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Review

TGF-β_1 and angiotensin networking in cardiac remodeling

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Abstract

The renin–angiotensin system (RAS) and transforming growth factor-β_1 (TGF-β_1) play a pivotal role in the development of cardiac hypertrophy and heart failure. Recent studies indicate that angiotensin II (Ang II) and TGF-β_1 do not act independently from one another but rather act as part of a signalling network in order to promote cardiac remodeling, which is a key determinant of clinical outcome in heart disease. This review focuses on recent advances in the understanding, how Ang II and TGF-β_1 are connected in the pathogenesis of cardiac hypertrophy and dysfunction. Increasing evidence suggests that at least some of the Ang II-induced effects on cardiac structure are mediated via indirect actions. Ang II upregulates TGF-β_1 expression via activation of the angiotensin type 1 (AT_1) receptor in cardiac myocytes and fibroblasts, and induction of this cytokine is absolutely required for Ang II-induced cardiac hypertrophy in vivo. TGF-β induces the proliferation of cardiac fibroblasts and their phenotypic conversion to myofibroblasts, the deposition of extracellular matrix (ECM) proteins such as collagen, fibronectin, and proteoglycans, and hypertrophic growth of cardiomyocytes, and thereby mediates Ang II-induced structural remodeling of the ventricular wall in an auto-/paracrine manner. Downstream mediators of cardiac Ang II/TGF-β_1 networking include Smad proteins, TGFβ-activated kinase-1 (TAK1), and induction of hypertrophic responsiveness to β-adrenergic stimulation in cardiac myocytes.

Keywords: Cardiac hypertrophy; Heart failure; Angiotensin; TGF-β; Smads; β-Adrenoceptors; Cross-talk

1. Introduction

Both the renin–angiotensin system (RAS) and transforming growth factor-β_1 (TGF-β_1) are key mediators of cardiac adaptations to hemodynamic overload, and are thus critically involved in the pathogenesis of cardiac hypertrophy and failure [1–4]. In situations such as hypertension or chronic myocardial infarction, the heart responds to increased afterload by initiating adaptive remodeling processes. These include cardiomyocyte hypertrophy, fibrosis, extracellular matrix (ECM) deposition, and alterations of cardiac gene expression [5–8]. Although these structural alterations represent the heart's efforts to maintain systolic function, they are deleterious over time and ultimately result in progressive heart failure [1]. On the molecular level, cardiac remodeling is mediated by activation of several neurohumoral systems including the RAS, TGF-β_1 and the β-adrenergic system. Recent studies indicate that angiotensin II (Ang II) and TGF-β_1 do not act independently from one another but rather act as part of a network that promotes cardiac remodeling. This review focuses on recent advances in the understanding, how Ang II and TGF-β_1 are connected in the pathogenesis of cardiac hypertrophy and failure. Furthermore, possible downstream mediators of the TGF-β_1/Ang II-connection are discussed.

2. The RAS and TGF-β_1 are critically involved in the pathogenesis of cardiac hypertrophy and failure

In humans, myocardial hypertrophy due to hemodynamic overload is characterized by increased deposition of ECM constituents, proliferation of cardiac fibroblasts, and hypertrophic growth of cardiac myocytes [5–8]. As a

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consequence of this remodeling process, decreased ventricular compliance contributes to diastolic dysfunction which over time is followed by the development of progressive contractile dysfunction and reentry arrhythmias [1,6]. Both the RAS and TGF-β_1 are critically involved in the development of cardiac hypertrophy due to pressure overload and the progression from compensated hypertrophy to heart failure.

2.1. Renin–angiotensin system

The importance of the RAS in cardiac remodeling and the beneficial effects of its inhibition on cardiac structure, function, and survival are well established. Numerous studies have shown that the RAS is activated in response to hemodynamic overload, and that activation of the (local) RAS contributes to myocardial hypertrophy, fibrosis, and dysfunction [1–3,9–11]. In addition, a large number of animal studies [12–15] and clinical trials in humans [16–24] have shown that inhibition of Ang II by angiotensin converting enzyme (ACE) inhibitors or angiotensin type 1 (AT_1) receptor antagonists prevents or reverses ventricular remodeling and improves survival in patients with heart failure.

The effector molecule of the RAS, Ang II, directly induces cellular responses in myocardial cells. However, it may activate distinct signaling pathways in cardiac fibroblasts versus cardiomyocytes, which may result in a differential regulation of genes in these two cell types [25]. In cultured cardiac fibroblasts, Ang II stimulates fibroblast proliferation, collagen synthesis, and the expression of ECM proteins such as collagen, fibronectin, and laminin via activation of the AT_1 receptor [26,27]. In cardiac myocytes, Ang II exerts a direct growth-promoting effect only on neonatal cells, whereas it does not strongly promote growth responses in adult cardiomyocytes [28,29]. In addition, Ang II-induced growth of neonatal cells involves the extracellular signal-regulated kinase (Erk) pathway, whereas growth responses induced by other stimuli, i.e. α-adrenoceptors, do not require Erk activation in adult cardiomyocytes [3,30]. It has therefore been postulated that Ang II may not directly stimulate cardiomyocyte growth and fibrosis in adult myocardium in vivo, but may do so indirectly by inducing the expression of growth factors such as TGF-β_1, which then act locally via auto-/paracrine mechanisms [31]. Recent studies indicate that this indirect effect may indeed be the major mechanism by which Ang II induces cardiac remodeling [32,33]. For example, Ang II-induced fibronectin mRNA synthesis in cardiac fibroblasts was shown to be mediated by autocrine or paracrine effects of TGF-β_1 [34].

2.2. Transforming growth factor-β_1

TGF-β_1 is a locally generated cytokine that has been implicated as a major contributor to tissue fibrosis in various organ systems [35]. Recent studies in humans and experimental models have shown increased myocardial TGF-β_1 expression during cardiac hypertrophy and fibrosis. The expression of TGF-β_1 mRNA is increased in left ventricular myocardium of patients with idiopathic hypertrophic cardiomyopathy and dilated cardiomyopathy [36–38], and in animal models of myocardial infarction, progressive coronary artery occlusion, and pressure overload [39–45]. TGF-β_1 is particularly expressed in hypertrophic myocardium during the transition from stable hypertrophy to heart failure in experimental models [46] and human heart failure [47], and—in addition to increased collagen content—is thus one of a few markers discriminating between compensated and decompensated cardiac hypertrophy. In the pressure-overloaded human heart, upregulation of ACE and TGF-β_1 correlated with the degree of fibrosis [48]. In vitro, TGF-β_1 induces the production of ECM components including fibrillar collagen, fibronectin and proteoglycans by cardiac fibroblasts [49–51], stimulates fibroblast proliferation and the phenotypic conversion to myofibroblasts [52–54], and promotes fetal gene expression in cultured neonatal cardiac myocytes [4,55], all hallmarks of cardiac hypertrophy. In addition, TGF-β_1 self-amplifies its expression in myofibroblasts [56]. Overexpression of TGF-β_1 in transgenic mice results in cardiac hypertrophy which is characterized by both interstitial fibrosis and hypertrophic growth of cardiac myocytes [57,58], whereas heterozygous TGF-β_1 (+/−)-deficient mice reveal decreased fibrosis of the aging heart [59]. Finally, functional blockade of TGF-β_1 signaling in vivo by neutralizing antibodies prevents myocardial fibrosis and dysfunction in pressure-overloaded rat hearts [60], and ECM deposition in a model of cardiac hypertrophy induced by long-term blockade of NO synthesis [40].

Taken together, these studies collectively indicate that the RAS and TGF-β_1 contribute to the pathological cellular events that are responsible for myocardial fibrosis, hypertrophy and dysfunction.

3. Evidence for a connection between Ang II and TGF-β_1 in cardiac tissue

Numerous studies provide indirect evidence for a functional link between Ang II and TGF-β_1 in the heart. Some studies also indicate that these secreted factors act in an auto-/paracrine manner, and furthermore suggest cross-talk between the various myocardial cell types and compartments such as cardiac myocytes, fibroblasts, ECM, and the vasculature.

In vitro studies have shown that TGF-β_1 mRNA and protein are readily upregulated by Ang II in cardiac fibroblasts, myofibroblasts, and myocytes [31,34,61–67]. Stimulation of human atrial tissue with Ang II also caused a significant increase in TGF-β_1 mRNA [68],

and chronic administration of Ang II was shown to induce myocardial TGF-β_1 expression in vivo irrespective of its effects on blood pressure [31,69,70]. Tissue culture experiments revealed that paracrine release of TGF-β_1 from fibroblasts mediates Ang II-induced cardiac myocyte hypertrophy as blocking antibodies to TGF-β_1 inhibit myocyte hypertrophy caused by conditioned medium of Ang II-treated fibroblasts [62]. The Ang II-induced upregulation of TGF-β_1 correlates with cardiac hypertrophy, fibrosis, and re-expression of a fetal cardiac genotype [29,31,62,65,68]. Furthermore, TGF-β_1 induction preceded the development of myocardial fibrosis and ECM production in various models [40,42,60]. Although Ang II-induced gene expression of ECM may be mediated by the AT_2 receptor [71], cardiac hypertrophy and the induction of TGF-β_1 as well as hypertrophy-associated genes such as atrial natriuretic factor (ANF), which may represent a marker differentiating between physiological and pathophysiological hypertrophy [72–74], have been shown to result from activation of the AT_1 receptor [66]. Ang II blockade by an AT_1 receptor antagonist reverses both cardiac TGF-β_1 expression and myocardial hypertrophy/fibrosis in rat models in vivo [31,40,75]. When viewed together, these studies demonstrate a strong correlation between Ang II, TGF-β_1 induction, and auto-/paracrine cellular responses in cardiac fibroblasts, the myocardial interstitium, and cardiomyocytes, which promote the development of cardiac hypertrophy (Fig. 1).

4. Is there a causal relationship between Ang II, TGF-β_1 and cardiac hypertrophy?

Although the above studies suggest a functional link between Ang II and TGF-β_1 in cardiac hypertrophy, a causal relationship has not been proven until recently. In a hallmark paper, Schultz et al. [32] tested whether Ang II would be able to induce cardiac hypertrophy and fibrosis in vivo in the absence of TGF-β_1. In TGF-$\beta_1^{-/-}$/Rag1$^{-/-}$ mice (which were created to overcome the lethal phenotype of TGF-$\beta_1^{-/-}$ mice which is due to an early-onset autoimmune multiorgan inflammatory disease [76]), the lack of the TGF-β_1 gene fully prevented the development of cardiac hypertrophy and dysfunction induced by subpressor doses of Ang II that was observed in wild type mice (Fig. 2). Disruption of TGF-β_1 signaling in knockout animals completely abolished the increase in left ventricular mass, the increase in myocyte size, the deterioration in systolic function (fractional shortening), and the induction of ANF [32]. This study provides the first direct evidence that Ang II-induced cardiac hypertrophy is mediated by TGF-β_1 and confirms the results from other studies which have suggested a functional link between Ang II and TGF-β_1 in myocardial remodeling in vivo (Table 1). These studies collectively indicate that TGF-β_1 acts downstream of Ang II and promotes myocyte growth and fibrosis in the heart. This paradigm is further supported by the fact that in mice overexpressing activated TGF-β_1 (cys^{223,225}ser), AT_1 receptor blockade with telmisartan is insufficient to prevent

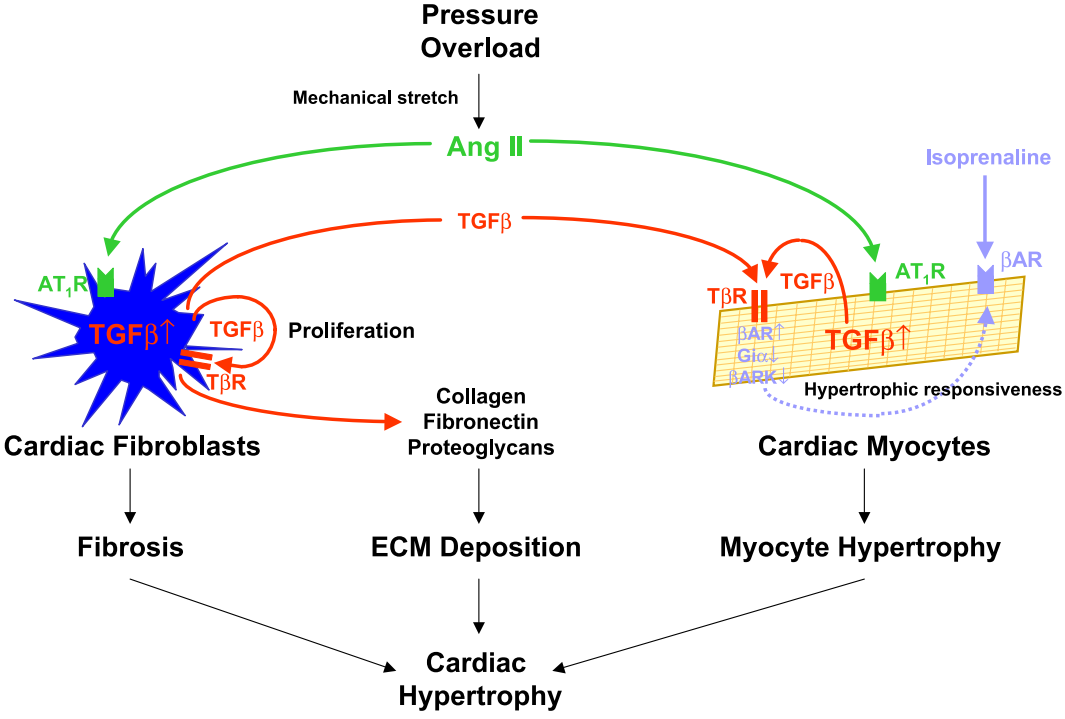

Fig. 1. Schematic diagram illustrating the networking between Ang II and TGF-β_1 in mediating cardiac hypertrophy via autocrine and paracrine mechanisms. (AT_1R = Angiotensin type 1 receptor; TβR = TGF-β receptor, β-AR = β-adrenergic receptor, ECM = Extracellular matrix, βARK = β-Adrenoreceptor kinase.)

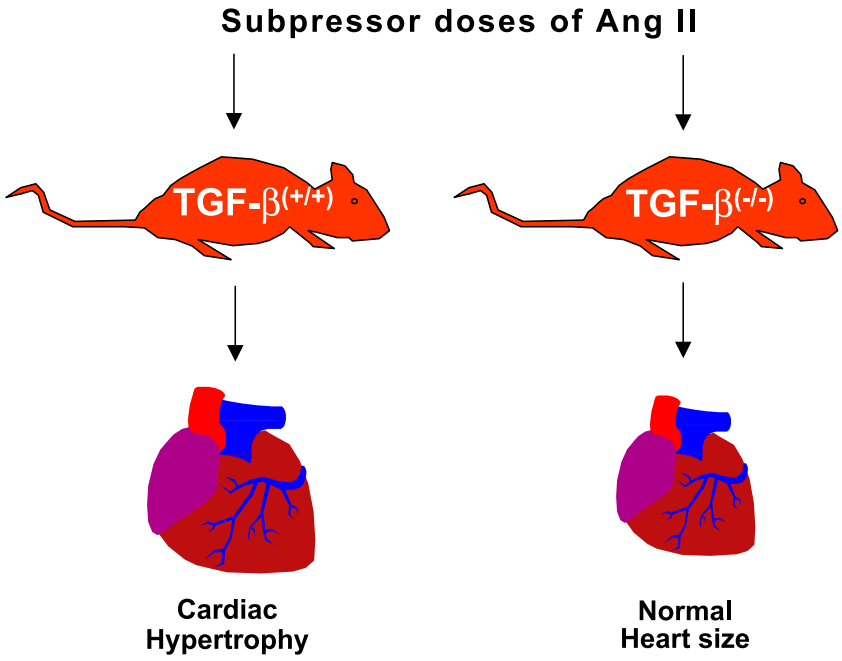

Fig. 2. Causal relationship between Ang II and TGF-β_1 in cardiac hypertrophy as demonstrated by Schultz et al. [32]. Hypertrophy in response to subpressor doses of Ang II was observed in wild type (TGF-$\beta^{+/+}$) but not in TGF-β-deficient mice (TGF-$\beta^{-/-}$), indicating that TGF-β is absolutely required for Ang II-induced cardiac hypertrophy in vivo.

cardiac hypertrophy and dysfunction, whereas disruption of TGF-β_1 signaling by administration of a TGF-β antagonist (sTGFβR-Fc) fully prevented the cardiac phenotype in transgenic mice [77]. Furthermore, reduction of TGF-β_1 mRNA in ventricular tissue was shown to attenuate left ventricular fibrosis and to improve survival of renin-transgenic rats [78].

In summary, Ang II upregulates TGF-β_1 expression via activation of the AT_1 receptor in cardiac myocytes and fibroblasts, and induction of this cytokine is absolutely required for Ang II-induced cardiac hypertrophy in vivo.

5. Molecular mechanisms of TGF-β_1 induction by angiotensin II

Cardiac hypertrophy and induction of TGF-β_1 expression are mediated by the Ang II type 1 (AT_1) receptor in vivo and

Table 1
In vivo studies demonstrating cardiac hypertrophy/fibrosis related to Ang II/TGF-β_1

Reference	Hypertrophic stimulus	TGF-β induction	Cardiac hypertrophy	Myocardial fibrosis	ECM induction	Prevention of cardiac hypertrophy by	
						AT_1R blockade	TGF-β inhibition
Crawford [70]	Ang II	+	n.d.	+	+	+	n.d.
Everett [66]	PO	+	+	+	n.d.	+	n.d.
Kim [69]	Ang II	+	+	n.d.	+	+	n.d.
Tomita [40]	NO Blockade	+	+	+	+	+	+
Nakajima [58]	TGF-β	+	+	+[a]	+[a]	n.d.	n.d.
Brooks [59]	TGF-$\beta^{(+/-)}$[b]	–	n.d.	↓	↓	n.d.	n.d.
Pinto [78]	Renin[c]	+	+	+	+	n.d.	+
Zhang [99]	caTAK1[d]	+	+	+	n.d.	n.d.	n.d.
Wenzel [31]	Ang II	+	+	+	+	+	n.d.
Kuwahara [60]	PO	+	+	+	+	n.d.	+
Schultz [32]	Ang II	+	+	–	n.d.	n.d.	n.d.
Schultz [32]	Ang II	TGF-$\beta^{(-/-)}$	–	–	–	n.d.	n.d.
Rosenkranz [57,77]	TGF-β	+	+	+	+	–	+
Tokuda [75]	PO	+	+	+	n.d.	+	n.d.

PO = Pressure overload; n.d. = not determined.
[a] Only in atrial tissue.
[b] Mice heterozygous for TGF-β.
[c] TGR(mRen2)27 transgenic rats.
[d] Constitutively active TGF-β-activated kinase-1.

in vitro [31,40,66,79–81]. Downstream of the AT_1 receptor, Ang II induces the activation of signaling cascades that regulate gene expression. It is well established that gene expression is regulated by the specific interaction of nuclear transacting proteins with corresponding *cis*-elements in the regulatory region of genes. A recent study investigating the intracellular signaling events that are required for Ang II-dependent upregulation of TGF-β_1 revealed that the induction of TGF-β_1 mRNA by Ang II in adult ventricular cardiomyocytes is mediated by NAD(P)H oxidase, and subsequent activation of protein kinase C (PKC), p38-MAP kinase, and nuclear Activating-Protein-1 (AP-1) binding activity [31] (Fig. 3). This is consistent with previous reports demonstrating that the increase of PKC activity observed in cardiac remodeling following myocardial infarction correlates with increased expression of the PKC-alpha, -beta, -epsilon, and -zeta isozymes [82]. Ang II-induced responses such as regulation of the sarcolemmal Na(+)–K(+) pump are mediated via PKC-epsilon, whereas TGF-β_1-induced collagen I expression is mediated via Smad3 and PKC-delta [83,84]. Ang II also induces *c*-fos, which is part of the AP-1 binding complex in cardiac myocytes [29,85]. Furthermore, it was previously shown that the AP-1 complex is involved in Ang II-mediated TGF-β_1 induction in smooth muscle cells [86], and Ang II activates AP-1 via transactivation of the epidermal growth factor receptor in cardiac fibroblasts [87]. The fact that Ang II does not induce TGF-β_1 expression in the presence of actinomycin D indicates that Ang II regulates TGF-β_1 expression at the transcriptional level in cardiac myocytes [31]. Ang II-stimulated upregulation of TGF-β_1 mRNA was also shown in cardiac fibroblasts, in which it depends on transactivation of the epidermal growth factor (EGF) receptor and subsequent Erk activation by Ang II [34]. The role of NAD(P)H oxidase in Ang II-mediated TGF-β_1 induction and cardiac hypertrophy was recently confirmed in gp91^{phox}-deficient mice, in which the lack of this membranous NAD(P)H oxidase subunit completely prevented Ang II-induced cardiac hypertrophy which was observed in wild type mice [88].

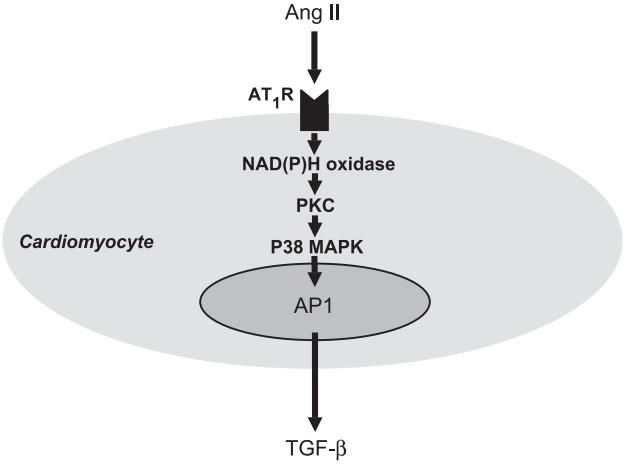

Fig. 3. Signal relay of Ang II-dependent induction of TGF-β_1 expression in cardiac myocytes (adapted from Ref. [31]) (AT_1R = Angiotensin type 1 receptor; PKC = protein kinase C; p38 MAPK = p38 mitogen-activated protein kinase; AP-1 = nuclear activating protein-1).

6. Downstream mediators of Ang II/TGFβ_1 in cardiac hypertrophy

Whereas the functional connection between Ang II and TGF-β_1 has been well characterized in recent years, only limited information is currently available on how they elicit their cardiac growth responses downstream of TGF-β receptors. Recent studies indicate that the downstream mediators of cardiac Ang II/TGF-β networking may include Smad proteins, TGFβ-activated kinase-1 (TAK1), and induction of hypertrophic responsiveness to β-adrenergic stimulation in cardiac myocytes.

6.1. TGF-β_1 signaling/Smad proteins

TGF-β_1 elicits its biological responses through a heteromeric receptor complex comprising two serine–threonine kinase receptors, termed TGF-β receptor types 1 and 2 (TβR1 and TβR2) [89,90]. Both TGF-β_1 ligand and the TβR1 and TβR2 receptors are present in the heart, and all are expressed in cardiac myocytes as well as in non-myocytes [4]. The classical signaling cascade of TGF-β receptors involves Smad proteins (R-Smads such as Smad 2 and 3), which are phosphorylated upon receptor activation, associate with Co-Smad (Smad 4) and subsequently translocate to the nucleus where they act as transcription factors [89–91]. Transcriptional control by Smads depends on interactions with other transcription factors, and their association with coactivators or corepressers determines the type of response. Depending on their binding partners, Smads may either activate or inhibit gene transcription [92].

Cardiac remodeling involves changes in Smad expression, and recent studies provide evidence for cross-talk between Ang II and Smads. In a rat model of myocardial infarction, Smads 2, 3, and 4 are upregulated in scar and remnant heart tissue [39,93], whereas Smad 7, an I-Smad which inhibits phosphorylation of R-Smads, is downregulated [94]. AT_1 receptor blockade was shown to attenuate the expression of Smads in this model, since administration of losartan normalized the increased expression of Smad 2 and Smad 4 in infarct scar and remnant tissue [93]. Normalization of Smad expression was associated with a significant reduction in cardiac fibrosis and improvement of myocardial function. Consistently, AT_1 receptor blockade significantly reduced the elevated Smad 2 and Smad 4 expression in cardiomyopathic hamsters, and this effect correlated with decreased fibrosis and expression of fibrillar collagen [95]. In cultured cardiac fibroblasts, Ang II directly promotes TGF-β_1/Smad signaling by elevating Smad 2 levels and inducing the translocation of phosphorylated

Smad 2 into the nuclei, and these responses also depend on the AT_1 receptor [93]. These studies indicate that cross-talk between Ang II and TGF-β_1 at the postreceptor level (Smad signaling) is associated with fibrosis in cardiac remodeling.

6.2. TGF-β-activated kinase-1

TGF-β-activated kinase-1 (TAK1) belongs to the superfamily of mitogen-activated protein kinase kinase kinases (MAPKKK) that couple extracellular stimuli to gene transcription, and has been shown to transduce TGF-β_1 signaling [96]. Together with Smads, TAK1 is involved in cardiomyocyte differentiation and cardiac development via induction of cardiac-restricted transcription factors Csx/Nkx-2.5, GATA-4, and ATF-2 [97,98]. A recent study demonstrated that cardiac hypertrophy and induction of TGF-β_1 after mechanical load by aortic banding were associated with a significant upregulation of TAK1 kinase activity in the mouse heart [99]. TGF-β_1 activates TAK1 in cultured ventricular myocytes, and constitutively activated TAK1 mimicks hypertrophy-associated TGF-β_1 responses such as induction of the skeletal actin (SkA) promoter, signaling to serum response factor (SRF) through p38, and the SRF-associated transcription factor ATF-6 in these cells [99]. Furthermore, overexpression of constitutively active TAK1 at pathophysiological levels in transgenic mice led to cardiac hypertrophy, fibrosis, fetal gene expression, severe myocardial dysfunction and early lethality [99]. Thus, TAK1 is induced in response to mechanical load and may serve as an essential mediator of Ang II/TGF-β_1-associated cardiac remodeling. Since ATFs bind directly to heterooligomers of Smads and are phosphorylated by TGF-β_1 signaling via TAK1 and p38 [100,101], they are common nuclear targets of the Smad and TAK1 pathways in TGF-β_1 signaling, and thus are good candidates for downstream mediators of Ang II/TGF-β_1-induced growth responses in the heart.

6.3. The β-adrenergic system

Recent studies indicate that β-adrenergic signaling may be involved in the growth responses of the heart by serving as a downstream mediator of Ang II/TGF-β_1 [57,77,102,103]. The detrimental effects of chronic and excessive adrenergic drive have been shown in a number of experimental studies and in man [104–110]. These studies have also shown that the consequences of enhanced β-AR function in the heart are largely dependent on the extent and duration of β-adrenergic overdrive. Stimulation of the sympathetic nervous system is critically involved in the development of myocardial hypertrophy and heart failure particularly by inducing cardiomyocyte hypertrophy [110]. Although the hypertrophic effect of catecholamines on cardiac myocytes in vitro is solely mediated via stimulation of α-adrenoceptors (ARs), myocardial hypertrophy in vivo may also be induced by selective stimulation of β-ARs [111,112]. Hence, autocrine and/or paracrine mechanisms may alter the responsiveness to β-AR stimulation in vivo. In vitro studies have shown that TGF-β_1 affects β-adrenergic signaling by modulating the number and function of β-ARs in various cell types [113–115]. In transgenic mice overexpressing TGF-β_1, the hypertrophic cardiac phenotype correlates with alterations of β-adrenergic signaling, which include an increase in myocardial β-AR density and downregulation of negative regulators such as $G_{i\alpha}$ and βARK-1 [57]. This observation is consistent with an in vitro study demonstrating that TGF-β_1 induces hypertrophic responsiveness to β-adrenergic stimulation in cardiac myocytes [102]. In isolated perfused hearts, TGF-β_1 overexpression promotes the isoprenaline-induced expression of hypertrophy-associated proteins including ANF and c-*fos*, and this effect depends specifically on induction of ornithine decarboxylase (ODC), the rate limiting enzyme of the polyamine metabolism [103]. It is interesting to note that chronic β-AR blockade in TGF-β_1 transgenic mice—which display alterations of β-adrenergic signaling—prevents cardiac hypertrophy and the induction of hypertrophic resposiveness to β-

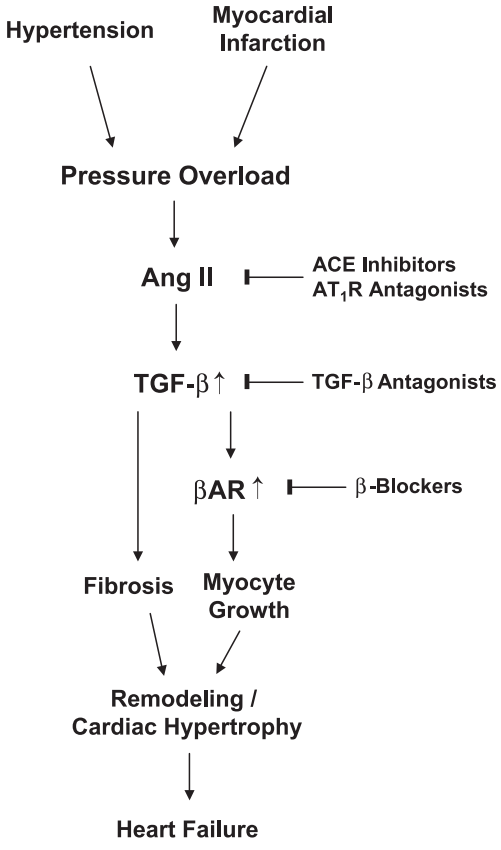

Fig. 4. Schematic diagram illustrating the connection between the RAS, TGF-β_1, and the β-adrenergic system in cardiac remodeling, and targeting of interventional strategies (AT_1R = Angiotensin type 1 receptor; β-AR = β-adrenergic receptor, ACE Inhibitors = Angiotensin converting enzyme inhibitors). Note that in addition to the RAS and TGF-β_1, other systems and mechanisms are also involved in the pathogenesis of myocardial hypertrophy and failure.

adrenergic stimulation, and furthermore improves the diminished functional responsiveness to catecholamines, whereas chronic administration of an AT_1 receptor antagonist did not affect the cardiac phenotype [77]. The latter observation could be expected from previous studies as TGF-β_1, which was induced by Ang II in other models of hypertrophy, is already present in transgenic mice, and AT_1 receptor blockade is expected to be insufficient in this scenario. These data indicate that β-AR-mediated growth responses may act downstream of Ang II/TGF-β_1 in cardiac remodeling, and enhancement of β-adrenergic signaling by TGF-β_1 may contribute to excessive catecholamine stimulation during the transition from stable hypertrophy to heart failure. Hence, networking between Ang II and TGF-β_1 in cardiac hypertrophy may also involve the β-adrenergic system (Fig. 4).

7. Conclusions

The RAS and TGF-β_1 play an essential role in the progression of cardiac remodeling. There is a large body of evidence that the development of cardiac hypertrophy, fibrosis, and dysfunction is controlled by a regulatory network involving the RAS and TGF-β_1 rather than by independent actions of individual players, although other systems and mechanisms are clearly involved [6,11,116]. Ang II induces the expression of TGF-β_1 in cardiac myocytes and fibroblasts. TGF-β_1 stimulates fibroblast proliferation, ECM deposition, and myocyte hypertrophy via autocrine/paracrine mechanisms, thereby mediating Ang II-induced cardiac remodeling (Fig. 1). In addition to TGF-β_1 signaling via Smad proteins and TAK1, β-adrenergic signaling may represent a pathophysiologically important component of this network as TGF-β_1 induces hypertrophic responsiveness to β-adrenergic stimulation in cardiac myocytes.

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