

IL-33/ST2 pathway as upper-hand of inflammation in allergic asthma contributes as predictive biomarker in heart failure

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Abstract

Allergic asthma is an inflammatory disorder of the bronchi, and as a major health problem, more than 350 million people suffer from asthma in the world. Many cardiovascular disorders resulted in the impairment of the heart's power to pump blood that leads to the HF. More than 25 million people worldwide live with HF. Accordingly, identifying the biomarkers to predict the onset of future asthma and HF is necessary. IL-33 is an inflammatory cytokine that has the main role in pathophysiology of asthma and HF. Also, in IL-33 receptor, the ST2 is involved in cardiac fibrosis and remodelling in HF and pathogenesis of allergic asthma. Increased sST2 in allergic asthma helps to control inflammation during asthma, but increased sST2 in HF is a predictable biomarker to present risk factor of HF during the time of the patients.

Keywords Allergy; Cardiovascular diseases; Cell signal; Cytokine; Receptor

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Introduction

Allergic asthma is a heterogeneous chronic inflammatory disorder of the bronchi. More than 350 million people suffer from asthma in the world, which is a major health problem because of high prevalence and mortality.^{1,2}

In asthma, many immune cells and inflammatory mediators are involved, including EOSs, mast cells, lipid mediators, and several interleukins. Asthma is characterized by AHR, variable airflow limitation, cough, wheeze, and shortness breath, which are induced by genetic predisposition and numerous environmental factors including such as allergens. Chronic inflammation and airway remodelling are main pathological features existing in asthma.^{3–5}

Allergic inflammation (type 2) is an important molecular mechanism in the asthma pathogenesis that is mainly regulated by Th2 cells. Airway inflammation is associated with the activation of immune cells (such as T cells, ILC2s, EOS,

and mast cells) and over production of inflammatory cytokines (such as IL-4, IL-5, and IL-13).^{6,7}

Many cardiovascular disorders resulted in the impairment of the heart's ability to pump (in or out) blood, which leads to the clinical syndrome of HF. It was estimated that more than 25 million people are living with HF worldwide. HF patients often present nonspecific symptoms and with a wide differential diagnosis. The symptoms, such as dyspnoea, orthopnoea, and paroxysmal nocturnal dyspnoea, are due to congestion, whereas others are due to lack of adequate cardiac output, including weakness, fatigue, and exercise intolerance. However, many patients with abnormal ventricular systolic function are asymptomatic and necessarily do not have the clinical HF syndrome. Indeed, along the developed HF, there are increasing numbers of cell injury, inflammatory, remodelling, and neurohormonal biofactors, whose measurements might relay important information about HF (Table 1). Accordingly,

identifying the biomarkers to predict the onset of future asthma and HF is necessary.^{8,9}

IL-33 is a member of the IL-1 cytokines family and, as an ‘alarmin’, senses damage in inflammation due to cell injury. It is also closely associated with the airway inflammation and asthma and can induce Th2 biased allergic airway inflammation. ST2 is a receptor of the IL-33 and consists of two common subtypes: sST2 and ST2L. ST2L is the specific IL-33 receptor and is mainly expressed on the Th2 and mast cells, whereas the sST2 is the decoy receptor that negatively regulates the IL-33/ST2 pathway.^{10–13}

It is believed that ST2 has immunomodulatory function and, importantly, is involved in cardiac remodelling and fibrosis in HF. Clinically, sST2 concentration is predicted by a phenotype of cardiac decompensation and remodelling, and its concentration is not affected by age, renal function, or body mass index.^{14,15} Preliminary data suggesting the benefit of elevated sST2 concentrations can be used to ‘guide’ therapy for prevention of HF complications, and therefore, recognition of ST2 and its pathway with IL-33 is important in asthmatic and HF patients.

IL-33/ST2 axis

The IL-33/ST2 axis plays a main role in allergic inflammation and asthma. IL-33 is usually secreted upon damage induced cell or immune cells that can alert the immune system. In allergic asthma, IL-33 is produced in immune cells during allergic inflammation. The sST2 inhibits binding of IL-33 to ST2L and negatively regulates IL-33, which is associated with several immune disorders.^{16–18}

Asthma is basically characterized by allergic inflammation, AHR, elevated IgE level, and increased Th2 cytokines levels. In allergic asthma, IL-33 is produced by mast cells after IgE-mediated activation and is able to trigger pro-inflammatory cytokines releasing. IL-33 is a strong inducer of type 2 immune responses (Th2). The IL-33/ST2 signalling pathway activates eosinophils in airway, which exacerbates airway inflammation. This pathway is important for the progression of allergy and IgE-dependent inflammation.^{19–22}

In asthmatic lung, IL-33 is expressed by ASMCS, which presents promise as a potential inflammatory marker for asthma. Therefore, IL-33 is involved in pulmonary inflammation, and ST2 is a therapeutic marker in asthma. The sST2 binds to IL-33, acts as a decoy receptor of IL-33, and suppresses IL-33 induced NF-κB activity, and expression of the IL-4, IL-5, and IL-13.^{23,24}

IL-33 plays an important role in initiating innate and adaptive Th2 immune responses, which is implicated in the pathogenesis of allergy and asthma. The basophils express ST2L in high levels and respond to IL-33 by producing pro-inflammatory cytokines such as IL-4, IL-5, IL-13, and GM-CSF.^{25,26}

Table 1 Heart failure’s biomarkers

NT-proBNP	Myocyte stretch BNP	Myocardial insult Myocardial injury Troponin I	MR-proADM	Oxidative stress Myeloperoxidase	Oxidized LDL
Angiotensin II	Renin aldosterone	Troponin T	MR-proADM	Arginine vasopressin	Arginine vasopressin system
Inflammation CRP	ILs TNF-α	Sympathetic nervous system Chromogranin A	MR-proADM	Arginine vasopressin	Arginine vasopressin system
		Remodelling Adiponectin	MR-proADM	Hypertrophy/fibrosis MMPs	Collagen propeptides
		Apoptosis GDF-15	MR-proADM	sST2	Gal-3

The IL-33 gene

The IL-33 gene is also described as a NF-HEV, which codes a 31 kDa protein that does not contain a signal sequence for secretion. The pre-IL-33 (precursor 31 kDa protein) is cleaved by caspase-1 into IL-33 (mature 18 kDa protein). IL-33 binding to ST2L on the cells stimulates the intracellular signalling pathway and activation of NF- κ B and MAPK. Therefore, IL-33 signalling via ST2L plays important roles in the production of Th2 cytokines, inflammation, and Th2 cell-mediated immunological responses. NF- κ B is a key regulator in the IL-33 signalling pathway and the Th2 cytokine genes expression. NF- κ B plays a critical role in Th2 cell-mediated immunological responses. Also, the p50 and c-Rel have a role in the development of allergic airway inflammation. The p50 is essential for the expression of transcription factor GATA-3 that can regulate the Th2 cytokine genes expression.^{6,27,28}

On the other hand, the sST2 level is elevated in asthma and also plays a critical role in Th2 cell-mediated diseases. In fact, sST2 effectively attenuated inflammatory responses and Th2 cytokines production and negatively regulates the Th2 cell-mediated immunological responses. The sST2 inhibits the binding of IL-33 to ST2L and the production of Th2 cytokines through signal of the IL-33 in allergic airway inflammation. Therefore, in allergic asthma, the sST2 has antagonistic effects on IL-33 signalling.^{29,30}

IL33 and ST-2 loci are strongly associated with the asthma development. Survival and activation of the eosinophil are increased by IL-33 and potentially important effect of IL-33 is ILC2s activation, which are a rich source of IL-13 and IL-5, which contribute to persistent asthma and airway inflammation.^{31,32}

IL-33/IL-17A

IL-33 cooperates with IL-17A to exacerbate AHR by initiating neutrophilic inflammation via CXCR2 signalling, which leads to additional Th2 responses. IL-31 is produced by Th2 cells implicated in the pathogenesis of allergic rhinitis and asthma. IL-31 displays an independent and unique role in the allergic rhinitis pathophysiology. Th17 is secreted from Th17. IL-25, IL-17A (also called IL-17), and IL-17F are involved in the allergic rhinitis and asthma pathogenesis. IL-17 triggers epithelium inflammation in the bronchi and nasal by stimulating innate immunity, inducing neutrophilic inflammation. As such IL-33/ST2 pathway, IL-17A and IL-31 may be considered critical players in the pathogenesis of allergic inflammatory disorders. The IL-31/Th17 immune response is generated by IL-33/ST2 pathway activation in CD3+ T-cells, and also, IL-33/ST2 is involved in IL-31/Th17 immune response of allergic diseases activation.^{33–35}

Furthermore, higher sST2 level together with higher IL-17A level in asthma shows exacerbations in terms of wheezing, coughing, and shortness of breath. The sST2 plasma level, together with the IL-17A production, may reflect the importance of IL-33/sST2 pathway and Th17 immunity in asthma, underlining the relevance in the severity of the immune response. Finally, whereas the IL-33/ST2 pathway involving IL-31/Th17 immune response is crucial for allergic asthma, the sST2 could be a potential target for therapeutic strategies in control of the asthma progression toward the more severe form.^{36–38}

IL-33 and immune cells

Moreover, the effect of IL-33 on the Th2, it was shown that CD8 T cells express ST2, and after activation of the TCR, CD8 T cells produce IFN- γ in response to IL-33 stimulation. However, in the absence of ST2, the number of IFN- γ producing CD8 T cells will increase. Also, in allergic dermatitis, ST2 inhibits in the recruitment of macrophages and neutrophils, as well as cytotoxic T CD8 cells, to the site of inflammation.^{39,40}

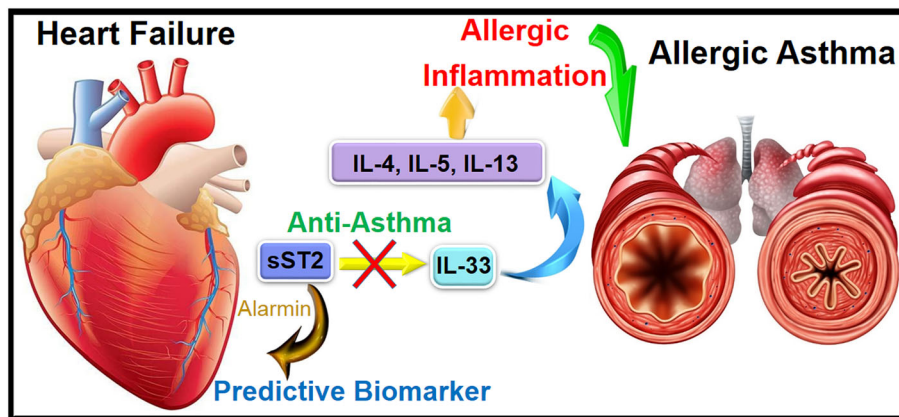
It has been showed that the IL-33/ST2 signalling pathway can enhance expression of the CCR3 that is important in facilitating the eosinophils mobilization from bone marrow to the peripheral blood and the trafficking to the inflammation site. It was demonstrated that in the BALF, IFN- γ is mostly produced by T CD8 cells, and ST2 may act as a negative regulator of IFN- γ producing T lymphocytes during allergic inflammation. Finally, suppressive T CD4 Foxp3 regulatory cells can also express ST2L. However, in the ST2 receptor absence, the Foxp3 and IL-10 mRNA is increased in the lung, suggesting that the inflammatory response regulation in the lung is not dependent on ST2-expressing Foxp3 regulatory T cells.^{41,42}

ST2 and heart failure

Cellular stretch induces IL-33, which protects against hypertrophy and fibrosis in mechanically strained tissues via activation of IRAK, MyD88, and ERK, and ultimately NF- κ B.^{7,43,44}

The ST2 in HF is essentially an inflammation marker and signals the presence and severity of adverse cardiac fibrosis and remodelling that can be a valuable reproducible evidence for prognostication in HF. The ST2 is expressed by cardiac fibroblasts and cardiomyocytes in response to mechanical stress that can be bind to IL-33. It was showed that circulating ST2 leads to cardiac remodelling, fibrosis, and ventricular dysfunction and also acts as a decoy receptor for IL-33. The high levels of sST2 block the favourable effects of IL-33 by

Figure 1 In allergic asthma, the immune cells including Th2, EOSs, mast cells, release inflammatory mediators, and allergic cytokines such as IL-4, IL-5, and IL-13, which initiate allergic inflammation and lead to beginning of main asthma symptoms include AHR, cough, wheeze, and shortness breath. IL-33 is closely associated with the airway inflammation and asthma and can induce Th2 cytokine secretion. ST2L is the specific IL-33 receptor and is mainly expressed on the Th2 and mast cells, whereas the sST2 is the decoy receptor that negatively regulates the IL-33/ST2 pathway. IL-33 binding to ST2L on the cells stimulates the intracellular signalling pathway, activation of NF- κ B, and MAPK. Therefore, IL-33 signalling via ST2L plays important roles in the production of Th2 cytokines, inflammation, and Th2 cell-mediated immunological responses. On the other hand, the IL-31/Th17 immune response is generated by IL-33/ST2 pathway activation in CD3+ T-cells, and IL-33/ST2 is involved in the activation of IL-31/Th17 immune response of allergic diseases. HF patients often present nonspecific symptoms and with a wide differential diagnosis. Some of the symptoms, such as orthopnoea, dyspnoea, and paroxysmal nocturnal dyspnoea, are due to congestion, whereas some are due to lack of adequate cardiac output, including weakness, fatigue, and exercise intolerance. The ST2 in HF is essentially a marker of inflammation and signals the presence and severity of adverse cardiac remodelling and fibrosis that can be value reproducible evidence for prognostication in HF. In heart failure, sST2 production is up-regulated, and increased sST2 in HF suspected patients could be alarming factor and present risk factor of HF.



limiting the activation of the cascade triggered by interaction of the IL-33/ST2L. Thus, higher level of sST2 is associated with adverse cardiac remodelling, increased myocardial fibrosis, and worse cardiovascular outcomes. In cardiovascular health, sST2 production is low, which permits IL-33/ST2L interaction at the cardiomyocyte level that leads to cardioprotective cascade activation by diverse intracellular kinases activation. In heart failure, sST2 production is up-regulated, and sST2 binds IL-33 as a decoy receptor limiting the activation of the cardioprotective cascade in the cardiomyocyte triggered by the IL-33/ST2L interaction. Moreover, sST2 plays a modulatory role in obesity-associated vascular remodelling. The sST2 is a biomarker in acute and chronic HF, and a rise in sST2 level provides important prognostic information and may open a new avenue for the ST2 modulation as a potential therapeutic target in HF.^{45–50}

Similar to sST2, Gal-3 and GDF-15 are currently candidate as biomarkers in HF that can be additive to other established markers such as cardiac troponins or natriuretic peptides. So the sST2 level is a useful parameter to monitor therapy.^{51–54} ST2 may be involved in LVH remodelling and is also a cardiac fibrosis marker. However, in LVH, its precise pathophysiological roles remain unclear. ST2 has emerged as a marker of inflammation, remodelling, and cardiac fibrosis and is also a BNP-independent predictor of cardiac mortality.^{55–57}

Conclusion remarkable

IL-33's biologic activity is increased by a some proteases (including neutrophil elastase and reduced by caspases). IL-33 has an important role in the allergic inflammation initiation that acts as a cytokine through the ST2 and stimulates the production of Th2 cytokines. The sST2 can regulate Th2 responses by neutralizing the IL-33 activity. Injury of the epithelium by allergen exposure leads to the release of IL-33 that then binds to ST2L on mast cells, ILC2s, Th2 cells, eosinophils, and basophils. IL-33 is a key regulator of CD4 cell differentiation into Th2 cells and is a chemoattractant for Th2 cells to lymph nodes and tissue. IL-33 signalling leads to expression of chemokines, pro-inflammatory cytokines, and lipid mediators [CXCL8 (IL-8), TNF- α , IL-5, IL-6, IL-13, and prostaglandin D2]. The ST2 is overexpressed preferentially on Th2 effector cells but not on Th1. Furthermore, in Th2-dependent allergic airway inflammation, neutralizing antibody administration against ST2 inhibits the development of Th2 effector functions. Although sST2 is highly produced in sera of asthmatic patients and has a role in Th2 cytokines production, sST2 directly binds to IL-33 and suppresses activation of NF- κ B, suggesting that the soluble ST2/IL-33 complex fails to bind to ST2L. Therefore, pre-treatment with sST2 may reduce production of IL-4, IL-5, and IL-13 from IL-33 stimulation. The sST2 acts as a negative regulator of Th2 cytokine production

by the IL-33 signalling, and in asthma, this suppression leads to attenuation of allergic inflammatory responses.

On the other hand, sST2 is a useful diagnostic and prognostic marker in human HF, and sST2 excess leads to cardiac fibrosis and ventricular dysfunction. The biomarkers such as sST2 have been included for additive risk stratification of patients with acute and chronic HF. BNP is the gold standard biomarkers in the diagnosis and prognosis of HF. As a novel biomarker, sST2 shows potential in determining the prognosis of HF, and higher post-operative sST2 is associated with increased incidence of cardiovascular event or mortality. Traditional methods of HF assessment are limited by cost, subjective interpretation, time consumption, or invasive nature.

Biomarkers offer convenient, objective, and safe. Whether for determining diagnosis and prognosis, the field of HF biomarkers is rich, and identifying predictable biomarker approaches for HF management produces opportunity for specifically tailoring care to the individual (Figure 1). At least, increased sST2 in allergic asthma can be useful and help to control and cure of inflammation during asthma attack. But increased sST2 in HF suspected patients could be an alarming factor and present risk factor of HF that may lead to cardiovascular problems in suspected peoples, and increased level of this biomarker should be considered about HF in present and future of patient's history.

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