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Review

Soluble ST2: A complex and diverse role in several diseases

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ABSTRACT

The Suppression of Tumorigenicity 2 protein (ST2) is a member of the interleukin (IL) 1 receptor family with transmembrane (ST2L) and soluble (sST2) isoforms that are (over)expressed in several cells in different conditions and following various triggers (e.g. inflammation, stress). The ligand of ST2 is IL-33, which on binding to ST2L results in nuclear signalling and immunomodulatory action in various cells (tumour, immune, heart). sST2, that is released in the circulation, functions as a »decoy« receptor of IL-33 and inhibits IL-33/ST2L signalling and beneficial effects. The importance and role of the ST2/IL-33 axis and sST2 have been evaluated and confirmed in several inflammatory, cancer and cardiac diseases. sST2 is involved in homeostasis/pathogenesis of these diseases, as the counterbalance/response on IL-33/ST2L axis activation, which is triggered and expressed during developing fibrosis, tissue damage/inflammation and remodelling. In clinical studies, sST2 has been recognised as an important prognostic marker in patients with cardiac disease, including patients with chronic kidney disease where specific characteristics of sST2 enable better assessment of the risk of End-Stage Renal Disease patients on dialysis. sST2 is also recognised as an important marker for monitoring treatment in heart failure patients. However, accurate measurement and interpretation of ST2 concentration in serum/plasma samples for routine and research applications require the use of appropriate methods and recognition of essential characteristics of both the methods and the analyte that may influence the result. sST2, as one of the most promising disease biomarkers, is deserving of further study and wider application in clinical practice.

1. Introduction

Biochemical markers alone or in combination with other diagnostic modalities are important tools for the diagnosis, treatment and monitoring of disease. They can provide a non-invasive assessment of prognosis, disease progression and the development of adverse life-threatening complications. Their higher sensitivity to detect early pathophysiological changes can indicate the role of specific pathophysiological mechanisms in disease onset, potentially facilitating the development of new treatment methods. Consequently, there is great interest in finding new biological (genetic) and biochemical markers. Biomarkers differ in their molecular structure, origin, diagnostic efficiency, and the biological materials (serum, tissue, cells, urine) in which they can be measured. For a biomarker to become established, a robust method of measurement must be developed, with appropriate analytical specificity, sensitivity and repeatability of results.

The Suppression of Tumorigenicity 2 protein (ST2) is one of the most promising and complex biomarkers, with an important role in several diseases. Twenty years ago, ST2 was first recognised as an essential factor of cell proliferation, with an influence on cancer development [1]. Later discovery of its inflammatory and immunomodulatory action led to connection with autoimmune and other inflammatory diseases [2–4]. Since then, the applications of ST2 have grown continuously. It has been found to be relevant in pulmonary diseases, sepsis and gastrointestinal diseases [5–7] and is becoming one of the important markers in the management of heart failure (HF), for the indication of disease development and as a prognostic marker for different HF populations [8–10]. ST2 also has a growing potential in tailoring and monitoring therapy of HF patients [11,12]. Recently, its role was confirmed in Chronic Kidney Disease (CKD), especially in End-Stage Renal Disease (ESRD). Its pathophysiological characteristics and independence of renal function, give added prognostic value to already established prognostic markers and allow improved identification of patients at high risk for hospitalisation and both cardiovascular (CV) and all-cause death [13–16].

We aim to present a comprehensive overview of the ST2 marker and summarize its various roles, biological characteristics, and established or potential clinical applications in different diseases.

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2. Biology and structure of ST2

The complexity of ST2 and its various effects may be explained by different origin, induction and expression of its gene in different cells. The ST2 gene was first described by Werenskiold and colleagues, who isolated it when searching for genes activated in response to oncogenes and serum growth factors [1]. Further investigations confirmed its connection with the induction of cell proliferation, which has an essential role in cancer development [4]. The ST2 gene encodes a protein that showed similarities with the immunoglobulin gene superfamily, especially with the interleukin (IL) −1 receptor [2,4,17]. ST2 is a member of the interleukin-1 receptor-like-1 (IL1RL1) family and the gene is located on human chromosome 2q12 [17,18]. Following alternative promoter splicing and 3′ post-transcription processing of ST2 mRNA, four protein isoforms of ST2 are produced. The two essential forms are a transmembrane form, ST2 ligand (ST2L) with molecular weight 67 kDa and three extracellular IgG domains, and a smaller secreted soluble form (sST2) with molecular weight 37 kDa, which has a similar extracellular structure but without the transmembrane and intracellular parts. Both molecules act as receptors that bind IL-33 and not IL-1α, IL-1β or IL-1R antagonists and therefore have an essential immunomodulatory function. Additionally, binding of IL-33 to ST2L, with the presence of additional interleukin-1 receptor accessory protein (IL-1RacP) receptor protein molecules, results in activation of mitogen-activated protein kinase (MAPK) and nuclear factor (NF-kB) signalling with various consequent effects in target cells. IL-33 binding with sST2 does not allow and blocks these effects [20] (Fig. 1).

ST2 molecules are expressed as a result of activation and response of the ST2 gene to stimulation by many inflammatory and cell growth factors (platelet-derived, acidic fibroblast and primary fibroblast growth factor), tissue plasminogen activator and the proinflammatory cytokines, like tumour necrosis factor-alpha (TNFα) and IL-1 [4,19]. This expression allows the synthesis of the ST2 receptor molecule in a variety of cells, such as embryonic, hematopoietic, tumour and immune cells, as it belongs to the Toll-like receptor (TLR) family [5,6,20]. It is present and expressed in fibroblasts and myocytes in the heart muscle [8].

3. ST2 as an immune response modulator

The presence and expression of ST2L were initially detected in the T-lymphocytic cell line (LyT), macrophages, in germ cells of the bone marrow and primary mast cells. It is also expressed in dendritic, natural killer cells and activated polymorphonuclear leucocytes (PMNL). Therefore, one of the first ST2 effects was described in association with the immune response in allergic and autoimmune diseases. Various studies confirmed that the role of ST2L in LyT is crucial for the activation and development of T helper type 2 lymphocytes (Th2) responsible for the development of allergic reactions and the production of cytokines IL-4, IL-5 and IL-13 [5,6,21]. This effect could be avoided by blocking the transmission of signals through the ST2L receptor with the help of antibodies that prevented the binding of the corresponding ligands. Additionally, the direct impact on the development and activation of T helper type 1 lymphocytes (Th1) was largely unchanged, which helped to demonstrate the important role of ST2L in the activation and regulation of Th2 cellular immune response [5]. Later, in the search for the key ligand that binds to ST2L, an important role of IL-33 was discovered.

IL-33 is a member of a big IL-1 cytokine family that regulates innate and adaptive immune systems to promote inflammatory responses [6]. In contrast to the action of IL-1, which is processed and released by live immune cells in response to infection or other triggers, IL-33 acts as an alarmin against injury-induced stress, pathogens, or cell death by activating local immune cells [21,22]. IL-33 is a cytokine with dual-function. The full-length IL-33 form acts as an intracellular gene regulator (transcription factor) in the nucleus. It repress the expression of NF-κB-regulated genes that are necessary for pro-inflammatory signaling. The mature IL-33 form serves as an extracellular cytokine following release when cells sense inflammatory signals or undergo necrosis [23,24]. Once released from damaged cells upon tissue injury or viral infection, full-length IL-33 can be processed by neutrophil-derived proteases into mature IL-33. It can bind to the membrane-bound ST2L receptor through its cytokine domain and triggers an inflammatory cascade. Although both forms can bind to and signal through their receptor ST2, mature IL-33 has a 10-fold higher affinity and bioactivity than full length IL-33 [25]. Most recently, tissue fibrosis, mucosal healing, and wound repairment have been found to be additional

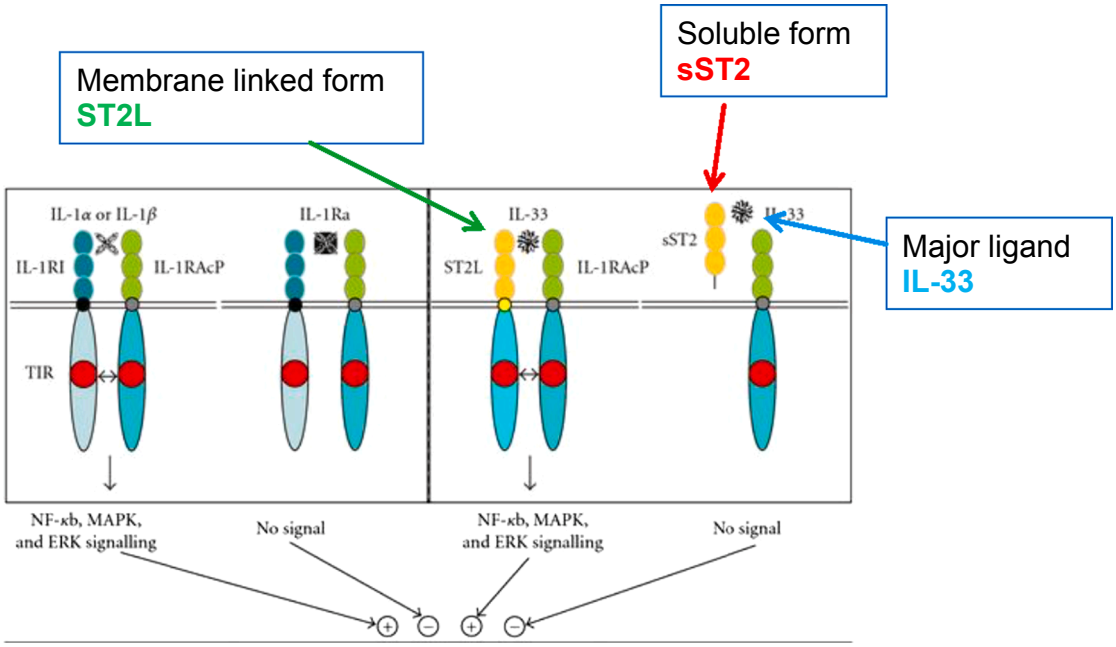

Fig. 1. The structure of ST2L and sST2 as the IL-33 receptor. (IL-1RAcP, interleukin-1 receptor supplemental protein; MAPK, mitogen-activated protein kinase; NF-kB, nuclear factor kB).

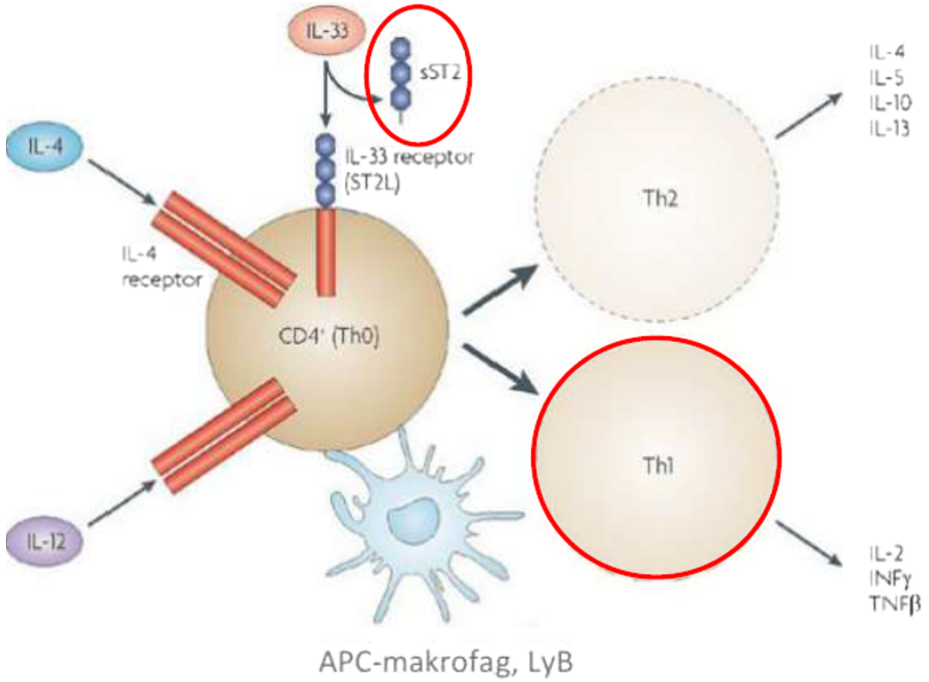

Fig. 2. Effect of sST2 on immune cells: Th2 immune response blocker. Red circles show the mechanism of sST2 action: by blocking IL-33 and preventing binding of IL-33 to ST2L on CD4 cells, sST2 modifies the immune response/activation and cytokine production from Th2 to inflammatory Th1 response.

possible actions of IL-33 during inflammation.

The next development was elucidating the role of sST2 as IL-33 soluble receptor and blocker of effects in target cells [6,21,22,26]. Specifically, sST2 bound to IL-33 prevents its binding to ST2L in the immune cell (LyT) [5,6] (Fig. 2). In this way, it also inhibits the activation of Th2 cell response and the release of anti-inflammatory cytokines (IL-4, IL-5, IL-10, IL-13), and modulates the response in the direction of Th1 activation, which results in the activation and release of inflammatory cytokines (TNF-α) and inflammation [21,26]. These processes cause various inflammatory and autoimmune diseases [7,21,22,26,27]. They are thought to be present in heart muscle, which in turn leads to a worsening of the condition [6,8,27].

The presence and expression of ST2 gene in various tissues and cells (embryonic tissues, tumour cells, immune cells, fibroblasts, vascular endothelial cells, myocytes) also indicate its broader role and influence in a broader spectrum of biological systems [4–8,20–28]. sST2 is widely distributed and is included in various immune responses and mechanisms resulting in different outcomes in different tissues. Therefore its potential pathophysiological role could make it a significant biochemical marker in the monitoring of a range of inflammatory diseases.

4. ST2 in cancer diseases

It is well known that IL-33 plays an essential and very complex role in cancer development [28–34]. It has been reported to be involved in oncogenesis, tumour growth, metastasis, neo-angiogenesis, and evasion of programmed cell death. As an immune-associated factor, IL-33 also affects the immunity and associated microenvironment of cancer through immune cells, such as myeloid-driven suppressor cells, dendritic cells and regulatory T cells [29] (Fig. 3). Wang et al. determined that IL-33 overexpression enhances robust outgrowth and metastasis in vitro/in vivo, while genetic knockdown of IL-33 limited the progression of non-small-cell lung cancer (NSCLC). The blocking action of IL-33 signalling may allow blocking of the outgrowth and metastasis of human lung cancer as a possible future therapeutic approach [30]. Although IL-33 has been demonstrated to be pro-tumorigenic in various cancers, for some cancer types (like colorectal cancer), the findings remain controversial [31,34].

Consistent with the close relation of ST2 with IL-33, subsequent studies also concerned and confirmed the characteristics of ST2 and its blocker receptor sST2 in the development of various cancers and its association with the onset of metastases in other organs in animals and humans [4,28]. The first discovery of the ST2 gene was associated with the induction of oncogene expression in mouse fibroblasts, where it should play the role of an inhibitor of the development of cancer cells [4]. This role is consistent with the observation that a soluble form of the IL-33 receptor (sST2) is downregulated in metastatic cells compared with low-metastatic colorectal cancer cells [31]. Bergis and colleagues found significantly higher values of sST2 in patients with stomach cancer and an association with a higher risk of developing metastases to other organs [28]. Jovanovic and colleagues have confirmed that exogenously administered IL-33 accelerates mammary tumour appearance, growth and metastases in murine 4 T1 breast cancer. They have also stated that the interleukin-33/ST2 axis promotes breast cancer growth and metastases by facilitating the intra-tumour accumulation of immunosuppressive and innate lymphoid cells [32]. Another study pointed out that IL-33 activated core stem cell genes via ST2 signalling pathway recruited macrophages and stimulated stem-like characters to promote carcinogenesis of colon cancer cells [33].

Other studies conclude that the IL-33/ST2 axis may have a significant, impact on the development of tumour development microenvironment (TME), though this remains controversial. Through recruitment of immune cells and by causing and promoting different cytokine production, IL-33/ST2 also influences tumour phenotype [29,34] (Fig. 4). Under pro-tumorigenic conditions, the activation of IL-33/ST2 on different target immune cells (mast cells, macrophages, T-regulatory cells) influences cancer pathology, including angiogenesis, invasiveness, immune protection, and metastasis [29]. On the other hand, under anti-tumorigenic conditions by recruitment of NK cells and CD8 + T cells, it could act in an anti-tumorigenic role to promote tumour regression and eradication [31,34]. Moreover, expression and blocking the action of sST2 influences the complex mechanisms of IL-33/ST2 signalling and its attenuation.

Yang et al. have confirmed that serum levels of IL-33 and sST2 were significantly higher in breast cancer patients in comparison with healthy volunteers and were positively correlated with serum levels of

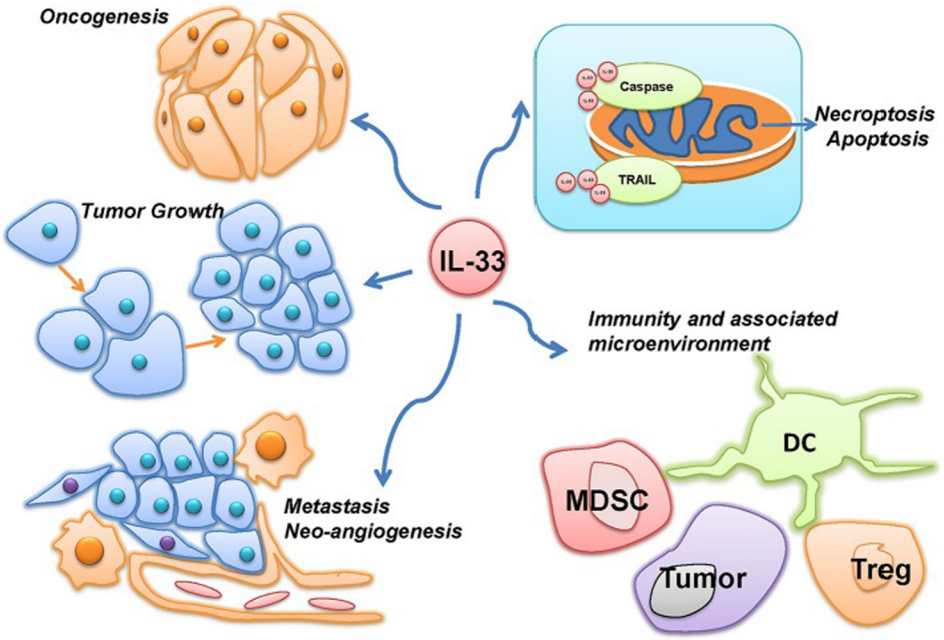

Fig. 3. IL-33 plays an important and very complex role in cancer development, affecting the immunity and associated microenvironment of cancer through immune cells. MDSC, myeloid-derived suppressor cells; DC, dendritic cells; Treg, regulatory T cells. (From Shen et al, Front Immunol 2018, CC BY license) [29].

several growth factors, like vascular endothelial growth factor (VEGF) [35]. Other studies have also revealed the association of sST2 with estrogen receptor (ER) – positive breast cancer and with factors that indicate poor prognosis [36]. The positive correlation of sST2 high serum concentration with poor prognosis and low survival rate was also confirmed in patients with pancreatic cancer [37]. Taken together, according to several studies, sST2 may serve as a noninvasive diagnostic, and prognostic marker for lung, gastric, breast, pancreatic, colon and other cancers. It may also be a useful tool for monitoring successful therapy, but this needs to be confirmed with further therapy-oriented studies.

5. ST2 in inflammatory and autoimmune diseases

ST2L is a cell-surface marker of T helper type 2 (Th2) lymphocytes and therefore IL-33/ST2 has an essential role in immune regulation and has been shown to be present in diseases associated with a predominantly Th2 response, such as asthma, pulmonary fibrosis, rheumatoid arthritis, collagen vascular diseases, sepsis, trauma, fibroproliferative diseases and ulcerative colitis [3,5,7,21–27].

5.1. ST2 in autoimmune diseases

sST2 is expressed and secreted by activated PMNLs, respiratory tract epithelium, endothelium keratinocytes, dermal fibroblasts, and cardiac fibroblasts. sST2 has an immunomodulatory effect in the development of Th1 cells and the production of cytokines (TNF-α). Both are crucial to the occurrence of autoimmunity. Therefore, sST2 has an impact on the development of autoimmune diseases suggesting the possibility of using it to monitor various autoimmune diseases, especially rheumatoid arthritis, which is characterised by inflammatory changes at the level of fibroblasts [38]. Thus, in patients with autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and Wegener's granulomatosis, several studies have confirmed substantially higher sST2 serum levels than in the healthy population, using immunoprecipitation methods and recombinant human ST2 protein [3,21–27,38].

5.2. ST2 in asthma

In the pathogenesis of asthma, chronic airway inflammation plays a crucial role. The inflammatory response is characterised by increased eosinophils, basophils, mast cells, and, most importantly, Th2 cells, which can be isolated from the lungs of patients with asthma [39].

Several studies have recognised ST2′s influence on atopic asthma and its acute conditions, in line with studies indicating ST2′s important role in immune, developmental mechanisms with influence on Th2 cells and production of IL-4, IL-5 and IL-13 [5,6,21]. Using a murine model of Th2-dependent allergic airway inflammation, and a neutralising antibody against ST2, Löhning et al were able to partially inhibite the development of Th2 effector functions in vivo [40]. In this way, they showed that ST2 could play an essential role in the development of Th2 responses in patients with asthma. Oshikawa and coworkers have confirmed significantly higher values of serum sST2 concentrations in asthma patients compared to healthy individuals or patients with other pulmonary diseases [41]. They also found a differential rise of serum sST2 level that correlates well with the severity of asthma exacerbation. Their results revealed that soluble human ST2 in sera could be related to Th2-mediated allergic inflammation by inducing acute exacerbation in patients with atopic asthma.

5.3. ST2 in pulmonary diseases

The IL-33/ST2 axis plays an important role in the development of respiratory and pulmonary diseases. Il-33 is overexpressed after fibroblast activation in the lungs of patients with idiopathic pulmonary fibrosis. Li and colleagues have confirmed that IL-33 acts as a profibrogenic cytokine. By signalling through ST2, recruiting and directing inflammatory cell function and enhancing profibrogenic cytokine production IL-33 influences the initiation and progression of pulmonary fibrosis [42]. It has also been reported that sST2 gene expression increases in the pulmonary fibrosis model induced by bleomycin [43]. Using murine alveolar cell lines, Oshikawa et al. have confirmed that ST2 expression is upregulated after inflammatory stimuli and that sST2 pretreatment of the cell lines prevented the inflammation process and significantly reduced the cytokine production [44]. Further clinical studies have shown that the result of this ST2 expression is the elevation

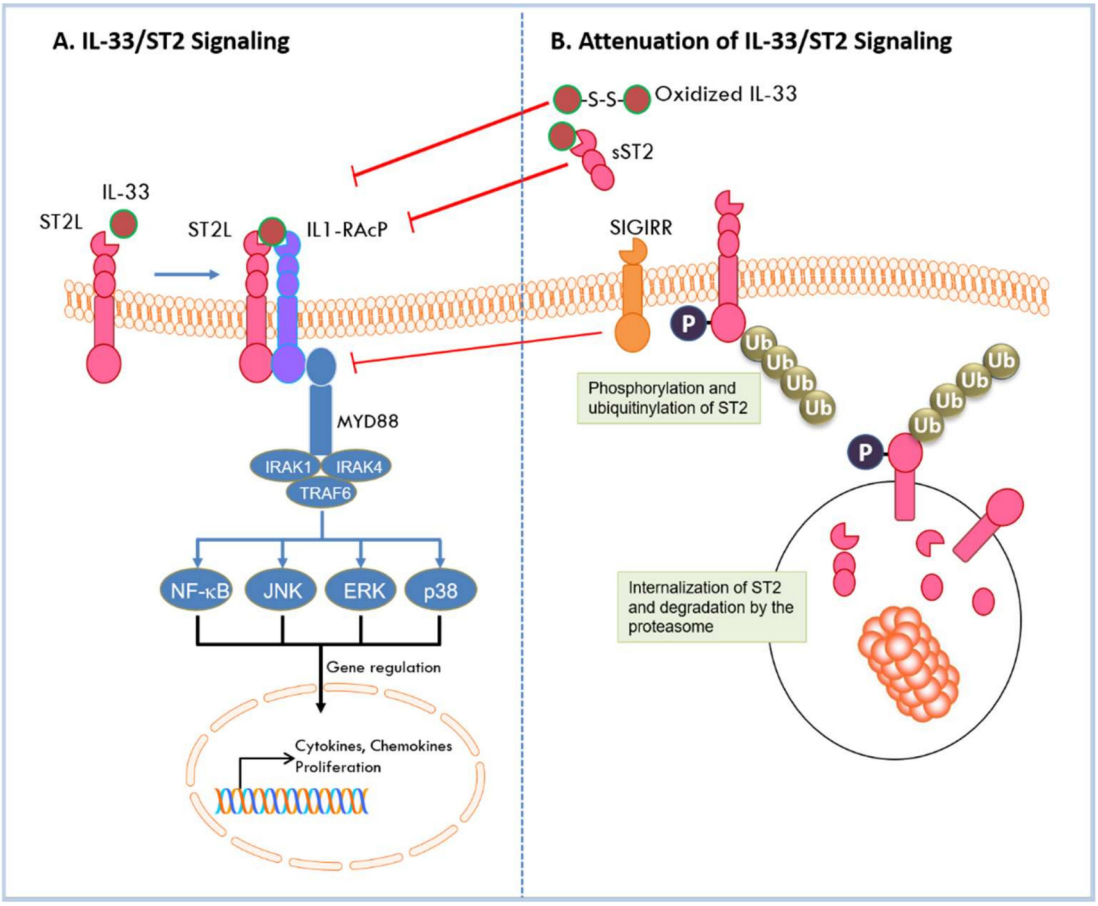

Fig.4. (A) Activation of the IL-33/ST2L complex. IL-33 is rapidly released from cells during necrosis or tissue injury, and signals through a cell surface receptor complex, ST2 (IL-1 receptor-like 1, IL1RL1) and IL1RAcP (IL-1 receptor accessory protein), to initiate inflammatory pathways in immune cells or cell proliferation. This clustered domain recruits signaling adaptor and kinases (including MyD88, IRAK1/4, TRAF6) in order to activate the transcription factors (ERK, NF-kB, p38, JNK) in tumor cells and generate a cancer-related inflammatory microenvironment, with tumor-promoting effects. (B) Attenuation of IL-33/ST2 signaling by different mechanisms: oxidation of IL-33 cysteine residues, sST2 blocking action as decoy receptor, inhibition of ST2/IL1-RAcP heterodimer by a single immunoglobulin domain IL1-R-related molecule (SIGIRR, TIR8), phosphorylation, ubiquitinylation and proteosome degradation (From Shen et al, Front Immunol 2018, CC BY license) [29].

of serum sST2 concentrations in patients with pulmonary fibrosis [45], which showed prognostic value for the prediction of mortality in these patients and in patients with other pulmonary diseases [46]. Other studies have demonstrated that in patients with acute dyspnea or acute respiratory distress syndrome (ARDS), where sST2 concentrations may be elevated (approximal ten times) above those expected in HF patients regardless of the cause, concentrations of sST2 provide important prognostic information not available from clinical variables or other biomarkers [45–47]. In this regard, sST2 concentration could help to define disease severity (exacerbations) and also to differentiate ARDS from HF. Oshikawa et al. have also confirmed that acute eosinophilic pneumonia is associated with increased sST2 in serum and bronchoalveolar lavage fluid, which showed the pathophysiological connection between IL and 33, eosinophil cells and sST2 production [47]. sST2 may be considered for added prognostic value in pulmonary diseases, as well as detection of active nonallergic pulmonary inflammation [48].

5.4. ST2 in sepsis

Sepsis causes sustained elevation in serum sST2 levels, irrespective of the source of infection [49]. The serum sST2 levels correlate with disease severity and mortality. Hoogerwerf and colleagues have found significant differences in cytokine levels (IL-6, IL-8, and IL-10) between survivors and non-survivors, where the cytokine levels were especially elevated in non-survivors and tended to decrease sharply after five days [49]. In contrast, soluble ST2 levels of non-survivors showed stable elevations until day 14 compared with survivors. This reflects the short circulating half-life of these mediators compared to sST2 [49,50]. The source of sST2 in sepsis is still not entirely known. Soluble ST2 is produced by fibroblasts underneath the vascular endothelium. Therefore we could speculate that sST2 is only released into the circulation upon disruption of the endothelial layer, in which case sST2 would be indicative of the extent of tissue injury. This would also explain the difference in duration of elevated sST2 levels in various inflammatory processes. The sustained elevation of sST2 also indicates the possible contribution of negative regulators of TLRs to the immunosuppressed state in septic patients.

Brunner and colleagues have confirmed that serum levels of sST2 were significantly increased in septic patients compared to trauma, abdominal surgery, and healthy controls. They concluded that sST2, a marker for Th2 cytokine-producing cells, is elevated in sepsis and trauma patients, providing further evidence for a shift from Th1- to Th2-biased cells [51]. Another study of hospital patients with suspected sepsis confirmed that in-hospital mortality was significantly higher in patients with sST2 concentrations above 35 ng/mL and patients with increased concentrations of both sST2 and PCT. These data and supporting studies led to the conclusion that measurement of sST2 in combination with other prognostic markers (PCT, galectin-3, presepsin) would be useful for risk stratification and prediction of prognosis in patients with suspected sepsis [52,53].

5.5. ST2 and inflammatory bowel diseases (IBD)

Several studies have confirmed that increased TLR2 expression in the lamina propria is associated with the pathogenesis of inflammatory bowel disease (IBD): ulcerative colitis (UC) and Crohn's disease (CD) [54]. Recently, soluble TLR2 (sTLR2) variants have been shown to counteract inflammatory responses driven by the cognate receptor, and increased production of sTLR2 by lamina propria mononuclear cells from ulcerative colitis patients has been confirmed [55]. Further studies have claimed that sST2 can predict the severity and progression of inflammatory intestinal disorders [56–58].

Excellent matching of the serum sST2 concentration with histological findings in patients with IBD (UC and CD), and excellent correlation with faecal calprotectin (an important biochemical marker of the activity of inflammatory processes in the intestine), suggest an important role for sST2 in the monitoring of IBD [7]. sST2 concentrations also correlated well with disease severity and inflammatory cytokines in UC and were able to differentiate active from inactive UC [57]. These results indicate a possible role of sST2 as a biomarker in follow up of these patients. Diaz-Jimenez and colleagues have confirmed this role using continuous sST2 measurement to follow changes in the inflammatory activity of UC patients on treatment. They found sST2, like faecal calprotectin, to be a useful biomarker in predicting clinical outcome in UC [58].

6. ST2 in hepatic diseases

IL-33/ST2 also has a profibrotic role in the pathogenesis of hepatic obesity-associated metabolic disorders, among which are type 2 diabetes and nonalcoholic fatty liver disease (NAFLD). They represent a spectrum of diseases that include liver steatosis, nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis, where immune reactivity and chronic low-grade inflammation play an important role [59]. Progression of NASH is thought to be associated with the increased mRNA expression level of IL-33 and ST2 that results in a further complex mechanism of activation of immune cells in the liver [60]. Pejnovic et al recently proposed a mechanism of liver fibrosis development involving the IL-33/ST2 axis: multiple signals from visceral adipose tissue and gut polarise liver-resident macrophages towards the M1 type and promote chemotaxis of immune cells and hepatocyte injury [59]. Subsequently, released IL-33 from damaged hepatocytes binds on ST2L and promotes the release of profibrogenic IL-13 and TGF-β from IL to 33R (ST2)-positive macrophages. Liver-resident innate lymphoid cells type 2 (ILC2s) might also respond to IL-33 by producing IL-13. Profibrogenic cytokines activate quiescent hepatic stellate cells, which transform to myofibroblasts, the key cells involved in the development of liver fibrosis [59].

The significance of sST2 as a potential biomarker of liver fibrosis has been highlighted in several studies which demonstrated that serum concentrations of sST2 were higher in patients with liver cirrhosis and hepatocellular carcinoma [61]. These data suggest an essential role of sST2 in the pathogenesis of hepatocellular carcinoma and liver cirrhosis as a possible marker of systemic inflammation.

A recent study showed a strong correlation between serum sST2 concentrations and fibrosis stage in patients with hepatitis B infection, suggesting that serum sST2 may be a reliable biomarker for follow-up and evaluating the response to therapy for liver diseases causing fibrosis, including NAFLD [62].

In the light of these studies, we speculate that sST2 could play an essential role in the homeostasis and pathogenesis of these diseases, as the counteractor/response on activation of the IL-33/ST2L axis that is triggered and expressed during developing fibrotic diseases. Further research is needed to evaluate the potential of sST2 as a prognostic marker in patients with liver fibrosis.

7. Source and influence of ST2 on the development of cardiovascular diseases

Increased cardiac loads (increased biomechanical stress, pressure and tension of the muscular structures) due to acute (infarct) or progressive heart failure (HF), myocytes, vascular structures (endothelial cells) and fibroblasts of the heart increase the expression, formation and release of both forms of ST2 as IL-33 [8,63,64].

ST2L as the transmembrane receptor is expressed on the surface of myocytes in heart muscle. Binding of IL-33, released from fibroblasts in the heart muscle upon biomechanical stress, high pressure and damage, results in several cardioprotective effects. Several studies have confirmed that binding of IL-33 to ST2L plays a central role in the processes of immune response, homeostasis, and the revitalisation of damaged (heart muscle) tissue. This binding reduces apoptosis of cells exposed to ischemic and inflammatory processes, caused by decreased circulation through the heart muscle tissue or infarction. It also reduces myocardial fibrosis, cardiomyocyte hypertrophy and thus maintains the ventricular function and allows longer patient survival [63–66].

In contrast, the soluble receptor sST2 is simultaneously released from fibroblasts and vascular structures and acts as a blocking receptor by competitively binding to IL-33 and preventing the binding of IL-33 to ST2L and its cardioprotective effects on heart muscle [65,66] (Fig. 5). Therefore, increased expression and release of sST2 enhances cell apoptosis, the development of fibrosis, hypertrophy, remodelling of the heart muscle and progression of HF.

8. sST2 as a marker of heart diseases

In line with the growing evidence for sST2′s role in the pathophysiological mechanisms of myocardial fibrosis and heart remodelling, several clinical studies have confirmed its potential role in the management of cardiac diseases, especially of HF [8–12,66–87]. Natriuretic peptides (NT-proBNP and BNP) are considered to be the gold-standard marker for the diagnosis and management of acute HF [71–73]. However, in view of the limited prognostic utility of natriuretic peptides and the fact that their role in guiding treatment has not yet been fully established additional biomarkers to fill these gaps are still required [74] and sST2 is an important candidate marker in this respect.

8.1. Prognostic marker of HF

Although NT-proBNP remains the best diagnostic marker for HF with acute dyspnea, sST2 is recognised as an important prognostic marker of HF, being a strong predictor of cardiovascular (CV) outcomes in both chronic and acute HF [8,9,12,66–79]. The first study to measure sST2 in patients with acutely decompensated heart failure (ADHF), was the Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department (PRIDE) Study, where measured serum concentrations of sST2 were significantly higher in patients with ADHF than non-HF patients [74]. Later studies using the more sensitive Presage ST2 assay (Critical Diagnostics, San Diego, CA, USA) have confirmed that increased serum/plasma concentrations (≥35 ng/mL) of sST2 are associated with higher risk for hospitalisation, and both cardiovascular and all-cause mortality in patients with HF [8,9,12,66–70]. Additionally, higher values are expected in patients with more advanced disease. Several studies have confirmed significant prognostic value for serum sST2 in chronic HF, where development and prognosis of the disease are strongly correlated with the extent of the fibrosis and remodelling process [68,78,79]. Since the modified guidelines for heart failure issued by the American College of Cardiology Foundation (ACCF / AHA) in 2013, sST2 has been ranked with new prognostic biochemical markers for risk assessment of myocardial fibrosis and predicting heart disease and life-threatening events. The proposed cut-off sST2 concentration in serum/plasma samples (using the Presage ST2 assay) for risk assessment and prognosis for the life-threatening CV events in these

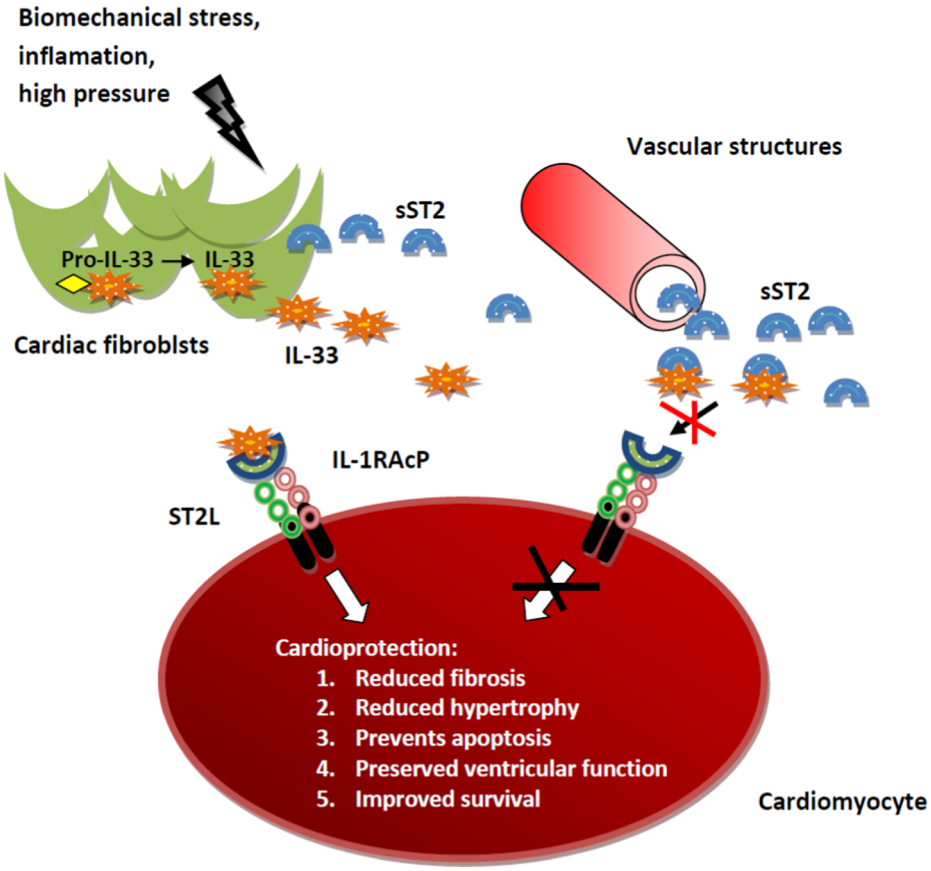

Fig. 5. The effect of IL-33 on binding to the ST2L receptor and sST2 action as its blocker. Sources of sST2 are cardiac fibroblasts and vascular endothelial cells in heart muscle, triggering by biomechanical stress, high pressure and inflammation.

patients is 35 ng/mL [9]. Gruson and colleagues have found that elevated sST2 is a better predictor of long-term cardiovascular death than natriuretic peptides in HF patients with reduced left ventricular ejection fraction (LVEF) [68]. Other investigators also have confirmed its better ability in comparison with NT-proBNP in the prediction of life-threatening CV events and death in HF patients with preserved LVEF [12,69].

Natriuretic peptides (NT-proBNP, BNP) and sST2 are independent markers since they are derived from various pathophysiological processes involved in the complex development of the disease. Numerous studies have confirm that their diagnostic and prognostic value is enhanced when they are used in combination and that sST2 adds value in this respect. [10–12,66–70,74]. In these studies, patients with elevation of both markers had the highest 1-year mortality rate. In a comparison of ST2 measurements with other biomarkers measured on admission in 5306 patients with ADHF carried out by the Global Research on Acute Conditions Team (GREAT), sST2 emerged as the most robust marker with the ability to reclassify death risk beyond a clinical model. sST2 was the best predictor of both 30-day and 1-year mortality [77]. Shah et al. have confirmed that sST2 level can predict of 4-year mortality independent of other traditional clinical, biochemical, and echocardiographic risk markers [80].

8.2. Treatment monitoring

The importance of sST2 is growing with several recent studies confirming its role in disease follow-up and treatment monitoring of patients with HF. Maisel and colleagues using serial testing in hospital have found that concentration and dynamic changes of sST2 respond in parallel with (successful) treatment, also due to its relatively short half-life [11,12]. They have also stated that the persistently high serum/plasma sST2 concentrations are associated with greater risk of short time life-threatening events and bad prognosis. In contrast, those patients whose sST2 values rapidly decreased after admission had a good outcome in the short term.

In these and other studies, investigators were able to classify patients regarding their response to therapy and to select optimal treatment [11,12,74,77–84]. Considering the ability of sST2 in prediction myocardial remodelling in chronic HF, successful monitoring has been shown mainly in anti-remodelling therapy (anti-β-blocker therapy) [85,86].

sST2 concentration has also demonstrated good prognostic ability in relation to decisions when to discharge the patient from hospital care [11,12,74,77–84].

We can conclude that the dynamic changes in sST2 from admission to discharge and the final value at the end of the hospitalisation both contribute to the prediction of long-term prognosis of HF patients [87]. This and ability of the long-term therapy guidance would add the value and benefits of sST2 as a useful biochemical marker in daily routine practice.

9. sST2 in chronic kidney disease

Studies of sST2 in Chronic Kidney Diseases (CKD) were initially applied to its potential use as a marker of CKD development. These studies have confirmed that sST2 is independent of renal function and therefore, could not be used as a diagnostic marker for CKD [88–90]. Relatively few studies have concerned the possible role of sST2 as a prognostic marker in CKD, especially for assessing the risk of development of cardiovascular and all-cause mortality in this diverse disease. The KDIGO classification divides CKD into five stages according to estimated glomerular filtration rate (eGFR) [91]. Since CKD patients and

especially end-stage renal disease (ESRD) patients on hemodialysis replacement therapy (CKD 5D) are prone to severe HF and various life-threatening events [92–94], the ability to assess disease prognosis and the risk of short-term life-threatening events or death is of great importance.

Several biomarkers for stratification of patients at high risk for cardiovascular or other life-threatening events are already in use in routine practice or in research studies, including NT-proBNP, TnI, and galectin-3 [95–101]. They differ according to the pathophysiological processes that they reflect, and their diagnostic accuracy and ability to predict risk for future life-threatening events or disease progression. Unfortunately, none of these currently satisfy the criteria for an excellent prognostic marker for the CKD population, and specifically for prediction of HF or cardiovascular events in patients with ESRD. Only a few studies of CKD (1–5 stages) and ESRD (5D) patients have evaluated sST2 as a potential prognostic marker [13–16,90,102–107]. Homsak et al. were able to confirm in a cohort of patients with CKD and ESRD that sST2 is independent not only of renal function but also of the hemodiafiltration (HDF) process. They found that sST2 serum concentrations were not statistically significantly different in respect of CKD stage (Table 1; unpublished data) and did not change after HDF (using high flux membrane) (Table 2) [13,15]. They confirmed a statistically significant difference between measured serum concentrations of NT-pro BNP before and after HDF (mean individual decrease was $-62.8 \pm 12.9\%$), whereby for sST2 this difference was not statistically significant [13]. These findings were consistent with the study of Mueller et al., which included only four patients on HDF and the majority of the patients were on (low-flux membrane) dialysis treatment [102]. Further studies of Homsak et al. and other researchers also confirmed that sST2 as a marker of fibrosis and remodelling is capable of stratifying patients with CKD [16,104,105] and especially ESRD patients [14,15,90,103] with respect to their risk of developing life-threatening events, hospitalisation and death.

The added value of sST2 is also reflected if multiple markers are combined. The combination of sST2 and NT-proBNP provides a better risk assessment than any of the individual markers [14–16,105]. The highest risk of cardiovascular and all-cause mortality has been found in ESRD patients with both elevated markers [15]. These findings confirm that sST2 is an independent prognostic marker that responds through other pathophysiological mechanisms than NT-proBNP. Therefore, when using multiple biomarkers, sST2 adds value to effective patient monitoring and could enable a better assessment of the risk of death of patients with CKD and, in particular, ESRD patients on substitution treatment with HDF.

Additionally, unlike NT-proBNP and galectin-3, sST2 is independent of HDF treatment and renal function and also has low biological variability [12]. These factors add to the value of sST2 for possible routine use for follow-up of ESRD patients, regardless of the timing of sample collection in relation to HDF. In this respect, NT-proBNP is a potentially useful prognostic marker in ESRD patients only if higher cut-off values (> 1500 pmol/L) [15] and possible concentration variations due to HDF treatment are taken into account [15,89,100,101].

10. sST2 characteristics

For sST2 to be used effectively in clinical practice it is essential to know the factors influencing measured serum concentrations. These effects may be physiological or the result of pathophysiological processes.

Table 1
Average concentrations of sST2 and NT-proBNP according to CKD stage (without CKD 5D stage).

CKD stage	1	2	3	4	5
Number of patients	8 (9%)	4 (5%)	29 (32%)	35 (39%)	15 (15%)
sST2 (μg/L)	24.8	20.3	29.2	25.2	26.8
NT-proBNP (pmol/L)	10.8	17.0	107.7	135.6	211.2

Numerous studies have shown that the measured concentrations of sST2 are independent of age, sex, and body mass index [11,12]. However, the population-based cohort study (Dallas study) did show a race dependence for sST2. A higher proportion of African Americans had detectable serum concentrations of sST2 than no–African Americans (44% vs 21%, respectively, $P < 0.0001$) [67].

As previously mentioned, unlike natriuretic peptides and galectin-3, sST2 values are not significantly influenced by renal function and are independent of eGFR [88–91]. sST2 concentrations also correlate well with inflammatory parameters such as CRP, which is consistent with its immunomodulatory role and its influence on the development of the inflammatory process [7,12,53].

10.1. Influence of vitamin D

Studies using lymphocytes cell cultures have confirmed that vitamin D enhances production of sST2 and inhibits IL-33 action via several mechanisms; by a direct action of vitamin D in promoting Th2 lymphocyte responses, by upregulated production of sST2 and by inducing of regulatory mechanisms to block the IL-33/ST2 effect and therefore inhibiting Th2-type cytokine responses [108]. As the effect of vitamin D on sST2 production is concentration-dependent, this finding supports therapeutic strategies to increase the level of vitamin D in the lungs to reduce asthma inflammation [108] and is consistent with studies indicating that vitamin D deficiency is an environmental factor that is strongly linked to asthma and its severity [109]. Several studies have confirmed the association of low levels of vitamin D with the higher risk for development of CV diseases [110]. Gruson and colleagues have postulated new interactions including involvement of the vitamin D/PTH axis in cardiovascular disease development [111].

10.2. Biological variability

For serial measurements in patients with chronic disease, biomarkers must have low biological variability (BV), and minimal on circadian rhythm. The biological variation of sST2 was recently assessed by Wu et al. [112]. In the absence of significant clinical instability of the study population, they found that the reference change value (RCV) for sST2 (30%) was much lower than RCVs observed with galectin-3 (60%) or NT-proBNP (92%). The calculated index of variation (influence of BV on measured results) was also much lower for sST2 (0.25) compared to galectin-3 (1.0) and showed that sST2 (unlike galectin-3) would be an appropriate biomarker for serial measurement, and therefore suitable for guiding therapy [12,112].

10.3. Stability

Stability of the biomarker is crucial for relevant, comparable and reproducible results both in routine determination and for long-term research studies, in which samples need to be frozen and stored for periods of months or years before analysis. Recently, Dieplinger and colleagues have demonstrated that sST2 is stable in plasma samples stored at −20 °C and −80 °C for at least 18 months, without relevant loss of residual immunoreactivity. The authors acknowledge that their findings may be restricted to the PresageTM ST2 assay, which is currently the only FDA approved and CE marked assay for routine use [113].

11. Analytical methods for the determination of serum/plasma sST2

Accurate measurement and interpretation of sST2 concentration in serum/plasma samples for routine or research applications requires

Table 2
Measured concentrations/difference of NT-proBNP and sST2 before and after HDF [13].

Parameter	before HDF median (IQR)	after HDF median (IQR)	difference (Z) before/after HDF	mean ± SD difference (%) before/after HDF
NT-proBNP (pmol/L)	728 (332–2832)	256 (140–813)	6.451; P < 0.001	−62.8 ± 12.9
sST2 (μg/L)	28.0 (18.8–36.8)	28.0 (19.0–37.5)	0.554; P = 0.579	−1.3 ± 8.6

NT-proBNP, amino-terminal pro-B-type natriuretic peptide; sST2, soluble ST2; HDF, hemodiafiltration; IQR, interquartile range; SD, standard deviation

appropriate methods, and an understanding of method characteristics that could influence the results obtained. All methods that have been used in studies to date were manual immunoassays, using antibodies against the sST2 molecule for detection. Most of them have been Enzyme-Linked Immunoassays (ELISA), that differ in the use of different (monoclonal, polyclonal, against different epitopes) antibodies for detection, in analytical sensitivity and specificity and in reproducibility. All these factors affect the quality of the results. Many of the studies discussed in this review, especially the very first studies (like the PRIDE Study) were performed using research-use-only versions of the sST2 assay, which have different performance characteristics and produce results which were not comparable with other assays [75]. Currently, there is only one FDA approved and CE marked assay on the market, the Presage ST2 ELISA assay (Critical Diagnostics, San Diego, CA, USA), that enables measurement of sST2 with sufficiently high sensitivity, specificity and reproducibility (within- and between- run CV < 10%) to meet routine quality demands [13,114,115]. This assay is the only sST2 test available which is appropriate for routine testing. When comparing results from different studies, it is important to recognise potential differences in results from different assays.

12. Discussion

Comparison of the presence and involvement of sST2 in the development of different diseases, shows that sST2 plays a different role in various pathophysiological processes followed by different mechanisms and kinetics of sST2 release into the circulation. Its action depends on the microenvironment, the characteristics of specific cell types, and the expression and release of sST2 from these cells and tissues [34]. Additionally, sST2 participates in complex interactions with the cells involved in different homeostatic mechanisms of the disease healing process. However, sST2 involvement/action is essentially connected with the expression of IL-33 and the membrane form ST2L on cells. Binding of IL-33 on ST2L causes significant intracellular effects and results in various immune regulatory functions, that can have a positive (protective/reparative) or negative (trigger, disease promoter) impact on disease development in different microenvironments and tissues [2–8,34]. In this respect, blocking of the IL-33/ST2L axis in different diseases can also result in dual and opposite effects of sST2. Therefore, expression of sST2 and elevated serum concentrations could be a sign of direct pathophysiological process and worsening of disease or a consequence and feedback effect of the IL-33/ST2L interaction in involved cells, synthesised to counteract of the disease process and possibly involved in homeostatic mechanisms of disease healing.

In some diseases (such as cardiac disease), the information obtained from several studies allows us to define the importance of sST2 clearly. In HF it has the role of an active driver of disease progression, blocking the protective effects of the ST2/IL-33 axis in heart muscle and causing cell apoptosis, fibrosis and hypertrophy [63–66]. These pathophysiological processes mean that the action and detection of sST2 in serum could predict the outcome of disease development. By measuring and following the concentration, we can predict life-threatening CV events, mortality and also adjust therapy [66–86]. The pattern of the concentration change allows us to define the patients who are likely to respond to treatment and those who should be hospitalised or discharged from the hospital according to defined risk categories [84–87].

A much more complex situation is seen in the development of cancer, where sST2 has been implicated in opposing roles of IL-33/ST2L. From the initial studies, the expression of the ST2 gene on cells is expected to suppress cancer by blocking the effect of IL-33, which is the main cytokine driver of cancer development [4]. However, the expression and binding effects of sST2 and ST2L/IL-33 are highly dependent on the specific microenvironment of other cytokines present and expressed, which create a much more complex mechanism for the development of individual cancers. Additionally, IL-33/ST2 signalling also induces the expression of cytokines that influence the development of several cancer pathologies (angiogenesis, invasiveness, metastasis, immune protection). In contrast, other data provide evidence that this signalling acts in an anti-tumorigenic role with promotion of tumour regression and eradication. The main reason for these opposite effects is the influence of IL-33/ST2 signalling on remodelling the tumour environment (TME) through recruitment of different immune cells that secrete diverse molecules which impact on tumour phenotype [29]. In this regard, recruitment and creation of pro-tumour and pro-inflammatory TME (mast cells, macrophages, MDSCs, neutrophils and T-regulatory cells) support tumour growth and advancement to malignancy, mediated by secreted cytokines that further activate IL-33 in cancer cells to sustain tumour growth. On the other hand, the recruitment of anti-tumour TME (NK cells, cytotoxic T cells) with the secretion of molecules/cytokines influences the suppression of tumor growth [34]. Several studies have confirmed both pro- and anti-tumorigenic effects of IL-33/ST2 in various cancers. Therefore, it is not possible either to explain the overall effect of sST2 on the development of various cancers, or to define the use of serum sST2 concentrations as a predictor of cancer development without knowing the exact pathophysiological process of each particular cancer. This complexity is also reflected in the different results of the clinical trials of sST2 obtained in some cancers (colorectal, lung cancer), where some researchers have observed an increase in sST2 concentration in the event of worsening disease [28,35,36], while others have argued against it [31,34] (Table 3).

The diverse role of the IL-33/ST2 axis has also been observed in inflammatory disease, where its endogenous signalling also exhibits varying immune regulatory functions during the progression of these diseases. In allergy disorders (pulmonary and skin allergy) that involve hyperreactive immune responses, IL-33 binding on ST2L on Th2 cells plays an essential pathological role of disease driver. In this regard, sST2 has an opposite function, and elevation in its serum concentration could be a sign of a positive regulatory loop in the remission of these diseases. The presence of sST2 could be used as a future therapeutic approach that could be served as a blocker of the disease progression. In line with this assumption is the positive effect of vitamin D on disease, which is believed to enhance the production of soluble sST2 in mucosal epithelial cells (bronchial and nasal) of the upper respiratory tract and therefore preventthe harmful action of IL-33 by blocking the expression of CD54 and cell aggregation in these cells [108,109]. A similar role of IL-33/ST2 and elevation of sST2 could be assumed in hepatic diseases (liver fibrosis, cirrhosis, NAFLD), where IL-33/ST2 has a profibrotic role in disease pathogenesis (Table 3).

However, IL-33/ST2L also mediates tissue-protective functions during the recovery phase following tissue injury (burn, brain stroke), including gastrointestinal diseases, like UC and CD [116,117]. In this regard, elevation of sST2 serum concentration represents and tracks disease progression (Table 3).

Table 3
The role of IL-33/ST2L and sST2, and the nature of change of sST2 serum concentrations in the progression of different diseases.

Disease	IL-33/ST2L effect on progression	sST2 conc. change	Role of sST2 as biomarker	References
Cancer	+ or –(depends on tumor)*	↑ or ↓**(depends on tumor)*	prognosis	[28–37]
Inflammation/sepsis	–	↑/↑↑	follow-up, prognosis	[49–53]
Autoimmune diseases (SLE, RA, WG)	–	↑	diagnosis	[3,21–27,38]
Asthma/allergy	+	↑**	therapy (healing) indication, prognosis	[40,41,119]
Pulmonary diseases (ARDS, fibrosis, cirrhosis)	+	↑**	diagnosis, prognosis	[46–50,116]
Gastrointestinal diseases (IBD)	–	↑	follow-up, prognosis	[7,55,57,58]
Hepatic diseases (fibrosis, NAFLD)	+	↑**	follow-up, prognosis	[59–62]
Heart diseases (HF: chronic, acute)	–	↑	prognosis, follow-up, treatment monitoring	[8–12,66–87]
Chronic kidney disease (CKD)				
Influence/according stage (1–5)	no***	≅	not for diagnosis prognosis	[88–90,117]
Mortality, CV event risk	–	↑		[14–16,92,103–105]

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; WG, Wegener's granulomatosis; IBD, inflammatory bowel disease (ulcerative colitis and Crohn's disease); ARDS, acute respiratory distress syndrome; NAFLD, nonalcoholic fatty liver disease (steatosis, nonalcoholic steatohepatitis, fibrosis, cirrhosis); HF, heart failure; CV, cardiovascular.

* Change depends on the expression and effect of IL-33/ST2 signalling in tumour cells: (1) pro-tumorigenic effect (with activation and recruitment of pro-inflammatory cells into the tumour microenvironment (TME) and promoting tumour growth and malignancy), or (2) anti-tumorigenic effect (with activation and recruitment of NK, cytotoxic T cells into anti-TME, leading to tumour regression)

** Change/elevation in sST2 concentration is/could be the result of the counter-action (healing process) on disease development by blocking the IL-33 and IL-33/ST2L effect on cancer/epithelial cells of the respiratory tract/hepatocytes and immune cells. Stimulation of this process could be the therapy target.

*** IL-33/ST2L pathway suppose to be involved in both processes, in tissue inflammation and repair. Further investigation is necessary to delineate the precise role of IL-33/ST2L [117].

Knowledge of the exact pathophysiological mechanisms of various diseases and the molecules that are important in their progression gives us much better opportunitues to detect, monitor and treat these diseases. Modulation of the IL-33/ST2 axis represents a promising strategy for treating all disorders that involve dysregulation of cytokine signalling. In this regard, sST2 could be an important and useful marker for monitoring these diseases. We have a good method for measuring sST2 in routine clinical practice and we have a good understanding of the characteristics relevant to its use as a biomarker. There are clear clinical recommendations for its use in HF, where it is established as a prognostic marker. But for other conditions /diseases, there are limitations on the routine use of sST2 remain an issue. We still need to verify its potential role in routine practice with precisely conducted therapy-oriented clinical studies to delineate its use as a biomarker for diagnosis, prognosis and monitoring. It will be important to use sST2 in combination with other biomarkers that arise from other pathophysiological processes and with other diagnostic/prognostic tools to enhance their diagnostic/prognostic power. The characteristics of sST2 (short half-life, low biological variability, changing in serum concentration according to disease progression) and its known prognostic value alone and in combination with other biomarkers and tools could be helpful in monitoring therapy, for defining treatment responders and monitoring treatment (combination or dose of chosen medications). Some of these goals are already realised in the treatment of HF patients. It is important to extend similar clinical studies to the other diseases discussed above to confirm broader potential usefulness of this biomarker in routine practice. In the case of the modulation capability of sST2 on IL-33/ST2 axis effects, it is also vital to extend research on the potential of sST2 as a future therapeutic target. Various studies suggest that sST2 could block the progression of some cancer diseases, allergy or inflammatory diseases, or be useful as an adjuvant treatment to increase the effectiveness of anticancer or antiallergic/inflammatory immunotherapies [34,116].

13. Conclusions

The ST2/IL-33 axis is one of the most diverse and ubiquitous signalling pathways that occurs in several complex pathophysiological mechanisms in different cells and tissues. Its action and the action of sST2 as its effect blocker are involved in and contribute to the development of inflammatory, autoimmune and cardiac disease, cancer and other conditions. Knowledge of the pathophysiology of ST2 helps us to understand, detect/diagnose, treat and monitor these diseases. In the light of the information gained from basic, molecular and clinical studies, and the development of accurate, sensitive and reproducible analytical methods, sST2 has become an important biochemic and an additional tool for managing a range of clinical conditions, particularly cardiac disease. In HF it already matches all essential criteria for a good prognostic and therapeutic marker. sST2 has important marker characteristics (low biological variability and independence of gender, age, renal function and HDF) that enhance its clinical value and make it one of the most promising disease biomarkers, deserving of further study and wider application in clinical practice.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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