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Signalling networks in focus

ST2/IL-33 signaling in cardiac fibrosis

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ABSTRACT

Cardiac fibrosis is a significant global health problem associated with nearly all forms of heart disease. In the heart interstitial fibrosis may be reparative, replacing areas damaged by myocyte loss after acute infarction, or compensative, responding to cardiac overload. However, after injury in chronic cases activated myofibroblasts contribute to the tissue imbalance of the newer molecules associated with cardiac fibrosis, interleukin (IL-33), and suppression of tumorigenicity 2 (ST2). Physiological stretching causes myofibroblasts to release IL-33 which binds the ST2 receptor (ST2L) on the cardiomyocyte membrane, promoting cell survival and integrity. But in chronic conditions, local and neighboring cells can increase the release of IL-33's decoy, soluble ST2 (sST2), which blocks IL-33/ST2L binding, promoting tissue fibrosis. We review recent studies that have illustrated novel aspects of ST2/IL-33 signaling mediating cardiac fibrosis, and some newer biomolecular targets for the prevention and treatment of maladaptive remodeling.

1. Introduction

Cardiac fibrosis is a significant global health problem associated with late repair in nearly all forms of heart disease (Teh et al., 2015). Scar tissue is the final cellular and tissue response to pathophysiological stress, during which the heart undergoes late remodeling to compensate both the loss of dying resident cells and the hypertrophic rearrangement of surviving cardiomyocytes (Ma et al., 2018). In pathological states such as hypertension, coronary occlusion, valve disorders and myocardial infarction, the left ventricle (LV) undergoes a series of biomechanical, molecular, cellular and extracellular matrix (ECM) changes that alter the LV chamber geometry and physiology (Ma et al., 2018). The increase of ECM deposition and/or the decrease of ECM degradation stiffens the ventricle wall; this is the main cause of diastolic dysfunction and alteration of cardiac pulse propagation through the myocardium, which leads to contraction abnormalities and arrhythmia (Nielsen et al., 2019). Structural rearrangements are accompanied by inflammatory edema and scar formation around perivascular areas, slowing oxygen and nutrient flow to myocardiocytes and triggering the pain chain that sustains myocardial remodeling (Nielsen et al., 2019). These events are due to the limited regenerative capacity of the myocardium after injury and repair processes to remove necrotic cardiac cells and promote scar tissue replacement so as to maintain cardiac structure and functional integrity. They depend on activated cardiac fibroblasts within the connective tissue, which secrete pro-inflammatory molecules related to ECM turnover, promoting a pro-fibrotic environment (Travers et al., 2016).

For these reasons, inflammation must be considered the fundamental component of myocardial remodeling, but although collagen deposition in the early stage is an indispensible and reversible physiological process of tissue repair, it can evolve through a progressive, irreversible fibrotic response (Nielsen et al., 2019). The result is the irreversible capacity for damaged tissue to reverse the pathological rearrangement and fully recover its normal functions.

The complexity of cardiovascular mechanisms associated with maladaptive remodeling means that the molecular patterns involved are numerous - and not yet fully understood. The mechano-sensitive signaling pathways are the main systems that have been investigated and are closely associated with cardiac fibrosis, since they are involved from the start to the late stage of remodeling responses (Broch et al., 2015).

The first biomechanical system induced during cardiac stretching is ST2/IL-33 (Broch et al., 2015; Tseng et al., 2018; Veeraveedu et al., 2017), composed of three mediators belonging to the interleukin-1 (IL-1) family: one is the suppression of tumorigenicity 2 (ST2) which exists in two main differently induced isoforms, with opposing biological activities driven by binding with the third component of this system, IL-33(Millar et al., 2017; Veeraveedu et al., 2017). Briefly, the ST2/IL-33 system is cardioprotective in both physiological and pathological conditions when IL-33, the main alarmin in the body released into the extracellular space during heart stretch responses by activated cardiac fibroblasts and cardiomyocytes, binding the transmembrane isoform of ST2 (ST2L), promotes cell survival and blocks pro-fibrotic intracellular

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signalling (Millar et al., 2017). In contrast, the ST2/IL-33 system becomes detrimental for the heart when the soluble form of ST2, known as sST2, is abnormally present in the extracellular space; while it acts as IL-33′s decoy receptor to silence STL/IL33 signaling in normal conditions, in pathological states it can sequester too much IL-33, stopping its cardioprotection through ST2L (Kotsiou et al., 2018; Millar et al., 2017).

An imbalance of sST2 levels in the cardiac extracellular space is one of the main events in the principal cardiovascular disorders involving detrimental biomechanical stretch responses, including coronary artery diseases (CAD), heart failure (HF), and valvular heart disease (VHD) (Gao et al., 2015; Kotsiou et al., 2018). Research is currently ongoing to identify any source and/or molecular mechanism involved in local and systemic sST2 production.

In view of the mechanical impact of the ST2/IL-33 system on the heart, here we provide a short review of advances in the understanding of ST2/IL-33 biomolecular mediators involved in the pathogenesis of cardiac fibrosis, briefly discussing current pioneering clinical strategies based on the ST2/ IL-33 system.

2. Pathogenesis

2.1. ST2L/IL-33 mechano-sensitive signaling system in the heart

Cardiac fibrosis is the end stage of different cardiovascular disorders, all involving injurious biomechanical stretching of the cardiac wall after acute or chronic hydrodynamic overload (Travers et al., 2016). Biomechanical stress is the principal inducer of the ST2/IL-33 system (Kotsiou et al., 2018), the main mechano-sensitive signaling system in the heart. Under biomechanical forces, damaged cardiac cells release first the IL-33 alarmin protein, to block local cardiomyocyte death and loss in tissue (Demyanets et al., 2013). IL-33, normally generated as a precursor in a full-length form of 30 kDa, becomes bioactive after cleavage by caspase-3 or -7 to an active 18 kDa molecular weight protein, promptly released from the nucleus into the extracellular space to promote cell survival, leading to a double definition as “alarmin” but also listed among danger-related molecular patterns (DAMPs) (Januzzi et al., 2015; Millar et al., 2017).

IL-33 was first described in 2005 and its mRNA is found in many organs and cell types, with strongest expression in non-hematopoietic cells such as fibroblasts and smooth muscle cells (Bae et al., 2012). The purpose of bioactivated IL-33 in the cardiac intracellular space is to promote cell survival and prevent pro-apoptotic and pro-fibrotic signaling, especially through the activation and recruitment of the type 2 helper T (Th2) immune response, to reduce detrimental ECM rearrangement (Bae et al., 2012; Brunner et al., 2011). The biological effect of activated IL-33 is traduced only by the ST2 transmembrane isoform (ST2L) and the ST2L/IL-33 complex which activates intracellular signaling to promote cell survival through the myeloid differentiation primary response 88 (Myd88) adapter protein, interleukin-1/-4 receptor-associated kinase (IRAK1/4) and TNF receptor-associated factor 6 (TRAF6); these pathways consequently activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), mitogen-activated protein kinase (MAPK or MAP kinase), extracellular signal–regulated kinases (ERKs), p38 and c-Jun N-terminal kinase (JNK) (Tseng et al., 2018).

ST2L/IL-33 signaling is regulated by the sST2 soluble isoform primarily secreted by resident cardiac fibroblasts in response to cardiac pressure and volume overload (Millar et al., 2017). Its purpose is to stop ST2L/IL-33 signaling, sequestering IL-33 from the extracellular space, functioning as a decoy soluble receptor avoiding excessive IL-33 stimulation (Tseng et al., 2018). The physiological feedback becomes detrimental when the sST2 decoy receptor abnormally raises its circulating level, silencing ST2L/IL-33 and promoting pro-fibrotic and pro-apoptotic signaling (Kotsiou et al., 2018). Physicians have therefore started to use sST2 as a biomarker of cardiac stress and fibrosis and its circulating level is currently approved as an additional stratification factor for HF (Dattagupta and Immaneni, 2018; Januzzi et al., 2015).

Different explanations are offered for the increase in sST2 circulating levels. The first is alternative splicing of the ST2 gene regulated by two different promoters for ST2L and sST2 proteins (Lipsky et al., 2012; Tago et al., 2001). The first variant is the longest transcript from the distal promoter, encoding the full-length transmembrane isoform of ST2; the second goes from the proximal promoter and is shorter than first one, encoding the sST2 protein (Lipsky et al., 2012). ST2 gene promoters are used in different cell types but this usage is not linked to the generation of alternative ST2 transcripts. In mast cells both ST2L and sST2 expression is regulated by the distal promoter, ile the serum-responsive proximal promoter is specially responsible for sST2 mRNA expression in fibroblasts (Lipsky et al., 2012). The absence of the proximal promoter in murine fibroblasts did not lower the circulating sST2 concentration, suggesting that fibroblasts are not the main source of sST2 (Lipsky et al., 2012).

During cardiac fibrosis Th2 cells are the main components of the adaptive immune response to different persistent inflammatory states such as shear stress in the heart, contributing to the maladaptive stress response through the release of fibro-cytokines including sST2 (Lecart et al., 2002). Activated Th2 cells produce soluble sST2 and express low levels of ST2L at their surface, suggesting that chronic maladaptive responses can up-regulate sST2 production from competent Th2 cells (Lecart et al., 2002).

In the light of these findings there is a pressing need to investigate the sST2 source(s), besides cardiac cells, that contribute to impaired ST2L/sST2 expression, promoting cardiac fibrosis.

2.2. sST2 sources besides the heart

The ST2/IL-33 system holds a predominant place, particularly on account of its pleiotropic functions in different tissues (Kotsiou et al., 2018). Recent findings about cardiac fibrosis indicate an exogenous source of sST2 from neighboring cardiac tissue. The sST2 circulating level is high in patients with primary disorders that directly affect the heart, (Kotsiou et al., 2018) and/or secondary comorbidities closely related to cardiac function, including atherosclerosis, obesity-related disorders, vasculature diseases and fat metabolism (Kotsiou et al., 2018)(Fig. 1). The ST2/IL-33 system is present in coronary plaques (Aimo et al., 2018), in which IL-33 is important for stability, since it can polarize M1 to M2 at the level of a carotid stenosis to slow progression of the plaque (McLaren et al., 2010). IL-33 also reduces the development of atherosclerosis through a Th1-to-Th2 switch, reducing accumulation of macrophage-derived foam cells in atherosclerotic plaques (Aimo et al., 2018; McLaren et al., 2010). IL-33 significantly limits foam cell formation in THP-1 macrophage culture and primary human monocyte-derived macrophages by reducing the uptake of acetylated and oxidized LDL (McLaren et al., 2010; Stankovic et al., 2019), lowering total and esterified cholesterol by boosting cholesterol efflux by macrophages through ST2L. In contrast, the increase of sST2 in atherosclerotic plaque is influenced by local M1 macrophage polarization but its role in predicting arthrosclerosis remains unclear (Aimo et al., 2018).

Other sources of sST2 are pre- and mature adipocytes, although endothelial cells in adipose tissue are the main source (Zeyda et al., 2013). Activation of the ST2/IL-33 system in severe obesity seems to be driven by leptin which plays a pivotal role in IL-33 fat cell expression, through the induction of oxidative stress, with a consequent increase in the release of local pro-inflammatory cytokines, monocyte transmigration and IL-33 activation (Zeyda et al., 2013). In murine adipose tissue ST2 was up-regulated in T-cells, which are also the main target of IL-33, to promote anorexic signaling in fat cells (Ragusa et al., 2017; Wasserman et al., 2012). Conversely, sST2 was up-regulated in obesity from hematopoietic and non-hematopoietic cells, promoting fat hyperplasia and hypertrophy, raising the risk of adverse cardiovascular

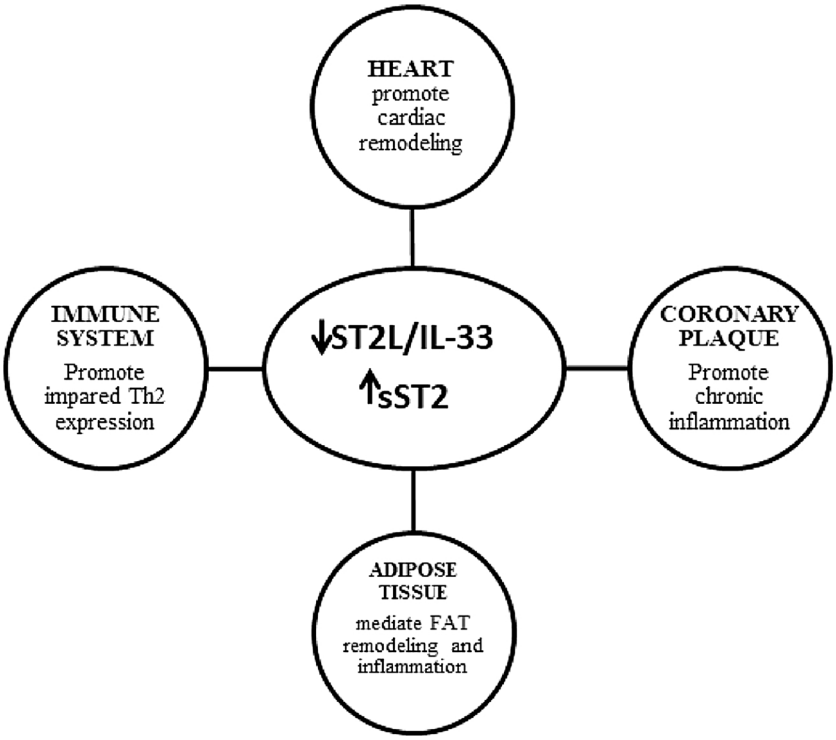

Fig. 1. sST2 besides the heart.

events through higher production of collagen I, fibronectin, pro-fibrotic factors and enhanced metalloproteinase (MMP) activities (Gruzdeva et al., 2018).

In view of the pivotal role of T-cells in pro- and anti-inflammatory signaling by the ST2/IL-33 system, more knowledge is needed about their interaction and regulation. Recent studies have pointed to the involvement of regulatory T (Treg) cells in the Th1/2 balance driven by ST2L/IL-33 signaling (Zhang et al., 2017), showing the direct involvement of these proteins in resolution of atherosclerotic lesions and cardiac damage, demonstrating the ubiquitous negative effect of the sST2 isoform in reducing Treg accumulation by ST2L/IL-33 in different non-lymphoid tissues.

2.3. ST2L/IL-33 promotes cardioprotection by Treg cells

Treg cells normally contribute to tissue homeostasis by promoting wound healing and repair in various tissues. In relation to cardiac fibrosis, Tregs limit tissue injury and promote cell regeneration, balancing scar tissue formation (Zhang et al., 2017). Treg signaling can improve cardiomyocyte survival after cardiac stretching damage, protecting them against adverse ventricular remodeling. Although the activation of Tregs is heterogeneous, some common factors regulate repair by these cells (Lam et al., 2019). The recently discovered mechanism that regulates “repair” Treg accumulation and function in the injured heart is the ST2/IL-33 system (Zhang et al., 2017). IL-33 controls Treg homeostasis ubiquitously in non-lymphoid tissues, driving a positive feedback in Treg activation by directly and indirectly enhancing the expression of Treg transcription factors like Foxp3, GATA3 and STAT5 which in turn promote the expression of ST2L in Treg, to resolve cardiac damage (Zhang et al., 2017).

The myocardium, besides cardiac fibroblasts and cardiomyocytes, IL-33 can also be produced by fibro/adipogenic progenitors (FAPs) (Zhang et al., 2017). FAPs generate fibroblasts and adipocytes which express IL-33 too and boost local tissue regeneration in aged smooth muscle fibers and contribute to Treg accumulation at the site of the lesion. ST2L constitutively expressed on muscle promotes Treg accumulation too, but its beneficial effect can be lost in chronic inflammatory disorders because of the increase of the sST2 isoform which can exacerbate IL-33′s effects on T-cell polarization and increase the Treg cells’ ability to inhibit M1 polarization and foam cell formation (de Oliveira et al., 2019; Zhang et al., 2017). This all indicates that the ST2/IL-33 system controls Treg expansion and function at the site of the lesion. However, there are reports that the beneficial effect of Treg cells induced by ST2L/IL-33 can be lost in different chronic disorders related to the high sST2 level, like the maladaptive chronic response occurring in cardiac disorders and obesity-related diseases (de Oliveira et al., 2019; Lam et al., 2019; Zhang et al., 2017).

3. Therapies

In the last few years a number of strategies have been tested to identify ways to regenerate the heart after tissue loss and degeneration. Pre-clinical studies and clinical trials, like the BOOST trial (French and Holmes, 2019), have reported that the intracoronary infusion of autologous bone-marrow-derived mononuclear cells (BMCs) 4–8 days after myocardial infarction (MI) improves the left ventricle ejection fraction (LVEF), although more recent BMC trials found no significant improvement in cardiac recovery, due to low regenerative capacity mainly associated with paracrine signaling (French and Holmes, 2019). They also showed that stem cell therapy becomes weak if not counterbalanced with early injection of autologous BMCs – within a few hours from the insult (French and Holmes, 2019; Lai et al., 2019).

Given that BMC trials have given mixed results, scientists were challenged to explore the clinical potential of other cell types, including cardiac fibroblasts (CF) and cardiac adipose-derived mesenchymal stem cells (cATMSCs) (Roura et al., 2018). The CFs’ ability to reprogram themselves and transdifferentiate into a cardiomyocyte (CM)-like phenotype has been demonstrated, using a cocktail of transcription factors to promote this conversion (Gata4, Mef2c, Tbx5) (Ieda et al., 2010; Roura et al., 2018).

The efficiency of differentiation into CMs has been greatly improved through modifications of intracellular signaling pathways and

environmental cues, as all these are fundamental for induction of neurons, and hematopoietic stem/progenitor cells to achieve successful cardiac reprogramming (Ieda et al., 2010). The main strategies are blockage of pro-fibrotic signaling, using transforming growth factor (TGF)-β inhibitors or protein kinases to modify intracellular signaling pathways. Activation of the Akt1 pathway promotes both CF reprogramming and their maturation into CMs. However, CFs have to overcome epigenetic barriers to become CMs (Ieda et al., 2010). During CF reprogramming inappropriate genes into the starting new population must be silenced, with pioneering transcription factors with particular binding capacity to open the chromatin structure (Ieda et al., 2010). Gata4 is the main pioneer factor in cardiac conversion. Recent studies have also demonstrated that epigenetic factors can promote cardiac reprogramming using polycistronic vectors to preferentially transcribe only genes associated with cardiac lineage, through the methylation of inappropriate genes (Ieda et al., 2010).

Another novel approach to combat scar formation after MI or chronic maladaptation is investigating human adipose cells and their use as reservoirs of mesenchymal stem cells as important progenitors for cardiac healing: they are easy to harvest with minimally invasive techniques and low morbidity and require only minimal manipulation. Adipose tissue surrounding the heart and pericardium - epicardial adipose tissue - is a good source of cardiac progenitors for myocardium, with cardiac cATMSCs. Bio-engineering studies are currently focused on artificial biocompatible scaffolds for cATMSC delivery to the site of the cardiac lesion.

In addition to the latest strategies for cardiac regeneration, a newer experimental approach uses engineered Tregs, on account of their repair function, in the cells and tissues previously discussed (Lam et al., 2019; Zhang et al., 2017). Engineered ST2 Tregs enhance the ability of IL-33 to polarize monocytes locally in an M2-like phenotype, suggesting that these Tregs may promote tissue repair in humans after cardiac damage. However, more investigation is required before we can exploit this function for cardiac fibrosis prevention (Zhang et al., 2017).

In pursuing the pharmacological potential of the ST2/IL-33 system, it is important to keep in mind the detrimental vs. protective roles of the ST2/IL-33 system, especially considering the need to identify first the pharmacological differences between ST2L and sST2. In view of the importance of the ST2/IL-33 system in the heart and adipose tissue and its involvement in one of the main systems used in cardiac repair, when combined with engineered Tregs, much more knowledge about the regulation of this system is still needed for future therapeutic approaches.

The increase of the sST2 isoform in the extracellular space can be mediated by different tissues and cells from patients with disorders closely related to cardiac diseases, like coronary plaque lesion, obesity and mediated immune responses. These all involve an imbalance of the expression of ST2L/sST2 isoforms, due to pro-inflammatory intracellular signaling which then mediates the systemic increase of the sST2 isoform, which excessively blocks IL-33 in the extracellular space, losing the cell and tissue protection mediated by ST2L/IL-33 signaling.

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