Histol Histopathol (2017) 32: 651-659

http://www.hh.um.es

Histology and Histopathology

From Cell Biology to Tissue Engineering

Review

The expression of Smad signaling pathway in myocardium and potential therapeutic effects

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Summary. Myocardial infarction (MI) is a life-threatening disease. The expression of Smad proteins in the ischemic myocardium changes significantly following myocardial infarction, suggesting a close relationship between Smad proteins and heart remodeling. Moreover, it is known that the expression of Smads is regulated by transforming growth factor-β (TGF-β) and bone morphogenetic proteins (BMP). Based on these findings, regulating the expression of Smad proteins by targeting TGF-β and BMP in the ischemic myocardium may be considered to be a possible therapeutic strategy for the treatment of myocardial infarction.

Key words: Myocardial infarction, Smad, TGF-β, BMP

Introduction

Myocardial infarction (MI) is one of the most serious heart diseases in the world and has high rates of morbidity and mortality. When the blood supply to the myocardium is suddenly stopped, cardiomyocyte necrosis occurs within minutes due to the lack of oxygen and nutrition. Cardiomyocyte loss is subsequently accompanied by post-infarction remodeling. Therefore, promising therapies for MI would lead to increased cardiomyocyte survival and proliferation and should potentially prevent or postpone the fibrosis process.

Smad proteins are intracellular proteins that transduce extracellular signals to the nucleus where they activate downstream gene transcription. Smad, small mothers against decapentaplegic, is a portmanteau of the Drosophila protein mothers against decapentaplegic (MAD) and the Caenorhabditis elegans protein SMA. The molecular mass of Smads ranges from 42K-60K, and there are two regions of homology at the amino and carboxy termini named Mad-homology domains MH1 and MH2, respectively (Massaous and Hata, 1997). The Smad MH1 domains interact with the MH2 domains via a proline-rich linker sequence that is in an inactive configuration (Heldin et al., 1997). Once Smads are activated and the interaction is unlocked, Smad proteins form a complex and translocate to the nucleus to regulate target gene transcription.

Smads are intracellular proteins that act as transcription factors to regulate the expression of many genes and participate in serine/threonine kinase signal transduction pathways (Massaous and Hata, 1997; Patterson and Padgett, 2000). The Smad signaling pathway is a key regulator related to tissue fibrosis in the liver (Xu et al., 2016), kidney (Isono et al., 2002; Meng et al., 2013; Xiao et al., 2014), and lungs (Lucarini et al., 2016). Increasing evidence suggest that Smad signals are involved in processes that underlie many heart diseases (Dixon et al., 2000; Hao et al., 2000; Schneiders et al., 2005; Bugyei-Twum et al., 2014; Zhao et al., 2015). Pressure overload induced by transaortic constriction

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DOI:10.14670/ HH-11-845

(TAC) results in excess cardiac fibrosis and myocardial hypertrophy, which are related to increased TGF-β signaling, and activates Smad2/3 and ERK1/2 within endothelial cells in cardiac blood vessels (Wei et al., 2012).

In this mini review, we elaborate on the diverse roles of Smad proteins in myocardial ischemia and examine some promising therapeutic strategies for MI that use pro- or anti-Smad proteins.

Smad signaling pathway and its regulation

Smad family proteins can be divided into the following three groups: Group 1, receptor-regulated Smads (R-Smads), which include Smad1, Smad2, Smad3, Smad5, and Smad8 (also known as Smad9); Group 2, common Smad (Co-Smad), Smad4, that acts as a co-factor and combines with activated R-Smads to form a complex that can translocate to the nucleus to regulate target genes; Group 3, inhibitory Smads (I-Smads), which include Smad6 and Smad7 (Moustakas et al., 2001). The intracellular distribution of Smad isoforms is changeable based on whether they are activated or not. Under non-activated conditions, most R-Smads are located in the cytoplasm, I-Smads are located in the nucleus, and Co-Smad is located both in the cytoplasm and the nucleus. Smads are activated once their C-terminal region is phosphorylated by a specific receptor by upstream regulators. Once Smads are phosphorylated and activated, R-Smads combine with Co-Smad to form a complex that translocates into the nucleus (Liu et al., 1997).

Classical activators of R-Smad signaling include TGF-β1 and members of the BMP family, both of which belong to the broader cytokine family. There is counter-regulation that modulates the biological activities between the TGF-β1 and BMP activating signaling pathways (Ebelt et al., 2013). In mammals, TGF-β induces Smad2 and Smad3 phosphorylation, which form heteromeric complexes with Smad4, while BMP activates the R-Smad1/5/8 complex to convey intracellular signals (Heldin et al., 1997). Smad1 is then phosphorylated after BMP-2 (Kretzschmar et al., 1997) or BMP-4 (Liu et al., 1996) activation. Smad5 and Smad8 are regulated by BMP-4 (Suzuki et al., 1997). In contrast, overexpression of Smad8 could inhibit the activation of BMP signaling (Tsukamoto et al., 2014). The effects of R-Smads can be blocked by I-Smads, which results in inhibition of TGF-β superfamily signaling (Imamura et al., 1997; Nakao et al., 1997).

TGF-β/Smad signaling pathway

Smads transduce extracellular signals from TGF-β ligands to the nucleus where they activate downstream gene transcription. Three isoforms of TGF-β have been identified, TGF-β1, TGF-β2, and TGF-β3, each of which is encoded by a distinct gene. Although these three isoforms have similar cellular targets, TGF-β1 is the prevalent isoform and is quite ubiquitous, while the other two isoforms are expressed in a limited number and type of cells and tissues (Letterio and Roberts, 1998). TGF-β1 has been reported to be involved in ventricular remodeling by promoting myocardial fibrosis (Edgley et al., 2012; Zhao et al., 2015; Khan et al., 2016) and mediating cardiomyocyte apoptosis (Schneiders et al., 2005) or cardiac hypertrophy (Huntgeburth et al., 2011). TGF-β combines with its receptors, which have specific type I and type II serine/threonine kinases (Shi and Massague, 2003). TGF-β first binds to its specific receptor type II (TβIIR), which is located on the cell membrane in an oligomeric form with activated kinase, to form the TGF-β-TβIIR complex. The latter complex recruits and binds to type I receptors (TβIR), which are also known as activin receptor-like kinase (ALK4), resulting in phospho-rylation of its GS domain (a region rich in glycine, serine and threonine residues) and new complex activation. The serine/threonine-kinase activity of this receptor complex phosphorylates and activates downstream R-Smad (Euler, 2015). Thus, activation of Smad signaling requires both TβIIR and TβIR. Smad7 negatively regulates the activation of this signaling pathway by binding to TβIR or by counteracting the effects of R-Smads to prevent the recruitment and phosphorylation of R-Smad proteins (Xu et al., 2016).

BMP/Smad signaling pathway

More than 12 BMP-related proteins have been identified. These proteins can be divided into the following groups based on their respective structures: the BMP-2/-4 group, BMP-5/-6/-7(OP-1)/-8 group, BMP-9/-10 group, and BMP-12/-13/-14 group (Katagiri and Watabe, 2016). BMP signaling is mediated by the activation of combinations of type I (BMP-RI) and type II (BMP-RII) serine/threonine kinase receptors (Miyazono et al., 2005). Activation of the BMP pathway is confirmed by increased phosphorylation of the "canonical" BMP effectors Smad1/5/8 (Sui et al., 2009). Different members of the BMP family have particular spatiotemporal expression profiles (Miyazono et al., 2005). As inhibitory Smad proteins, both Smad6 and Smad7 specifically block the activation of the BMP/Smad signaling pathway (Imamura et al., 1997; Ishisaki et al., 1999).

Angiotensin and Smad proteins

Angiotensin II (Ang II) has a positive effect on the Smad protein pathway. Ang II regulates rapid phospho-Smad2 (P-Smad2) nuclear translocation in isolated fibroblasts (Hao et al., 2000). In vascular smooth muscle cells, Smad2 and Smad3 can be activated when TGF-β is blocked and Ang II has a greater effect on activating Smad3 than Smad2 (Rodriguez-Vita et al., 2005). Ang II activates the Smad pathway, resulting in an increase in myocardial collagen expression along with Smad2 and Smad3 phosphorylation (Pokharel et al., 2004; Ikeda et

al., 2005). Ang II stimulates cardiac fibrosis in several different models of heart failure (Schieffer et al., 1994; Gu et al., 2012). Additionally, Ang II infusion stimulates cardiac fibroblast production of IL-6, which activates TGF β/Smad and results in cardiac fibrosis (Crabos et al., 1994; Ma et al., 2012).

Activation of Smad signaling

The activation of Smad signaling through R-Smad, Co-Smad and I-Smad have been reviewed previously (Flanders, 2004). Briefly, Smad activation is initiated by the binding of R-Smad to membrane receptors, including TGF-β and BMP receptors, which results in R-Smad phosphorylation. Then, phosphorylated R-Smad is released and binds to Co-Smad (Smad4) to form a heteromeric complex that translocates to the nucleus, where it regulates various transcription factors and induces several transcriptional responses. I-Smads (Smad6 and Smad7 for the BMP pathway and Smad7 for the TGF- β/activin pathway) play an important role in Smad binding to Type I receptors and in preventing R-Smad recruitment and phosphorylation. I-Smads can also block the effects of R-Smad by promoting the E3 ubiquitin ligases Smad ubiquitination regulatory factors 1 and 2 (Smurf 1 and 2) to target, ubiquitinate and degrade Type I receptors.

Smad signaling in myocardial infarction

Smad signaling in infarcted myocardium

The expression of Smad proteins in infarcted or fibrotic myocardium is different from that in the normal myocardium. No matter whether it is assessed in early or late stage cardiomyopathy, the expression of Smad proteins is correlated with cardiac fibrosis and elevated collagen synthesis levels (Hao et al., 1999; Dixon et al., 2000).

Changes in TGF-β signaling have been reported in a variety of heart diseases, including cardiac hypertrophy (Rosenkranz et al., 2002), transaortic constriction (TAC) induced cardiac fibrosis and myocardial hypertrophy (Wei et al., 2012), and myocardial infarction (Hao et al., 1999; Vilahur et al., 2011; Li et al., 2012). TGF-β upregulation results in Smad signaling pathway activation in the heart under pathophysiological conditions (Hao et al., 1999; Yang et al., 2015). The expression of Smad2, 3 and 4 is upregulated at the infarct scar as well as in the peri-ischemic border zone (Hao et al., 1999) and is closely correlated to increased collagen type I expression (Hao et al., 2000). In contrast, expression of Smad7 and TβIR are down-regulated in both the scar tissue and border area; this lasts for approximately eight weeks post-MI (Wang et al., 2002). It has been demonstrated that excessive TGF-β signaling alters cardiac and muscle performance through the intracellular Smad pathway. For example, a heterozygous mutation in Smad4 (S4) is introduced into Sgcg mice (sgcg/S4 mice) to reduce but not ablate Smad4. Sgcg/S4 mice displayed improved cardiac function (Goldstein et al., 2014). Smad7, an inhibitory Smad in the TGF-β pathway, is required for arch artery remodeling (Papangeli and Scambler, 2013). However, BMP-2 is upregulated in the ischemic myocardium accompanying acute MI (Chang et al., 2008). Coronary artery bypass grafting (CABG) and dilated cardiomyopathy (CMP) patients also displayed increased expression of BMP4 mRNA (Wu et al., 2014; Banach et al., 2016; Sanders et al., 2016).

Cross-talk exists between BMP and TGF-β in their regulation of different signaling pathways. For example, BMP-2 induces Smad1/5/8 phosphorylation through TGF-β1-receptor types (ALK1, 2 or 3) (Ebelt et al., 2013). BMP receptor-ligand (e.g., BMP-7) binding can activate Smad1/5/8 signaling and induce the expression of inhibitors of differentiation 2 and 3 (ID2 and ID3). ID2 and ID3 can prevent Smad2/3 phosphorylation and thus counteract TGF-β/Smad signaling (Weiskirchen and Meurer, 2013). It has been indicated that excessive TGF-β1 signaling and reduced BMP signaling have been implicated in pulmonary arterial hypertension (PAH) disease pathogenesis. TGF-β also represses BMP-mediated Smad signaling in pulmonary artery smooth muscle cells via Smad3 (Upton et al., 2013).

Smad signaling associated with cardiac pathophysiology

Activation of most R-Smads may be related to cardiac dysfunction, cardiomyocyte apoptosis and cardiac fibrosis. In a pressure overload model caused by aortic banding, pharmacological inhibition of Smad2 signaling using the small molecule inhibitor SM16 attenuated cardiomyocyte hypertrophy and preserved cardiac function (Bjornstad et al., 2012). Schneiders et al. (2005) have reported that Smad proteins are involved in cardiomyocyte apoptosis. TGF-β1 treatment of cardiomyocytes enhances the number of apoptotic cells expressed, increases caspase 3/7 activity and decreases Bcl-2 expression and the mitochondrial membrane potential with Smad7 upregulation (Heger et al., 2012). More importantly, Smad proteins are associated with cardiac fibrosis (Hao et al., 2000; Araujo-Jorge et al., 2002; Dixon et al., 2000; Wang et al., 2005; Lucarini et al., 2016). Activation of the TGF-β/Smad pathway results in increased transcription of genes related to the production of extracellular matrix components, such as fibronectin, type 1 collagen, and connective tissue growth factor (CTGF), which leads to fibrosis development (Gabriel, 2009). The function and morphology of Smad3-null hearts under normal, non-ischemic conditions is similar to that of wild-type hearts. Following myocardial infarction, the inflammation levels in the hearts of Smad 3-null mice were not significantly different from those of the hearts of wild-type mice. However, fibrotic remodeling and diastolic dysfunction were attenuated and ventricular dilatation was reduced in association with reduced collagen

deposition in the hearts of Smad3 knockout mice (Bujak et al., 2007). These results reveal that TGF-β/Smad3 have a strong influence on fibrosis post-MI. The reduced contraction functions in Smad3-deficient hearts following MI may be related to the TGF-β anti-proliferative effects on isolated fibroblasts through the Smad3 signaling pathway (Dobaczewski et al., 2010).

Smad4 is a central mediator of TGF-β/BMP signaling that controls numerous developmental processes as well as homeostasis in adults. Specific deletion of Smad4 in smooth muscle cells results in vascular defects that lead to embryonic lethality in mice, which may be attributed to decreased VSMC differentiation, proliferation, and migration as well as cell attachment and spreading (Mao et al., 2012).

Inhibitory Smads also display the beneficial effects of reducing apoptosis and fibrosis. Smad6 signaling is involved in cardiomyocyte apoptosis. Smad6 knock-down in mice induces many cardiovascular disorders (Galvin et al., 2000). Smad7 can block myocardial fibrosis (Wang et al., 2005) by reducing the expression of type1 collagen and alpha smooth muscle actin, which prevents excessive scar formation (Wang et al., 2002; Kopp et al., 2005). Cardiac Smad7 is largely reduced in hypertensive hearts and induced by subcutaneous Ang II infusion. Overexpression of cardiac Smad7 protected against the decrease in the left ventricular (LV) ejection fraction (EF), increase in LV mass, and cardiac inflammation and fibrosis. Treatment with Smad7 halts the progression of cardiac injury by blunting the decrease in EF, increasing LV mass, and blocking TGF-β/Smad3-mediated cardiac fibrosis (Wei et al., 2013). Moreover, Smad3 has been reported to have a beneficial effect on inhibiting hypertrophic growth; for example, Smad3-/- fibroblasts exhibited impaired collagen lattice contraction compared with wild-type cells (Graf and Schaefer-Graf, 2010).

BMP-2 is able to decrease the infarct size and reduce apoptotic cell death following MI in mice; it also enhances the beating frequency and contractile performance of isolated cardiomyocytes in *in vitro* studies (Ebelt et al., 2013). Masaki et al. (2005) showed that BMP2 and Smad1 significantly increased survival and diminished apoptotic death in rat neonatal cardiomyocytes during hypoxia-reoxygenation conditions. BMP-9 has been shown to be involved in angiogenesis (Ricard et al., 2012; Long et al., 2015). At high concentrations, blocking BMP-9 promotes endothelial cell proliferation (Scharpfenecker et al., 2007), while at low concentrations, increasing BMP-9 enhances endothelial cell proliferation and angiogenesis in Matrigel™ plug assays (Scharpfenecker et al., 2007).

BMP-Smad signaling may also be involved in cardiomyocyte differentiation and proliferation. The differentiation of the BMP antagonist noggin over-expressing P19CL6 (P19CL6noggin) in cardio-myocytes is very low; however, co-overexpression of Smad1 and Smad4 restores the ability of P19CL6noggin to differentiate into cardiomyocytes (Monzen et al., 2001). Transcription factor Tbx20 (T-box) induces adult cardiomyocyte proliferation by activating the BMP/Smad1/5/8, PI3K/Akt, and Hippo/YAP signaling pathways (Xiang et al., 2016).

Potential therapeutic effects by regulating Smad signaling

BMPs have shown some beneficial effects on cardiac development and anti-apoptosis by acting on Smad proteins. Exogenous BMP-7 reduces myo-fibroblast generation, inflammatory reactions and expression of MCP-1, TGF-β, and collagen I alpha2 chain in burned corneal tissue (Saika et al., 2005) by inhibiting Smad2/3 signaling and activating Smad 1/5/8 signaling. BMP-7 gene delivery reduces wound healing in rabbit cornea and prevents fibrosis *in vivo* (Tandon et al., 2013). BMP-2 may have a considerable therapeutic potential for curing chronic myocardial ischemia by improving the contractility of cardiomyocytes and preventing cardiomyocyte cell death (Ebelt et al., 2013). Injection of BMP-2 reduces the infarct size in mice in a left anterior descending artery ligation model. Mice treated with BMP-2 are characterized by reduced cardiomyocyte apoptosis rates. *In vitro*, BMP-2 increases the frequency of spontaneously beating neonatal cardiomyocytes and the contractile performance, preserves cellular adenosine triphosphate stores, and decreases the rate of apoptosis. BMP-2 specifically induces the phosphorylation of Smad1/5/8 proteins without activating the TGF-β pathway (Ebelt et al., 2013). BMP-4 and BMP-9 can promote endothelial cell differentiation and regulate angiogenesis (Jumabay et al., 2012; Cagavi et al., 2014). Human recombinant BMP-4 promoted survival after H_2O_2 injury in HL-1 cells, and also protected cardiomyocytes against hypoxia-reoxygenation injury (Wu et al., 2014). Inhibition of BMP1-3 has been suggested as a therapeutic method for heart tissue fibrosis following acute MI (Cvjeticanin et al., 2014).

Low-intensity pulsed ultrasound (LIPUS) might be a useful tool for heart cell therapy because it can activate the BMP-2/Smad1/5/8 pathway and promote cardio-myocyte differentiation (Bernal et al., 2015). It has been reported that chromodomain-helicase-DNA-binding protein 7 (CHD7), an ATP-dependent nucleosome remodeling factor, is a novel interaction partner of the canonical BMP signaling pathway nuclear mediators Smad1/5/8 in the embryonic heart. Moreover, CHD7 associates with the enhancers of the critical cardiac transcription factor Nkx2.5 that contain functional Smad1-binding elements in a BMP-dependent manner. CHD7 is recruited by Smad1/5/8 to the enhancers of BMP-targeted cardiogenic genes to epigenetically regulate their expression (Liu et al., 2014).

PARM-1, prostatic androgen repressed message-1, plays an important role in the cardiomyogenic differentiation of stem cells. PARM-1 overexpression induces BMP-2 mRNA expression in undifferentiated

P19CL6 cells and enhances both BMP-2 and BMP-4 mRNA expression in the early phase of cardiomyogenesis. PARM-1 overexpression also enhances Smad1/5/8 phosphorylation (Nakanishi et al., 2012).

However, other opinions exist on the cardioprotective effects of the BMP/Smad signaling pathway. ATP-binding cassette (ABC) transporters are a large family of membrane efflux transporters that transport a variety of substrates including clinically relevant pharmaceutical agents. Recent studies have identified Abcc6, an ABC transporter, as a novel modulator of cardiomyocyte survival after I/R. The cardioprotective effects of Abcc6 may be related to inhibition of the BMP/Smad signaling pathway (Mungrue et al., 2011). Gremlin 2, another BMP antagonist, inhibits BMP-2 pro-inflammation and improves cardiac function post-MI (Sanders et al., 2016). Furthermore, secreted Frizzled-related protein 2 (sFRP2) significantly enhances stem cell engraftment *in vivo* through the inhibition of both the Wnt and BMP /Smad1/5/8 signaling pathways (Alfaro et al., 2010).

In contrast to BMP, the activation of the TGF-β/Smad signaling pathway plays a critical role in cardiomyocyte death and myocardial fibrosis. Chen et al. (2007) reported that the endothelial nitric oxide synthase (eNOS)/nitric oxide system can protect cardiomyocytes from apoptosis by suppressing TGF-β/Smad2 signaling and blocking Smad2 phospho-rylation. Pitavastanin, a HMG-CoA reductase inhibitor, can suppress cardiovascular remodeling by reversing the upregulated TGF-β1-Smad2, 3 signaling pathway (Yagi et al., 2008). βIIV5-3, protein kinase cβII inhibitor, alleviates myocardial damage by inactivating TGF-β1 and inhibiting Smad2/3 phosphorylation (Palaniyandi et al., 2011). Transient receptor potential vanilloid type 1 (TRPV1), a factor that inactivates the TGF-β/Smad2 signaling pathway, can significantly reduce post-MI fibrosis and preserve cardiac function (Huang et al., 2010). High-mobility group box 1 (HMGB1), a pro-inflammatory cytokine, has been reported to attenuate ventricular remodeling by decreasing TGF-β1 and p-Smad2, upregulating Smad7, and suppressing collagen I and III expression (He et al., 2013). Angiotensin-(1-7) could reduce vascular remodeling in a rabbit abdominal aorta injury model via inhibiting both neo-intimal formation and collagen secretion by down-regulating TGF-β1 levels and inhibiting the Smad2 pathway (Zeng et al., 2009). Post-conditioning effectively reduces collagen synthesis and improves cardiac repair, which may be related to attenuating TGF-β1 and p-Smad2/3 expression and up-regulating Smad7 expression (Wang et al., 2013).

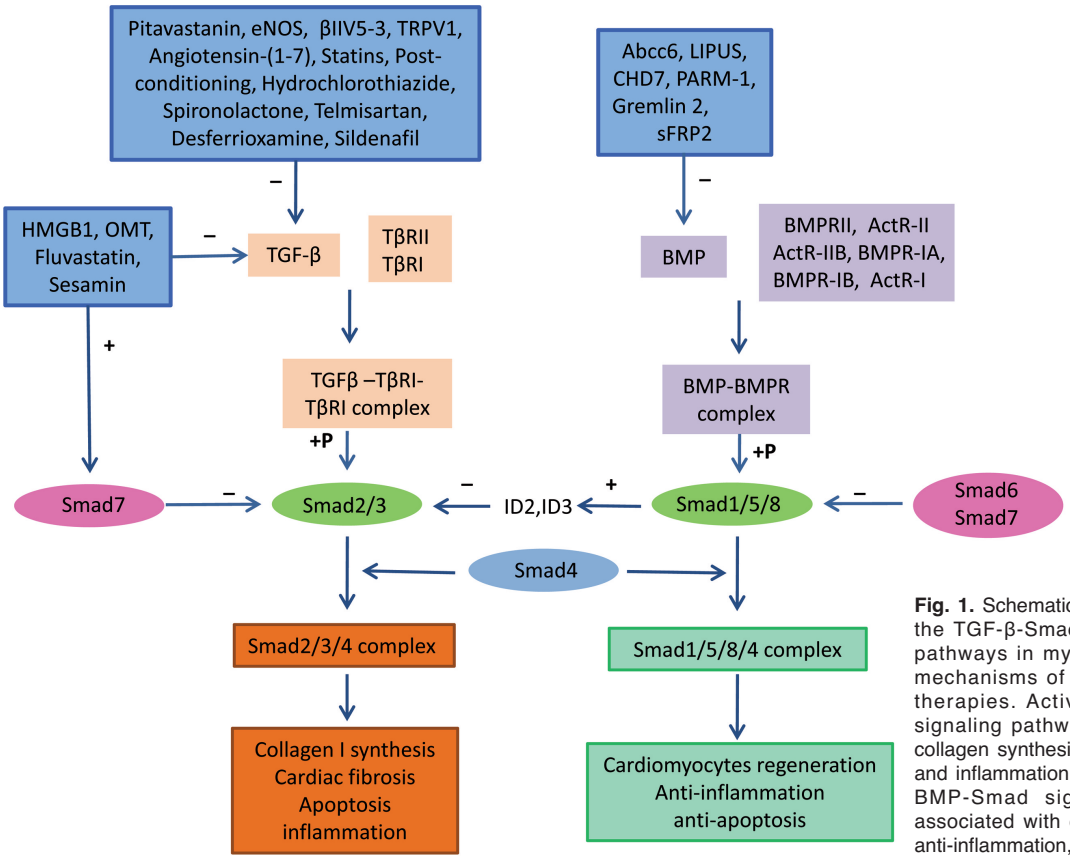

Fig. 1. Schematic representation of the role of the TGF-β-Smad and BMP-Smad signaling pathways in myocardial infarction and the mechanisms of some associated potential therapies. Activation of the TGF-β-Smad signaling pathway may be associated with collagen synthesis, cardiac fibrosis, apoptosis, and inflammation. In contrast, activation of the BMP-Smad signaling pathway may be associated with cardiomyocyte regeneration, anti-inflammation, and anti-apoptosis.

Furthermore, many synthetic medicines are considered to improve myocardial infarction through inhibiting the TGF-β/Smad signaling pathway. Statins have been reported to ameliorate ventricular remodeling via the TGF β1/Smad signaling pathway in rats (Xiao et al., 2016). Fluvastatin, a synthetic HMG-CoA reductase inhibitor, has been found to significantly alleviate myocardial fibrosis by regulating TGF-β1/Smad7 expression post-MI (Zhai et al., 2008). Hydrochlorothiazide and spironolactone, which are used to treat hypertension, effectively reduce cardiac remodeling by alleviating pro-inflammatory cytokine levels and blocking the TGF-β signaling pathway in a congestive heart failure model (Luo et al., 2011). Telmisartan, an Ang II receptor antagonist, can reduce myocardial local Ang II levels and inhibit myocardial fibrosis in hypertensive left ventricular hypertrophy (LVH) by affecting the TGF-β1/Smad signaling pathway (Zhang et al., 2014). It is well-known that doxorubicin increases cardiomyocyte apoptosis, which is secondary to increasing TGF-β/Smad pathway gene expression. Desferrioxamine attenuates doxorubicin-induced acute cardiotoxicity through the TFG-β/Smad p53 pathway (Al-Shabanah et al., 2012).

Sesamin can attenuate hypertensive myocardial fibrosis by suppressing the TGF-β1/Smad signaling pathway. Sesamin markedly reduces TGF-β1 and Smad3 phosphorylation in cardiac tissues and increases Smad7 protein expression. Protein expression of type I and III collagen is also significantly down-regulated (Zhao et al., 2015). Sildenafil, an inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase 5 (PDE5), prevents cardiac fibrosis by inhibiting TGFβ-induced Smad signaling (Gong et al., 2014). In isolated cardiac fibroblasts, sildenafil blocked TGF-β1-induced cardiac fibroblast transformation, proliferation and collagen synthesis (Gong et al., 2014). Oxymatrine (OMT), a component extracted from a traditional Chinese herb named Sophora japonica (Sophora flavescens Ait), significantly reduces left ventricle weight/body weight, prevents myocardial fibrosis in an acute MI model, and downregulates $T\beta R_1$ and Smad3 expression (Shen et al., 2011). OMT can also promote Smad7 expression and inhibit Smad3 expression (Wu et al., 2008).

It has also been suggested that transplantation of cardiospheres enhances angiogenesis and reduces fibrosis in chronically infarcted myocardium, leading to a partial reversal in cardiac dysfunction. The underlying mechanism may involve the inhibition of TGF-β1/Smad signaling by cardiosphere-secreted soluble endoglins (Tseliou et al., 2014).

Conclusions

Smad proteins are involved in many pathological processes in myocardial infarction. Various isoforms play different roles in ischemic myocardium remodeling after being stimulated by either TGF-β or BMP. Smad protein regulation by biomolecules, synthesized medicines and products extracted from some herbal medicines (plant sources) may be considered to be promising therapeutic strategies for treating myocardial infarction (Fig. 1).

Acknowledgements. This work was supported by National Institutes of Health grants HL105176 and HL114654 (Meifeng Xu), National Natural Science Foundation of China (Grant no. 81270214, Wei Zhu).

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Accepted November 15, 2016