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Chapter 4

# Signaling Pathways of Cardiac Remodeling Related to Angiotensin II

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**Abstract**

Heart failure affects more than 23 million people worldwide, and its prognosis remains poor. Hypertension is one of the most prominent human health problem and places individuals at a higher risk for heart failure. Several factors interplay the development of hypertension contributing for decompensated heart hypertrophy. The renin-angiotensin system (RAS) has been shown to be the foremost regulator of blood pressure. Many evidences have pointed out the importance of RAS and its key mediator, angiotensin II (Ang II), on signaling pathways involved in cardiac remodeling. The Ang II-induced hypertrophic effects seem to be related to increased reactive oxygen species (ROS). Under oxidative stress conditions, as those observed in hypertension and heart failure, the matrix metalloproteinases (MMP) is activated. Ang II is connected with TNF-$\alpha$ and TGF-$\beta$ by ROS-NF-$\kappa$B-MMP mechanisms, which are involved in heart failure. The rationale of the present chapter is structured on the progression of heart failure related to Ang II, TNF-$\alpha$ and TGF-$\beta$ by common signaling pathways. Pharmacotherapeutics approaches to the heart failure abound, but the mortality rates remain high. This chapter will also describe molecular mechanisms involved in heart failure highlighting that TGF-$\beta$ and/or TNF-$\alpha$ inhibitors could contribute to treatment to this serious clinical condition.

**Keywords:** heart failure, renin-angiotensin system (RAS), hypertension, transforming growth factor-beta (TGF-$\beta$), tumor necrosis factor (TNF)-$\alpha$, metalloproteinases (MMP)

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## 1. Introduction

Cardiac remodeling is generally triggered due to cardiovascular diseases, such as myocardial infarction, pressure overload, idiopathic dilated cardiomyopathy or volume overload [1].

Cardiac remodeling is also the most common factor in heart failure progress, a chronic disease defined as a complex syndrome. In this sense, heart failure is associated with intensive and progressive cardiac structural and functional modifications, leading to impaired cardiac output [2, 3].

More than 23 million people worldwide are affected by heart failure. In the United States, approximately 5 million patients have heart failure and this number increases by more than half a million cases per year [4]. It is estimated that an increase in the 46% in the prevalence of heart failure from 2012 to 2030 in people with 18-year old or more [5].

There are several criteria to diagnose heart failure as revised by Roger VL [6]. These criteria are important to determine the kind of heart failure treatment and also contribute to improving the accuracy of epidemical data. Despite the progress of the heart failure treatment, mortality rates are still high. Nowadays, the available treatments for heart failure improve the survival rates but raise hospitalizations as well as hospital readmissions. Among these treatments, there are angiotensin-converting enzyme inhibitors (ACEi) and beta-adrenoceptors blockers that alleviate the symptoms in individuals with advanced heart failure and depressed ejection fraction in end-stage disease [7]. Therefore, heart failure is a growing public health problem, in which a projection from 2012 to 2030 heart failure will account more than $69 billion in health-care cost in the United States. It will be a significant increase from 127% [5].

Several risk factors are associated with heart failure, such as smoking, obesity, diabetes mellitus, coronary heart disease and hypertension among others. Hypertension—chronic elevation of blood pressure—is the most prominent human health problem, and it is the main comorbidity linking obesity, cardiovascular and metabolic diseases. According to Framingham study, hypertension is considered the major risk factor attributed to heart failure, and its prevalence in hypertension exceeds 50% [6, 8]. Hereupon, hypertension is the cause of deaths because it often coexists with heart failure and also places individuals at a higher risk for kidney failure, stroke, etc.

## 2. The progression of cardiac remodeling in hypertension

Hypertension-induced cardiac remodeling is an initial adaptive response of the heart in order to compensate the increased left ventricle wall stress induced by an augmented hemodynamic load. This remodeling is named adaptive hypertrophy, which is featured by growing inwards of the left ventricle and septum wall, resulting in a reduction in left ventricle chamber (**Figure 1**) [2, 3]. The structural changes may occur due to additional contractile-protein units within the cardiomyocytes leading to an expansion in the myocyte width. In parallel to the cellular growth, the cardiac extracellular matrix is also hypertrophied. An important hallmark in

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chronic hypertension is the intensive turnover from the extracellular matrix, resulting in a progressive collagen deposition [3]. Amount evidences have shown that the cardiac fibrosis could contribute to initial diastolic dysfunction harming the re-lengthening of myocytes during diastole [2, 8, 9]. Thus, despite being called "adaptive", this hypertrophy generates several maladaptive molecular and/or cellular mechanisms triggered in the initial remodeling.

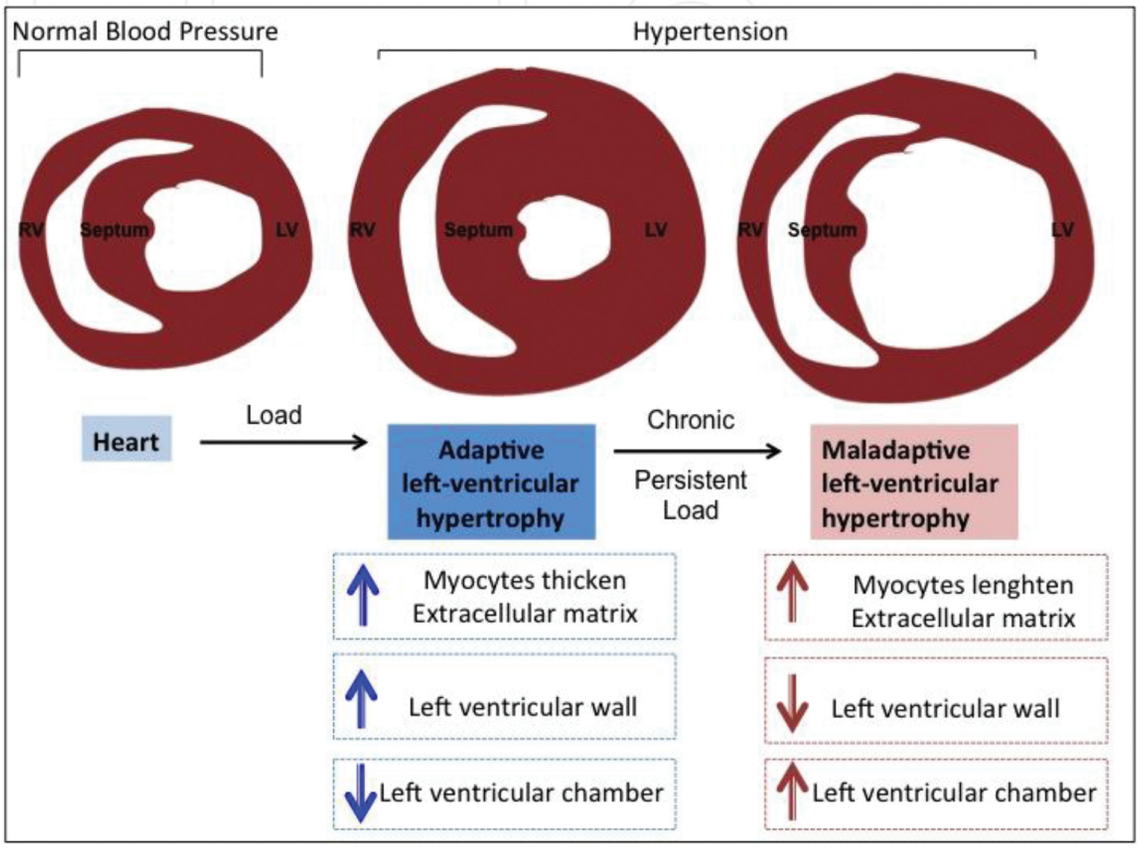



**Figure 1.** The hypertension induced progression from adaptive hypertrophy to maladaptive hypertrophy. Cardiac remodeling is progressive in hypertension. Initially, an adaptive hypertrophy occurs in the left ventricle that grows inwards reducing the left ventricle chamber. The cardiac remodeling may progress to maladaptive hypertrophy. The left ventricular chamber is dilated and left ventricle and septum wall are thinned. The strength of cardiac contraction may be reduced mainly due the loss of contractile proteins. The heart is therefore considered decompensated, which may result in heart failure. Both, adaptive and maladaptive hypertrophies are characterized by increased heart size and weight. RV: right ventricle and LV: left ventricle.

Hypertensive patients may progress from adaptive to maladaptive hypertrophy, which is characterized by increased left ventricle chamber accompanied by thinning of a left ventricle and septum wall (**Figure 1**). The myocytes are still hypertrophied, but the length is increased [1–3, 9]. The mechanisms involved in the transitions from adaptive to maladaptive hypertrophy are poorly understood. Nonetheless, some studies point out to the excessive matrix extracellular degradation during maladaptive hypertrophy disrupting the cellular organization [2], which could contribute to myocytes lengthening and left ventricular chamber dilatation. It has been also accepted that cell death is associated with this alteration in myocytes [2, 10].

Pathogenic cellular and interstitial changes in hypertension-induced cardiac remodeling are orchestrated by several molecular mechanisms that may be transduced from mechanical force into myocardial growth. In this regard, renin-angiotensin system (RAS) is activated in hypertension and may be involved in cardiac hypertrophy and failure. Clinical and experimental studies have shown significant benefit conferred by pharmacological blockade of RAS [7, 11–13] arousing interest by mechanisms underlying the action of angiotensin II (Ang II).

## 3. Angiotensin II and cardiac remodeling

Ang II is the primary effector peptide of the RAS. The hypertrophic effects of this peptide on the heart are associated with its vasoconstrictor and hypertensive properties. However, it is currently known that independently of its blood pressure effects, Ang II is a powerful hypertrophic agent. *In vitro* studies show that Ang II activates different hypertrophic signaling pathways in cardiac myocytes [11]. In addition, the crucial components to initiate synthetic route to Ang II production are present in the heart. Thus, Ang II is also locally synthesized at the myocardium, acting as an autocrine factor [11]. Increased cardiac Ang II synthesis is mediated, *in vitro*, by cardiomyocyte under stretch conditions [14]. Similarly, the rise in cardiac Ang II was also observed in hypertrophied heart from animals after overload pressure as well as in patients from end-stage heart failure, which suggests the hypertrophy have resulted from local RAS activation [11, 15].

The Ang II hypertrophic effects are mediated by the activation of specific receptor AT1 that plays a crucial role in heart failure pathophysiology, but both AT1 and AT2 receptor are present in the cardiac tissue [16–19]. The AT1 receptor is 7-transmembrane domain coupled to Gq protein (GPCR). Ang II is able to perform the signaling transduction to adaptive and maladaptive remodeling pathway [2]. AT1 receptor stimulated by Ang II leads to the protein kinase C activation [17], which in turn activates the mitogen-activated protein kinase (MAPK). The intracellular signaling cascade generated from MAPK is constituted by a phosphorylation-based amplification network and results in hypertrophic signals to cardiac adaptive or maladaptive remodeling [2, 10]. Three MAPKs, such as p38 kinases, c-Jun-terminal kinases (JNK) and ERK 1/2 have been described as signaling pathways in cardiac myocytes or extracellular matrix changes along the heart failure progression [10].

In the compensatory response to overload pressure, ERK 1/2 activation has been related to adaptive changes and increased width of the myocytes [20]. Further, some studies have suggested that JNK could contribute to maladaptive remodeling due to its pivotal role in cell death [2, 10, 21]. The MAPK signaling from cardiomyocyte cytoplasm drives to nuclei where transcriptional factors such as factor nuclear kappa B (NF-kB), activating protein-1 (AP-1) and Smad are intracellular proteins to transduce extracellular signals from transforming growth factor beta ligands to the nucleus where they activate downstream gene transcription, rising the transcription of key proteins and developing essential function to the cardiac remodeling progression [22–25].

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The NF-kB is an oxidative-sensitive transcriptional factor [26]. Likewise, multiple signal transduction pathways are activated in response to reactive oxygen species (ROS) [27]. In this regard, emergent evidences have shown that Ang II-mediated hypertrophic response may be dependent of increased ROS production, particularly during hypertension [25, 28–30].

Several studies have confirmed the key role of ROS in the genesis and progression of cardiac remodeling [28, 31, 32]. Low levels of ROS are important to many downstream regulators in a physiological condition such as ion channel, receptors, kinases, phosphatases and transcriptional factor. However, increased ROS production characterizes oxidative stress, disrupts redox signaling within the cells and the interstice, promoting activation of calcium/calmodulin-dependent protein kinase I (CaMKI), increased NF-kB, AP-1 and other transcriptional factors signaling [33, 34]. Oxidative stress also elicits post-transductional pathways that result in activation of some proteins, e.g., matrix metaloproteinases (MMP) [35]. Consequently, oxidative stress has been associated with cardiac contraction dysfunction, increased collagen deposition and myocytes hypertrophy that contribute to cardiac dysfunction, myocyte hypertrophy and cell death [27, 35].

Considering the relevance of ROS to cardiac diseases, a substantial body of studies has investigated which enzyme could be more important to ROS synthesis. Along the progression of cardiac remodeling, a family of complex enzymes termed nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase) seems to play a central position to ROS production [27, 29]. Increased expression and activity of NADPH oxidase have been persistently observed in both preclinical and clinical studies of heart failure [27, 36]. There are seven Nox family isoforms (Nox1-5 and DUOX1 and 2), and the main cardiac enzymes are Nox2 and Nox4 [37].

Nox4 contribute to myocyte hypertrophy and cardiac fibrosis induced by AngII [38]. However, the role of Nox4 to cardiac hypertrophy is not yet fully comprehended [39].

Amount evidences show Nox2 associated with detrimental effects in the heart [27, 39]. The low-level activity of Nox2 is continuously present in the presence of nanomolar ROS levels but may be increased at the Ang II, endothelin, transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-$\alpha$ presence as well as due to mechanical force [27]. Interestingly, Ang II-induced cardiac hypertrophy and fibrosis were reduced in knockout mice for Nox2 when compared to the wild type [38]. Currently, the contribution of Nox2 to Ang II hypertrophic effects appears to involve ERK1/2, Akt and NF-kB signaling [27, 41, 43]. In addition, increased Ang II-induced MMP activation and expression seem to be dependent of ROS [30, 42, 44] resulting in cardiac adaptive remodeling and fibrosis [43, 44]. **Figure 2** summarizes relationship between Ang II-induced cardiac remodeling and Nox2.

The important signaling in Ang II-induced fibrosis predominantly requires the differentiation from fibroblast into myofibroblast cells [3]. This phenotypic transformation from fibroblast is characterized by $\alpha$-smooth muscle actin ($\alpha$-SMA) expression and increased production of extracellular matrix, which is a key event in connective tissue remodeling involved in the heart failure progression [3, 45]. Rossi [9] has shown an intensive and progressive accumulation of collagen, accompanied by increased heart weight in hypertensive subjects. In addition, the study revealed an association among connective matrix, cardiac systolic and diastolic dysfunction in

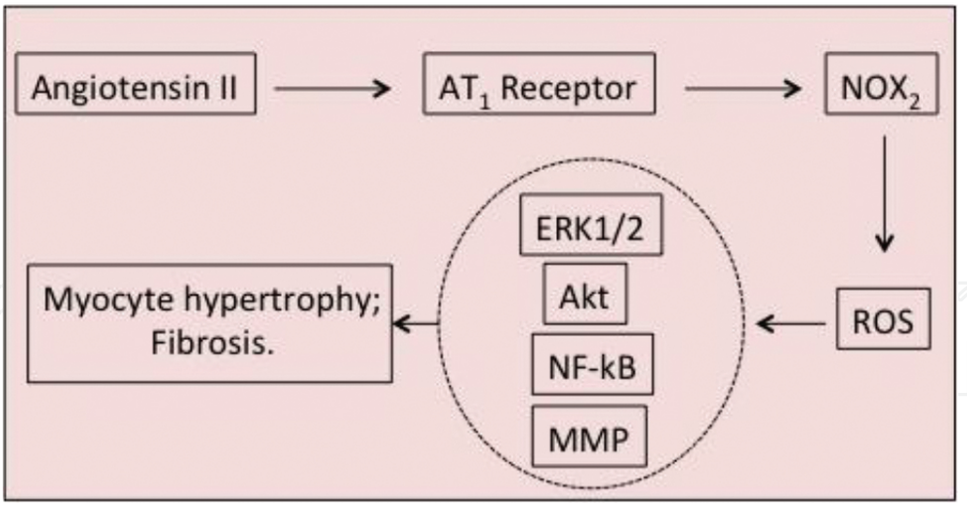



**Figure 2.** Main pathways concerning Ang II-induced cardiac remodeling. Nox2 is activated by Ang II via AT1 receptor, triggering ROS formation, which activates intracellular pathways related to the cardiac hypertrophy. Nox2: NADPH oxidase isoform 2; ROS: reactive oxygen species; Akt: serine/threonine-specific protein kinase; ERK1/2: extracellular.

hypertension suggesting that collagen deposition could contribute to decreased myocardial compliance and disrupted heart electrical properties [9]. Currently, it is well known the relevance of fibrosis not only to the structure of the cardiac hypertrophy but also to the heart dysfunction [46]. Collagen is the main component of the extracellular matrix in the myocardium, which is synthesized by fibroblasts. However, its deposition in the heart during hypertension also depends of its degradation [3]. Thus, a large body of studies has shown the contribution of the MMP, which is the main proteases to collagen degradation, strongly contributing to the cardiac remodeling after pressure overload or infarct [28, 47]. The imbalances between MMP and endogenous tissue inhibitor (TIMP) are key mechanisms to control the collagen formation and deposition [2, 3, 48]. Indeed, some transcriptional factors such as AP-1 and NF-kB may modulate the MMP activity increasing its MMP expression and also TIMP expression [28, 47]. Posttranslational mechanisms such as oxidative stress, particularly peroxynitrite and hydrogen peroxide, may activate MMP and inhibit TIMP activity [35, 49, 50], suggesting a possible mechanism to ROS-induced fibrosis in hypertensive rats [51]. Thus, MMP activity is regulated at three levels: (i) transcriptional level, (ii) endogenous inhibitors and (iii) factor activators (ROS). Interestingly, Ang II may increase MMP activity involving redox-sensitive signaling in fibroblast, thus triggering NF-kB and AP-1 transcriptional factor activation [52]. In fact, antioxidant therapy reverses Ang II-induced cardiac hypertrophy and MMP activity in left ventricle from hypertensive rats [30]. Taken together, Ang II promotes myocyte on the heart and matrix extracellular hypertrophy by similar mechanisms involving redox signaling, which not only activates the RNA expression of proteins in the myocytes or fibroblasts, but also rises the activity of enzymes already present in the heart, such as MMP.

Furthermore, it must be recognized that Ang II induces inflammation by triggering cardiac remodeling. The proinflammatory effects of Ang II have been described since 1970 by Finn Olsen [53]. Thenceforward, several studies have supported the contribution of the inflammatory processes associated with Ang II to cardiovascular disorders, including hypertension and

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heart remodeling [23, 25, 54]. Since inflammation contributes to this important clinical condition, numerous evidences have reported the connection between Ang II and two pivotal mediators for heart remodeling, the cytokines transforming growth factor (TGF)-β [23] and the tumoral necrosis factor (TNF)-α [25].

## 4. Angiotensin II and TGF-β in cardiac remodeling

Increased expression of TGF-β was found in the myocardium during cardiac hypertrophy and heart failure [55]. Classically, TGF-β is a multifunctional cytokine recognized as a powerful profibrotic factor. Three isoforms of the TGF-β family have been identified in mammals [56], but TGF-β1 has been constantly associated with several cardiovascular diseases, particularly during the transition from adaptive cardiac hypertrophy into heart failure [56–59]. The overexpression of TGF-β1 induced fibrosis and myocyte hypertrophy in transgenic mice after they were 8 weeks old [58]. Upregulated TGF-β1 mRNA is found in the pressure-overloaded human heart [60], as well as in the dilated cardiomyopathy [57]. The latent form of TGF-β1 is composed of 390-amino acid complexed with the signal peptide and the large amino-terminal prodomains (known as latency-associated proteins, LAPs) which are required for correct folding and dimerization of the carboxyl terminal domain of the growth factor (the mature peptide) [61]. TGF-β1 can be released and activated by the proteolytic cleavage, which disrupts its non-covalent attachment with LAP [62]. The intracellular signaling induced by TGF-β underlies the activation of serine/threonine kinases receptor resulting in Smad phosphorylation, which is responsible to activate target genes [61]. TGF-β may also promote the regulation of the transcription by TGF-β-activated kinase-1 (TAK1) triggering p38 MAPK phosphorylation and activating transcriptional factor (ATF)-2 [56].

Myriad experimental studies reported Ang II-mediated TGF-beta induction, particularly of its expression [63–65]. AT1 receptor seems to be involved with TGF-β upregulation expression at the transcriptional level in as much as losartan treatment inhibited the rise of this cytokine in animals after Ang II infusion [63].

Since AT1 activation produces ROS via NADPH oxidase, Wenzel et al. [63] demonstrated that the induction of TGF-β in cardiomyocytes was diminished in the presence of NADPH oxidase inhibitors. Consistently, antioxidant treatments have shown decreased cardiac TGF-β expression in the experimental model of RAS activation [23, 30]. The redox signaling involved in Ang II-induced TGF-β upregulation seems to be dependent on p38 MAPK and AP-1 pathway, such was observed in ventricular cardiac myocytes [23, 63]. In this regard, the first direct evidence about the causal relation between two important factors for cardiac hypertrophy (Ang II e TGF-β) was observed in TGF-β1-deficient mice. The marked cardiac hypertrophy and the impaired cardiac function induced by chronic suppressor doses of Ang II were not observed in TGF-β1-deficient mice [66]. Thus, cardiac TGF-β is required to hypertrophy signaling induced by Ang II, which in turn activates its AT1 receptor upregulating this cytokine expression.

TGF-β and Ang II are involved in fibroblast differentiation and MMP activity control [3]. In this regard, an imbalance between MMP/TIMP is possibly another common signaling consequently

involved in the heart hypertrophy. Ang II-induced increased MMP transcriptional expression has been reported by several studies [30, 42, 44]. Despite AP-1 contribution to the transcription of MMP-2 [47], the NF-kB inhibition attenuated MMP-2 upregulation in both heart and aorta from 2-kidney and 1-clip (2K1C) hypertensive rats [44]. Transgenic mice overexpressing cardiac MMP-2 presented marked decompensated hypertrophy, including not only collagen deposition but also significant systolic dysfunction [67]. MMP-2 seems to degrade some contractile proteins from heart sarcomeres, such as myosin and troponin [35], which have constantly been associated with impaired heart capacity to contract in experimental models of heart disease [68]. In this regard, several findings have stated that MMP-2 inhibition ameliorates remodeling and cardiac dysfunction [35, 47, 69]. In addition, Ang II-induced MMP activation may be associated with adaptive remodeling and cardiac dysfunction in 2K1C rats [69]. The Ang II activates MMP-2 by mechanisms involving NADPH oxidase activation and ROS formation [30, 42]. In this sense, TGF-β could increase MMP-2 activation since this cytokine also increases ROS formation. Indeed, some studies have shown increased TGF-β levels and MMP-2 activity in the left ventricle from hypertensive rats [3, 30]. Hence, the TGF-β-dependent mechanisms to Ang II-induced cardiac remodeling may involve MMP-2 activation by redox signaling. However, future studies are necessary to support the causal relation between MMP-2 activation and TGF-β in Ang II hypertrophy.

## 5. Angiotensin II and TNF-*α* in cardiac remodeling

The proinflammatory cytokine TNF-*α* was first defined as an antimutagenic. Nowadays, amount findings revealed a wide range of pleitropic TNF-*α* effects including cell proliferation, apoptosis and production of other proinflammatory cytokines [2].

Growing body of evidences evaluated the role of TNF-*α* in many diseases, particularly in cardiovascular disease. TNF-*α* has been found upregulated in myocardial from humans and animals with heart failure [70]. A wide variety of cells including macrophages, fibroblast and endothelial cells produce TNF-*α*. It has been described that cardiomyocytes themselves are capable of synthesizing TNF-*α* [71]. Bryant et al. [72] have shown that TNF-*α* synthesized by cardiomyocytes was sufficient to cause severe cardiac remodeling suggesting maladaptive hypertrophy, which may also occur in human heart failure.

The TNF-*α* is secreted as a cell surface protein (homotrimeric type II transmembrane protein) containing 233-amino-acid, which is activated by proteolytic cleavage to a 76-amino-acid signal peptide [73, 74]. The TNF-*α* released as a mature protein, which acts as a soluble cytokine through its two receptors: TNF receptor 1 (TNFR1) and TNFR2 [75, 76]. Despite the homology between TNFR1 and TNFR2 in extracellular domains, both intracellular domains of TNFR1 and TNFR2 are different. Once activated, TNFR1 leads to recruitment of a protein TRADD (TNFR1 associated death domain protein), which subsequently interacts with three other intracellular proteins forming a complex. When activated, TNFR2 directly recruits TRAF2 and TRAF1 (TNF receptor-associated factor). These differences in TNFR-induced intracellular signaling suggest each receptor has distinct cellular functions. In this sense, dual effects of TNF-*α* have been

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suggested during the progress of cardiac disease. Low concentration of TNF-α has been associated with the protective effects while its high concentrations present deleterious effects [77]. This study did not evaluate the TNF-α receptors contribution. However, other evidences have been shown that the effects of the two receptors on heart failure were opposite, TNFR1 showed proapoptotic and prohypertrophic while TNFR2 developed antiapoptotic and antihypertrophic effects [78]. In addition, other findings have suggested that TNFR1 is responsible for the major deleterious effects produced by TNF-α in hypertrophic signaling [79, 80]. Moreover, soluble TNFR1 is a predictor of mortality and heart failure in patients with acute myocardial infarct [81]. Preclinical studies demonstrated that TNFR1 plays an important role in Ang II-induced fibrosis in rats while TNFR2 did not affect the increased collagen deposition in response to Ang II infusion [80].

TNF-α-induced intracellular signaling involves canonical NF-kB activation. The complex of intracellular protein is formed when TNFR1 is activated, specific mitogen-activated protein kinase kinases (MAPKKs) are phosphorylated consequently activating c-Jun N terminal kinase (JNK), AP1 and p38 MAPK signaling pathways. Taken together, TNF-α-induced intracellular signaling controls the expression of inflammatory proteins and antiapoptotic genes. Another signaling complex is triggered as a response to the TNFR1 activation resulting in stimulation of the effective caspases, which in turn lead to apoptosis [82].

TNF-α has induced increased ROS formation in endothelial cells by a mechanism dependent of NADPH oxidase subunit: p47 phox subunit [83]. Indeed, cardiomyocytes hypertrophy was induced by recombinant human TNF-α at least in part due to ROS generation [84]. Through experimental models of heart failure, TNF-α inhibition decreased oxidative stress and apoptosis improving cardiac remodeling and dysfunction [85]. Thus, ROS seems to foster a key function in the cardiac hypertrophy induced by TNF-α.

As described above, it is possible to observe common signaling pathways between TNF-α and Ang II. Since Ang II notably has increased TNF-α *in vivo* [86] and *in vitro* studies [87], some evidences have reported a potential role of TNF-α in Ang II-induced cardiac hypertrophy [25, 88–90]. In this context, chronic Ang II infusion promotes cardiac hypertrophy, which was attenuated in TNF-α knockout mice [89]. These findings were further confirmed by the pharmacological inhibition by etanercept, an inhibitor of TNF-α, which blunted cardiac hypertrophy in mice under Ang II infusion [25]. Indeed, the authors showed the involvement of TNF-α in the intracellular signaling in Ang II-induced hypertrophy. Both TNF-α and Ang II induced activation of NF-kB, p38 MAPK and JNK. Accordingly, heart TNF-α knockout mice attenuated the activation of NF-kB, p38 MAPK and JNK signaling in Ang II infusion, suggesting TNF-α is required to induce Ang II cardiac hypertrophy by intracellular signaling pathways [25]. It was observed that the TNFR1 deficient mice did not develop fibrosis under Ang II stimulation, while TNFR2 deficient mice showed increased collagen accumulation in the heart under Ang II infusion [88], which may indicate a promising role of TNF-α in activating TNFR1 as crucial signaling to Ang II inducing cardiac remodeling.

Ang II and TNF-α are involved in increased production of ROS, which in turn activate NF-kB. In this regard, Sriramula et al. [25] also suggest that redox signaling induced by Ang II may be dependent of TNF-α. The authors have found that the increased mRNA, 2 expression and

also the expression of other NADPH oxidase isoforms were blunted in TNF-α knockout mice, which have resulted in lower levels of ROS. Collectively, all findings point out to a causal relation between hypertrophic signaling of Ang II and TNF-α that involve redox pathways on NF-kB, JNK and p38 activation.

## 6. Conclusion

Ang II and these cytokines (TGF-β and TNF-α) activate some intracellular pathways involved in hypertrophy, including increased ROS production through NADPH oxidase. Ang II activates NF-κB, which is a possible mechanism to Ang II-induced increased levels TNF-α and other proinflammatory cytokines. NF-κB and ROS pathway seems to be also involved TGF-β-increased MMP activity. In addition, cytokines, TNF-α and TGF-β, and Ang II are closely related with a MAPK, which is a known key pathway involved in cardiac hypertrophy and MMP regulation. Taken together, Ang II is associated to the TNF-α and TGF-β by mechanisms involving ROS-NF-κB-MMP then contributing to the heart failure.

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