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New prognostic biomarker in cardiovascular field: ST2 (IL1RL1)

Reşat Dikme[1], Mahmut Padak[1], Mustafa Göz[2], Mahmet Salih Aydın[2], Ömer Göç[1]
[1]Vocational School of Health Services, Perfusion Techniques Program,
[2]Department of Cardiovascular Surgery, Faculty of Medicine, Harran University, Şanlıurfa, Turkey

Abstract

As a result of natural immunity in the heart ST2 (IL1RL1) that protects the heart against excessive pressure load and tension, has two important isoforms (ST2L–membranebound, sST2-soluble). As ligand of ST2L and sST2 is interleukin 33 (IL33), the connection of ST2L to IL33 stimulates cardioprotective signal cascade whereas connection of sST2 to IL33 causes annihilation of these positive effects. As a high level of sST2 shows that the heart is under dense stress, this situation causes cell death, tissue fibrosis, decreased cardiac functions and an increase in progression rate of disease. That is why in cardiovascular disease sST2 is accepted as a biomarker of poor prognosis. It was obtained that the increase of sST2 over normal concentration multiplies negative situations related to cardiovascular diseases 3 times more. In 2013 in ACCF/AHA (American College of Cardiology Foundation/American Heart Association) guidelines, sST2 that was defined as "novel biomarker" for HF (Heart failure), is an independent biomarker from natriuretic peptides and cardiac troponins and is an important sign in cardiovascular diseases. ST2 is not affected by factors such as age, body mass index and kidney function disorder.

Keywords

ST2; Interleukin 1 Receptor-Like 1; sST2; Soluble sST2; Cardiovascular Diseases; IL1RL1

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Corresponding Author: Reşat Dikme, Harran University Yenişehir Campus Vocational School of Health Services, Haliliye, 63300, Şanlıurfa, Turkey.
GSM: +905354587844 F.: +90 4143183209 E-Mail: rdikme@harran.edu.tr
ORCID ID: 0000-0001-9157-7830

Introduction

Interleukins (IL) are effective in the formation of cardiac remodeling, they also show a cardioprotective effect by functioning as signal molecules between cardiomyocytes and fibroblasts during the proinflammatory period. Especially IL33 can behave as a cytokine and transcriptional featured nuclear factor helps to protect heart and form signal among cells [1, 2]. ST2 (Interleukın 1 Receptor-Lıke 1, IL1RL1, T1, IL1RL1, Fit1, IL33R, DER4) plays a part in important steps in this period and inflammatory response [3].

As a result of valvular heart disease, hypertension, coronary artery disease (CAD) and myocardial infarction, pathophysiological processes such as cardiomyocyte hypertrophy and cardiac fibrosis occur. All these processes are given as a response to mechanical overload and wall stress is tried to be pulled to normal limits in this way. As these responses are given deadly situations show up mostly. When there is mechanical overload in heart, IL33 shows paracrine effect between cardiac myocytes and fibroblasts [1]. Although this cytokine is mainly produced in the heart by fibroblasts, they are produced by myocytes during cell necrosis [1, 4]. IL33, which's gene expression is supported by TNF- α (tumor necrosis factor α) and IL-1 β, prevent hypertrophy formation against pro hypertrophic factors [5]. In the studies done with rat, there are obtained findings of IL33 decreases heart hypertrophy and fibrosis when there is cardiovascular overload. The same results are achived with IL33, that is applied to fibroblasts in a cell culture environment, similar to these data protecting heart [6].

During cellular stress with the liberalization of IL33, IL33 shows the effect by connecting to ST2. ST2, which was discovered in 1989, is the member of interleukin-1 (IL1) receptor protein family and it plays a central role in immune response and organization of inflammatory response [7]. Many studies were done regarding IL1 family that is named as cytokines due to their intercellular communication capacities. These studies helped to clarify the connection between the rising body temperature and infection or inflammation. Among wide physiological role of IL1 family, there is stimulation and inhibition of cells.

The discovery in 1989 was made by two independent labs studying on growth and stimulated fibroblasts [8]. ST2 has been known as an orphan receptor (receptor associated with immune and inflammatory) for 15 years (1989-2005) however in 2002 it was obtained that it was secreted by cardiac cells as a response to myocardial stress and defined as IL33 receptor in 2005 [9]. ST2 that is in Q arm of the 2nd chromosome (2Q12) consists of 13 exons, 40536 base and 556 aa [7].

ST2 İsoforms

As a result of natural immunity ST2 that protects the heart against excessive pressure load and tension, has two important isoforms. These isoforms are membranebound form-ST2L and soluble sST2 (Figure 1).

As a membrane receptor ST2L is also known as IL1RL1-Beta whereas soluble receptor sST2 is known as IL1RL1-Alfa [2]. The third known isoform of ST2 is a variant form which is STV is defined as dominant in the gastrointestinal system [10]. Different forms of ST2 are formed with alternative splicing of the same mRNA. ST2 gene that is formed with the processing of alternative splicing of 3 of the same mRNA and gene promoters, has proximal and distal promoters and is modified with transcriptional regulation [2].

sST2 was first used in 2002, it is a potential biological biomarker for the cardiac disease and this situation was emphasized with a finding that sST2 mRNA is highly inducted after mechanical stress or treatment with IL-1β in cultured rat cardiomyocytes. In this study, sST2 concentrations were obtained from the blood of rats following myocardial infarction [5].

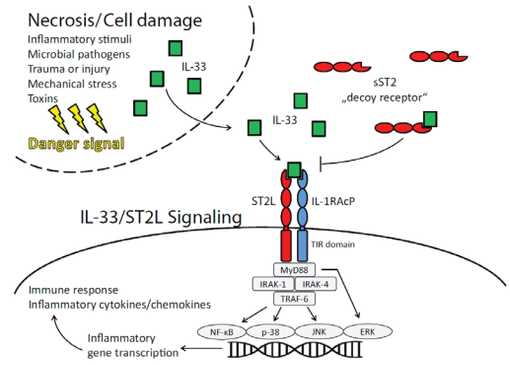

Figure 1. Two different isoforms of ST2 (ST2L ve sST2)

In a study done by Baba et al. two GATA patterns (1 and 2) were obtained in the upstream part of the region where transcription of the ST2 gene starts. In the same study especially in ST2 mRNA expression, it was found out that GATA2 provides the main control and as a result, GATA patterns were obtained to play an important role in the last expression of ST2 [11]. The data regarding inner control of differential transcription of sST2 and ST2L is not well-known and this situation is limited with hematopoietic cells (GATA2, neurotrophin p75 receptor) [11]. At sST2 levels, genetic factors affect 40% of interindividual variability [12].

Membranedependent ST2L has 3 domains. One of the domains is "extracellular immunoglobulin G domain", the other one is "single transmembrane domain" and the last one is "intracellular domain". Soluble sST2 does not have transmembrane and intracellular domain however it can move freely in the periphery cycle having with 9 aa C terminal sequence [2,13]. As ST2 act is complex and not quite unrealized, it is strictly connected with the effect style of IL33.

IL33 causes inflammatory gene transcription by bounding ST2L and as a result immune response is formed with stimulation of production of cytokines/chemokines. IL33 bounds to ST2L receptor via IL1RAcP accessory protein. IL1RAcP accessory protein increases bounding affinity of IL33 to ST2L [14]. As bounding of ST2L to IL33 shows the effect by stimulating cardioprotective signal cascade (decrease of cardiac injury, prevention of apoptosis, the decrease of inflammatory effect, the decrease of hypertrophy and fibrosis, protection against mechanical warning and damage), bounding of sST2 to IL33 causes disappearance of these positive effects [1]. sST2 decreases the positive effects of IL33 by acting as a trap receptor (decoy receptor) [1]. By bounding IL33, sST2 decreases the usability of IL33 by interacting with sarcolemmal (cell membrane of muscle fiber) receptor. That is why one rise in sST2 can decrease the cardioprotective effect of IL33 over cardiac cells and create a negative prognostic effect over general cardiovascular risk profile [1].

According to multiple clinical studies, sST2 myocardium infarction showed up as a clinically beneficial prognostic biologic biomarker in patients having cardiovascular diseases such as acute dyspnea and coronary failure with a low-risk community-based population [15]. According to the study done by Weinberg et al. increased sST2 levels just after myocardium infarction case, showed up as a negative prognostic factor [5].

Warning sequence occurs within the cell due to working of IL33/ST2L signal with NF-kB (nuclear factor kappa B), p38, JNK (jun N-terminal kinase) and ERK (extracellular signal-regulated kinases) pathway (Figure 2) [16]. IL33/ST2L also contributes to the immune response by excreting cytokines associated with TH2 in inflammatory diseases [17].

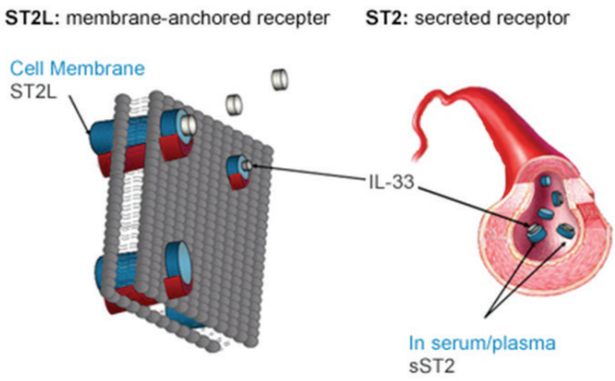

Figure 2. Intracellular pathways activated with interleukin-33/ST2L signal [10].

Kakkar et al. showed an increase of IL33 secretion from cytoplasmic vesicles in the mechanical stress of living cells [16]. In another study parallel increased secretion of both ST2L and sST2 from cardiomyocytes and cardiac fibroblasts under biomechanic stress, was determined [18]. In a study done with rats, ST2 became the most stimulated molecule among thousands of gene transcription as a result of biochemical stress. In another study in models of ventricles overloaded with pressure, treatment with IL33 prevented hypertrophy whereas in hypoxia IL33 saved cardiomyocytes from apoptosis. In ischemia-reperfusion MI IL33 treatment reduced infarction size, ventricular dilatation was refined, caspase 3 was repressed and apoptosis inhibitors increased [17]. IL33 can make these positive effects via ST2L. As a result of the blocking of ST2L by anti ST2L, the antihypertrophic and antiapoptosis effect of IL33 disappeared. In annihilation of the positive effect of IL33 by adding sST2, the same situation was observed. These studies present the importance of ST2.

Now the source of the sST2 cycle in healthy individuals and patients having different diseases cannot be obtained completely. This is especially valid for cardiac disease. In a study done in neonatal rat heart myocytes, the source of the sST2 cycle in cardiac disease was found as myocardial derived [5]. In addition to this, newer studies showed that in human cardiac disease dominant source of sST2 may be vascular endothelium cells rather than human myocardium [19]. As all the studies are evaluated together it was found out that sST2 is produced by cardiac fibroblast, cardiomyocytes, macrovascular (aorta and coronary arteries) and microvascular endothelium cells in damage and stress condition.

sST2 Concentration Measurement

The level of sST2 can be obtained by making its quantitative measurement. In human serum/plasma for sST2 measurement, the first immunosorbent analysis related to enzyme was done in 2000 [20]. As high-level sST2 indicates that the heart is under stress, this leads to cellular death, tissue fibrosis in the heart as well as a decrease in cardiac functions and progress of the disease. That is why sST2 is accepted as a biomarker of ingravescent prognosis in individuals in cardiovascular disease [2]. As soluble sST2 is an urgent biomarker which is an important indicator of mortality, hospitalization requirement and negative results that may show up in patients with heart failure, it is a rather strong parameter for cardiovascular diseases. In recent years the reference values for sST2 in the cycle are derived from a subset of Framingham study (Framingham heart study) (Figure 3). According to this study there showed up important differences between males and females. In the study as reference range for sST2 in male sampling (n = 462) was found as 11-45 ng / mL, it was found as 9-35 ng / mL in female sampling (n=674) [21]. The results of the study regarding the reason for genderspecific differences and its possible results were not clarified [21].

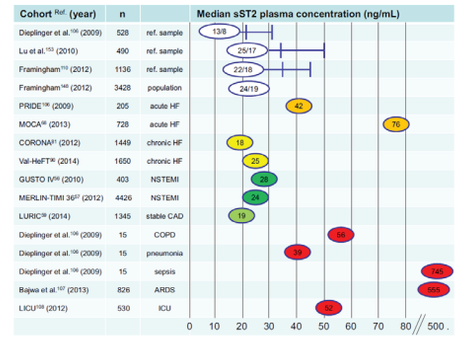

Figure 3. Serum/plasma concentration studies of s ST2 [22].

In many previous studies as the normal average value of sST2 is 18 ng/ml, concentrations over 35 ng/ml strongly states increased risk in terms of cardiovascular diseases. It was obtained a value over 35, increases negative situations related to cardiovascular diseases 3 times more [10]. The basic reason for serum/plasma sST2 concentration difference generates from using different enzyme-linked immunosorbent assay (ELISA) kits. Today sST2 studies with ELISA method are generally done via 3 kits (Presage sT2 assay, R-D sT2 assay, MBL sT2 assay).

The Penn Heart Failure Study (PHFS) revealed that high sST2 levels give a predictive idea about death, heart transplantation or hospitalization in patients having heart failure [23]. According to the PHFS study, it was obtained that patients having sST2 value over 35 ng/ml carry 2.8 times higher risk of exposing negative results in 30 days compared to individuals having low sST2 concentration. According to the same study relative risks of exposing negative results in terms of cardiac diseases in the following 4 years in individuals having an sST2 level higher than 35 ng/ml, persist at 1.8 times. Since high sST2 level can reflect worsening of disease before changing symptoms of cardiac diseases visibly, treatment profile can be improved by evaluating sST2 level in plasma in patients having chronic heart failure.

According to new researches about ST2, HT, cardiac failure and cardiovascular mortality risk increases in asymptomatic individuals having high sST2 values and in this way these people become a candidate for therapeutic interventions. According to an analysis done by the Framingham Heart Study Cohort, at least in 25% of asymptomatic individuals in terms of CAD, ST2 level gives important data. Among these patients, the ones having the highest sST2 values after an average of 11.3 years, sST2 levels were associated with 32% of cardiac failure and

45% of death with increased risk. According to the results of another study, sST2 also shows itself as a strong ischemic biomarker, especially it can predict cardiomyopathy etiologies. In these individuals making suitable risk classification by using sST2 level, will provide benefit.

In 2013; ST2 was defined as "novel biomarker" for HF (Heart failure) in ACCF/AHA (American College of Cardiology Foundation/American Heart Association) directory [24]. In clinical studies done with patients having an acute myocardial infarction (AMI) or acute coronary syndrome, it was clearly revealed that increased sST2 is associated with disappointing results [25]. After AMI, early measuring sST2 in patients can be helpful in the prediction of recovery of negative left ventricle functionally. Although sST2 measuring in patients applied to ER with acute chest pain is not valuable for acute myocardium infarction or acute coronary syndrome diagnosis, lately sST2 is shown as an independent predictor about cardiovascular mortality and all long term reasons of disease in patients having stable CAD [26]. In the last term as sST2 becomes a biomarker independent from natriuretic peptides and cardiac troponins in the evaluation of HF, it is also an important sign in STEMİ, NSTEMİ, coronary artery, valvular diseases, cardiomyopathy, coronary bypass and cardiac surgery, acute cardiac allograft rejection and acute Kawasaki disease [27, 10].

Result

An optimum biologic biomarket that is used in diagnosis and prognosis should primarily be independent of other factors. For example, a biomarker that is used in cardiovascular diseases should not be in relation with other circumstances and should not be affected by mixing factors that can affect blood concentrations. In order to become a reliable biomarker that is used in a disease, there should be an "optimal provision". ST2 is not affected by factors such as age, body mass index and kidney function disorder [27]. According to the results of studies done on in vitro stability of sST2, it stays stable in analytic room temperature for 48 hours, at 4°C for at least 7 days, at -20 °C and -80 °C for at least 1.5 years [28]. Increasing data about actions of sST2 and ST2L on cardiovascular system directed doctors thinking to evaluate sST2 plasma levels as a new marker regarding cardiac failure and ischemic cardiac diseases. Defining of new biological biomarkers that can obtain ingravescent findings of clinical conditions of a disease earlier, stop or decrease negative results of disease is a chief step in clinical diagnosis development. Moreover, new biomarkers such as ST2 can be used to diagnose the benefits of early treatment and obtain a prognosis of disease [13].

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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