A and IL-33 in the lung [71]. Increased plasma concentrations of sST2 were also reported in a mouse model of chronic obstructive pulmonary disease [72].

3.2.2. Studies in humans

Increased concentrations of sST2 were initially reported in the serum and broncho-alveolar lavage of a patient with acute eosinophilic pneumonia [73]. sST2 decreased with corticosteroid treatment in parallel with the reduction in eosinophils in broncho-alveolar lavage [73]. Increased serum sST2 concentrations were observed in allergic respiratory diseases, such as chronic asthma [74], chronic obstructive pulmonary disease [75], allergic rhinitis [76], non-allergic respiratory diseases [77], polytrauma involving the thorax [78], and acute respiratory distress syndrome [79]. In general, the sST2 peak correlates with severity and worse outcome [74,75,77]. However, other studies were unable to identify this correlation [80,81]. IL-33 is expressed in human small airway epithelial cells, lung fibroblasts and bronchial smooth muscle cells [82]; additionally, higher concentrations of IL-33 were found in patients with asthma or allergy than in healthy subjects [76].

The A allele of the -26999G/A polymorphism within the ST2 gene has been associated with asthma and its severity but not with sST2 serum concentrations [83]. In contrast, the polymorphisms in the IL1RL1 gene control the relative abundance of ST2L versus sST2 [84].

3.3. Burn injury

3.3.1. Studies in experimental models

To our knowledge, no studies have analysed the involvement of the IL-33/ST2 signalling pathway in mouse models of burn injury. However, in a mouse model of haemorrhagic shock and tissue trauma, IL-33 activated a subset of innate lymphocytes (ILC2) in the lungs. ILC2 cells induce the expression of IL-5 by lung neutrophils, culminating in early lung injury [85].

3.3.2. Studies in humans

The activation of the IL-33/ST2 signalling pathway was investigated in only two human studies [86,87]. In an observational cohort study on patients with a 10–30% total body surface area burn, sST2 concentrations at day 3 after admission were the best predictor of survival, whereas increased plasma concentrations were significantly associated with mortality [86]. Similar findings were also reported in another study on burn patients with a total body surface area greater than 10% [87]. Compared to healthy individuals, these patients had increased concentrations of circulating sST2 and reduced concentrations of circulating IL-33. High sST2 concentrations were also a strong independent predictor of mortality in this study [87].

3.4. Graft-versus-host disease

3.4.1. Studies in experimental models

Increased plasma concentrations of sST2 were reported in minor histocompatibility antigen-mismatched allogeneic haematopoietic stem cell transplantation and human-to-mouse xenogenic experimental models by day 10 and day 20 after transplantation, respectively [88]. Consistent with the tropism of graft-versus-host disease for the gastrointestinal tract, the intestine was the major source of sST2, particularly stromal cells, endothelial cells and intestinal T cells. In addition, the administration of two doses of anti-ST2 mAb in the peri-transplant period was sufficient to reduce the severity of acute graft-versus-host disease and graft-versus-host disease mortality, retaining substantial graft-versus-leukaemia effect activity [88].

Increased IL-33 concentrations were also found in the gastrointestinal tract of mice post-conditioning [89]. Exogenous administration of IL-33 worsened graft-versus-host disease. Conversely, ST2−/− or IL33−/− mice had significantly lower graft-versus-host disease mortality [89].

Combining high-throughput screening and computational analyses, three chemical series of small-molecule ST2 inhibitors were discovered [90]. After the evaluation of toxicity, these compounds were further

Table 1
Utility of sST2 measurements in different clinical settings for diagnosis, prognosis and therapy guidance in human disease.

Disease	Diagnosis	Prognosis	Therapy guidance
Heart disease	No	Yes	Ongoing
Pulmonary disease	No	Yes	Not established
Burn injury	No	Yes	Not established
Graft-versus-host disease	No	Yes	Not established

used in allogeneic haematopoietic stem cell transplantation mouse models. Two of these compounds demonstrated a reduction in sST2 concentrations and amelioration of graft-versus-host disease without compromising the graft-versus-leukaemia effect. At day 70, these treated mice were graft-versus-host disease/leukaemia free. By contrast, the control group had worse outcomes [90].

In a mouse chronic cardiac rejection model, the daily administration of IL-33 prolonged the survival of treated animals. In addition, treatment with IL-33 promotes the development of a T helper 2-type immune response that supports the expansion of T regulatory cells and myeloid-derived suppressor cells and reduces antibody-mediated rejection [91].

3.4.2. Studies in humans

ST2 plasma concentrations at day 14 after allogeneic haematopoietic stem cell transplantation is a prognostic biomarker of the development of graft-versus-host disease, steroid-refractory graft-versus-host disease and death in patients who underwent allogeneic haematopoietic stem cell transplantation [92]. Patients with high ST2 values had a higher risk of developing treatment-resistant graft-versus-host disease and a higher risk of death within 6 months after therapy. By contrast, patients with low ST2 values had a lower mortality rate [92]. Increased IL-33 concentrations were also reported in patients during graft-versus-host disease [89]. Moreover, involvement of the IL-33/ST2 signalling pathway was reported in other transplantation settings, such as heart transplantation. In fact, increased sST2 concentrations were found in acute cardiac allograft rejections [89].

Although the reduction in graft-versus-host disease through ST2 inhibitors has been proven in experimental models, no studies have investigated the usefulness of these inhibitors in humans. As the results from preclinical studies are promising, further studies could be performed on these inhibitors in human disease.

4. Assays for the measurement of sST2 concentrations in the human circulation

In nearly all published studies on humans, sST2 plasma/serum concentrations have been measured with immunoassays. Most methods follow the enzyme-linked immunosorbent assay (ELISA) format [7]. One of these ELISAs has been cleared for clinical use by the United States Food and Drug Administration (FDA) and has also received the Conformitè Europèenne (CE) mark [7,93]. The other commercially available ELISAs are research assays. However, a quantitative point-of-care assay for the quantitative measurement of sST2 is also available [94].

As with many immunoassays, the different assays for sST2 are not standardized. Thus, it should be emphasized that results for one method do not necessarily indicate results from another. For the different sST2 assays described in the literature, a large bias between the methods can be observed [7,93].

5. Summary and conclusions

The ST2 gene products are structurally very similar in both mouse and humans, suggesting that the gene is produced by duplication and divergence. In humans and mice, alternative promoter activation and splicing produce ST2L and sST2. ST2L represents the longest transcript, whereas sST2 is the truncated and soluble isoform. ST2L is the biological receptor for IL-33, a member of the IL-1 family. Human and mouse IL-33 are approximately 55% identical at the amino acid level. The IL-33/ST2L signalling pathway is downregulated by the neutralization of IL-33 by binding with sST2, the decoy receptor of IL-33. IL-33 functions as a danger signal or an alarmin by signalling the presence of tissue damage to local immune cells after exposure to pathogens, injury-induced stress, or death by necrosis. Then, IL-33/ST2L signalling leads to inflammatory gene transcription and ultimately to the production of inflammatory cytokines/chemokines and an immune response.

As specified earlier in this review, the IL-33/ST2L signalling pathway has been suggested to play a role in multiple pathological conditions, such as cardiovascular disease, pulmonary disease, burn injury, and graft-versus-host disease. Increased circulating concentrations of sST2 in different diseases suggest that sST2 is not specific for a distinct disorder but is rather a marker of inflammatory disease. As inflammation plays an important role in the natural history of many diseases, the value of measuring plasma concentrations of sST2 has been demonstrated in evaluating multiple pathological conditions. Thus, the blood-based biomarker sST2 is not specific for a single disorder but rather represents a general marker of disease and mortality. Accordingly, sST2 is of limited value for diagnostic purposes. However, strong evidence indicates that plasma concentrations of sST2 provide prognostic information in multiple diseases and several settings (Table 1).

As outlined previously, many studies have addressed the role of sST2 in heart disease. However, although the release of sST2 by cardiac cells under specific stressor stimuli in animal models has been proposed, the cardiac origin of sST2 in the circulation of human individuals is still debated. For example, the plasma concentrations of sST2 in human heart failure seem to reflect extra-cardiac production and are thus only indirectly associated with cardiac function.

In contrast to clinical studies, preclinical animal studies allow the investigation of the IL-33/ST2L and sST2 signalling pathways at multiple levels, including RNA and protein expression at the tissue level and in the circulation. Therefore, most of the available data regarding sST2 and the IL-33/ST2L pathways are from preclinical studies, particularly from in vitro studies, thus limiting the knowledge in humans. Although animal data indicate a therapeutic effect of sST2 in different induced disease models, the usefulness of sST2 in clinical settings and its therapeutic inhibition in human individuals remain to be proven.

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