Review

Cross-regulation between the renin–angiotensin system and inflammatory mediators in cardiac hypertrophy and failure

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Abstract

One of the major conceptual advances in our understanding of the pathogenesis of heart failure has been the insight that heart failure may progress as the result of the sustained overexpression of biologically active “neurohormones”, such as norepinephrine and angiotensin II, which by virtue of their deleterious effects are sufficient to contribute to disease progression by provoking worsening left ventricular (LV) remodeling and progressive LV dysfunction. Recently, a second class of biologically active molecules, termed cytokines, has also been identified in the setting of heart failure. Analogous to the situation with neurohormones, the overexpression of cytokines is sufficient to contribute to disease progression in heart failure phenotype. Although important interactions between proinflammatory cytokines and the adrenergic system have been recognized in the heart for over a decade, the nature of the important interactions between proinflammatory cytokines and the renin–angiotensin system has become apparent only recently. Accordingly, in the present review, we will discuss the evidence which suggests that there is a functionally significant cross-talk between neurohormonal and inflammatory cytokine signaling in cardiac hypertrophy and failure. © 2004 European Society of Cardiology. Published by Elsevier B.V. All rights reserved.

Keywords: Angiotensin II; Renin–angiotensin system; Heart failure; Tumor necrosis factor; Inflammation

1. Introduction

One of the major conceptual advances in our understanding of the pathogenesis of heart failure has been the insight that heart failure may progress as the result of the sustained overexpression of biologically active “neurohormones”, such as norepinephrine and angiotensin II, which by virtue of their deleterious effects are sufficient to contribute to disease progression by provoking worsening left ventricular (LV) remodeling and progressive LV dysfunction [1–3]. This understanding has provided the therapeutic rationale for using angiotensin converting enzyme (ACE) inhibitors to inhibit the renin–angiotensin system and the use of β2-blockers to antagonize the adrenergic system in patients with heart failure. Nonetheless, despite the significant strides that have been made in the treatment of heart failure, many patients will ultimately “escape” from neurohormonal antagonism [4,5] with the result that heart failure progresses despite optimal therapeutic antagonism of all of the known neurohormonal targets.

Relevant to this discussion is the recent observation that a second class of biologically active molecules, termed cytokines, has also been identified in the setting of heart failure [6,7]. Moreover, recent studies have shown that, analogous to the situation with neurohormones, the overexpression of cytokines (e.g. tumor necrosis factor, interleukin-1 [8–10]) is sufficient to contribute to disease progression by virtue of the direct toxic effects that these proteins exert in the heart and the circulation. Whereas the neurohormonal and cytokine systems have been regarded heretofore as functionally distinct biological systems, recent studies from this and other laboratories [11–15] suggest that the renin–angiotensin system and inflammatory cytokines can cross-regulate each other, with the result that neurohormonal and cytokine...
systems may participate in self-sustaining and/or self-amplifying positive feedback loops. Accordingly, in the present review, we will discuss the evidence which suggests that there is a functionally significant cross-talk between neurohormonal and inflammatory cytokine signaling in cardiac hypertrophy and failure.

2. Cross-talk between the renin–angiotensin system and proinflammatory cytokines in the adult heart

Although important interactions between proinflammatory cytokines and the adrenergic system have been recognized in the heart for over a decade [16–18], the nature of the important interactions between proinflammatory cytokines and the renin–angiotensin system has become apparent only recently. Indeed, whereas angiotensin II was traditionally viewed as a circulating neurohormone that stimulated the constriction of vascular smooth muscle cells, aldosterone release from the adrenal gland, sodium reabsorption in the renal tubule, and/or as a stimulus for growth of cardiac myocytes or fibroblasts [19], it is becoming increasingly apparent that angiotensin II provokes inflammatory responses in a variety of different cell and tissue types. Mechanistically, angiotensin II activates a redox sensitive transcription factor termed nuclear factor-kappa B (NF-κB) [20] that is critical for initiating the coordinated expression of a classical components of the myocardial inflammatory

Fig. 1. Angiotensin II-induced myocardial TNF biosynthesis in the adult heart. (A) TNF mRNA expression (RNase protection assay) was assessed ex vivo in diluent and angiotensin II (10^-7 M) treated (0–180 min) buffer perfused Langendorff hearts, in the presence or absence of 10^-6 M PD123319, an AT2 receptor antagonist (AT2a) or 10^-6 M losartan, an AT1 receptor antagonist (AT1a). (B) Myocardial TNF protein production was assessed in the superfusates of the angiotensin II treated hearts using ELISA, in the presence or absence of PD123319 (10^-6 M) or losartan (10^-6 M) pretreatment. The main panel of B shows the dose-dependent effects of angiotensin II (10^-10 to 10^-7 M), whereas the inset shows the time course (0–180 min) for TNF protein synthesis following stimulation with either diluent (solid circles) or 10^-7 M Ang-II (open triangles). Key: AT1a = AT1 receptor antagonist [losartan]; AT2a = AT2 receptor antagonist [PD123319]; *p < 0.05 and **p < 0.01 compared to diluent treated hearts. Reproduced with permission, American Heart Association [31].
observational studies that have shown that treatment with angiotensin converting enzyme inhibitors attenuates TNF mRNA biosynthesis following ischemia reperfusion injury [24] and acute myocardial infarction.

Indeed, Wei et al. [25] performed acute coronary artery ligations in rats and then followed the animals for 28 days or 81 days before beginning treating them with quinapril [26]. Consistent with previous reports, the authors reported an infarct-induced increase in the mRNA levels of proinflammatory cytokines, including tumor necrosis factor (TNF), interleukin-1β (IL-1β), IL-5 and IL-6 [27,28]. While Wei et al. noticed that starting quinapril either at day 21 (for 56 days of treatment) or day 81 (for 3 days of treatment) had little effect on cardiac hemodynamics or ventricular remod-

response, including increased expression of proinflammatory cytokines, nitric oxide, chemokines and cell adhesion molecules [21,22]. Moreover, recent experimental studies have shown that pathophysiologically relevant concentrations of angiotensin II are sufficient to provoke TNF mRNA and protein synthesis in the adult heart through a NF-κB dependent pathway [23].

Fig. 1 shows that treatment with angiotensin II resulted in a rapid increase in TNF mRNA (Fig. 1A) and protein synthesis (Fig. 1B) in isolated bufferperfused hearts. In this study and an earlier study [24], stimulation of isolated adult cardiac myocytes with angiotensin II resulted in increase either in TNF mRNA and protein biosynthesis, suggesting that the increase in TNF biosynthesis in the intact heart was mediated, at least in part, at the level of the cardiac myocyte. The effects of angiotensin II on TNF mRNA and protein synthesis were mediated exclusively through the angiotensin type I receptor (AT1R), insofar as pretreatment with the AT1R antagonist losartan completely abolished the effects of angiotensin II on TNF biosynthesis, whereas pretreatment with the AT2R receptor antagonist PD123319 had no effect on angiotensin II induced TNF biosynthesis (Fig. 1B). Stimulation with angiotensin II led to a rapid increase (30 min) in NF-κB binding activity in isolated bufferperfused hearts, suggesting a possible role for this pathway in terms of mediating the effects of angiotensin II on TNF biosynthesis (Fig. 2). Consistent with our results regarding the role of the AT1R in angiotensin II-induced TNF mRNA and protein synthesis, there was no NF-κB activation in the hearts that had been pretreated with losartan prior to angiotensin II stimulation, whereas pre-treatment with the AT2R antagonist PD123319 had no effect on angiotensin II induced NF-κB activation (Fig. 2). These experimental studies are in accord with prior experimental


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Fig. 2. Angiotensin II induced activation of NF-κB. Buffer perfused Langendorff hearts were treated for 180 min with 10⁻⁷ M angiotensin II, in the presence or absence of PD123319 (10⁻⁶ M) or losartan (10⁻⁶ M) pretreatment (60 min), and myocardial biopsies taken every 30 min. Electromobility shift assays were performed on the myocardial extracts from the biopsies using radiolabeled consensus sequences for NF-κB. To determine the specificity of the DNA-protein binding, the nuclear extracts were treated with a 25× and 50× excess of unlabeled oligonucleotides. Key: AT1a = AT1 receptor antagonist [losartan]; AT2a = AT2 receptor antagonist [PD123319]. Reproduced with permission, American Heart Association [31].
eling, they did observe that treatment with quinapril for 3 days led to a significant attenuation in the mRNA levels for TNF, IL-5 and IL-6. However, animals treated with quinapril for 56 days had a nonsignificant trend towards lower levels proinflammatory cytokine mRNA levels relative to nontreated controls. These authors suggested the important possibility that one of the mechanisms of action of ACE inhibitors in preventing disease progression in heart failure may occur through attenuation of cytokines. Support for this thesis is also suggested by clinical studies, wherein treatment of heart failure patients with an AT1R antagonist resulted in a significant decrease in circulating levels of inflammatory mediators (TNF), and/or cell adhesion molecules (intercellular adhesion molecule-1 and vascular adhesion molecule-1) [29,30].

Although previous experimental and clinical studies have suggested that activation of the renin–angiotensin system in heart failure patients with an AT1R antagonist resulted in a significant decrease in circulating levels of inflammatory mediators (TNF), and/or cell adhesion molecules (intercellular adhesion molecule-1 and vascular adhesion molecule-1) [29,30].

A recent experimental study suggests that the effects of angiotensin II on TNF biosynthesis are mediated, at least in part, through the protein kinase C (PKC) pathway. Figs. 3A and B shows that stimulation with angiotensin II led to a rapid increase in the second messenger for PKC, namely diacylglycerol (DAG). DAG mass increased rapidly within 10 min following stimulation with angiotensin II. Pretreatment with losartan completely prevented the angiotensin II mediated increase in DAG mass, whereas pretreatment with the AT2R antagonist PD123319 had no effect on angiotensin II induced DAG mass. Angiotensin II stimulation led to a rapid (15 min) three-fold increase in PKC activity in cultured cardiac myocytes, whereas there was no significant change in PKC activity in diluent treated myocytes (Fig. 3C). Consistent with the effects of losartan on DAG mass, the angiotensin II–induced increase in PKC activity was completely inhibited by losartan, as well as the PKC antagonist chelerythrine (Fig. 3C). This study further
showed that stimulation of isolated buffer perfused hearts with the PKC agonist phorbol 12-myristate-13-acetate (PMA) mimicked the effects of angiotensin II in terms of TNF mRNA and protein synthesis, whereas chelerythrine completely abrogated angiotensin II-induced TNF mRNA and protein synthesis [31]. Thus, this study suggests that angiotensin II provokes NF-κB activation and TNF biosynthesis in the adult mammalian heart in a PKC dependent manner.

As noted at the outset, there is also increasing evidence that inflammatory mediators are capable of upregulating various components of the renin–angiotensin system in a variety of mammalian tissues, including the heart. As one recent example, TNF stimulation has been shown to increase the density of angiotensin type I receptors (AT₁) on cardiac fibroblasts [32], as well as increase the sensitivity of these cells to the profibrotic actions of endogenous angiotensin II [33]. Moreover, studies using transgenic mice with cardiac restricted overexpression of TNF have shown that targeted overexpression of TNF leads to an increase in angiotensin II peptide levels in the heart [15]. In this study, several components of the renin–angiotensin system, including angiotensinogen, renin, angiotensin converting enzyme (ACE) and angiotensin I and II peptide levels were serially examined in a transgenic mouse line with cardiac restricted overexpression of TNF (MHCsTNF). There was a significant increase in ACE mRNA levels (Figs. 4A and B) and ACE activity (Fig. 4C), as well as increased angiotensin II peptide levels (Fig. 4D) in the hearts of the MHCsTNF mice relative to littermate controls. Importantly, the expression of renin and angiotensinogen was not increased in MHCsTNF mice compared with littermate controls. Thus, this study suggested that the increased levels of angiotensin II peptide levels in the MHCsTNF mice was principally the result of increased ACE activity, as opposed to increased activation of the more proximal components of the renin–angiotensin system, namely renin and angiotensinogen. This study also raised the interesting possibility that there was increased myocardial scavenging of renin and/or angiotensin I in the hearts of the MHCsTNF

Fig. 6. Effects of TNF on MAPK phosphorylation and activity. (A–C) To determine the time course of MAPK phosphorylation and activity after TNF stimulation, isolated adult feline cardiac myocytes were stimulated continuously for 0–60 min with either diluent or 200 U/ml of TNF. Myocyte proteins were separated on a 10% SDS-PAGE and immunblotted. Blots were probed with either anti-p44/42, anti-p38 or anti-JNK antibodies, to determine total levels of these MAPKs, or with phospho-specific antibodies to p44/42, p38 or JNK, to determine the degree of phosphorylation (i.e. activation) of these MAPKs, as described [56]. (D–E) MAPK activity was determined by measuring the degree of phosphorylation of specific transcription factors that are downstream from p44/42, p38 and JNK, respectively, namely, Elk-1, ATF-2 or c-Jun. Briefly, myocyte protein extracts were incubated overnight with an excess of agarose-conjugated antibody against p44/42, p38 or JNK. Immunoprecipitates were incubated in a kinase buffer supplemented with 200 mM ATP and Elk-1, ATF-2 or c-Jun substrates. The resultant substrate proteins were fractionated on SDS-PAGE substrate phosphorylation and immunoblotted using phospho-specific antibodies for Elk-1, ATF-2 or c-Jun (all reagents from Cellular Signaling), as described [56]. Autoradiographs were quantified by laser densitometry. Data are expressed as the fold increase (mean ± S.E.) from control values, for myocyte cultures stimulated with 200 U/ml TNF at 0 min; *p < 0.05 compared to baseline.
mice, since the angiotensin I peptide levels were similar in the MHCsTNF and littermate control mice, whereas the levels of angiotensinogen were less in the MHCsTNF mice. Finally, it was suggested that activation of the renin–angiotensin system was functionally significant in the TNF transgenic mice. That is, treatment of the MHCsTNF mice from 4 to 8 weeks of age with losartan significantly attenuated the cardiac hypertrophy phenotype in the MHCsTNF mice without any significant effect on peripheral hemodynamics. As shown in Fig. 5, treatment with losartan normalized LV mass and wall thickness, suggesting that interactions between the renin–angiotensin system and inflammatory mediators, play an important role in the development of cardiac hypertrophy and left ventricular remodeling. This statement notwithstanding, these studies did not exclude the possibility that the upregulation of the renin–angiotensin system in the MHCsTNF mice may be secondary to the development of a cardiomyopathy in the MHCsTNF mice.

3. Angiotensin II and tumor necrosis factor signaling converge on common signal transduction pathways

The literature reviewed in the foregoing section suggests that the renin–angiotensin system and inflammatory mediators can cross-regulate each other, raising the interesting possibility that these two systems may participate in self-sustaining and/or self-amplifying positive feedback loops. Relevant to this discussion is the recent observation that the renin–angiotensin system and inflammatory mediators converge on common signal transduction pathways, most notably the mitogen activated protein kinase (MAPK) pathway, raising the intriguing notion that the convergence of these two pathways on MAPK signaling may serve to amplify or propagate stress signals within the heart. As noted in a recent review by Sugden et al., the three major MAPK subfamilies in the heart include extracellularly responsive kinases (ERKs), c-Jun N-terminal kinases (JNKs) and p38 kinase [34–36]. In addition a fourth member of the MAPK family, Big MAPK-1 (BMK-1) has recently been cloned [37]. Recent studies suggest that angiotensin II and TNF signaling activate ERK, JNK and p38 in cardiac myocytes. For example, ERKs are rapidly phosphorylated in cultured neonatal cardiac myocytes in response to stimulation with angiotensin II [38], as well as TNF and interleukin-1β (IL-1β) [39]. JNKs are activated in neonatal cardiac myocytes by IL-1β, TNF [39], and angiotensin II [40–42]. Finally, p38 activation in neonatal cardiac myocytes has been reported in relation to stimulation with angiotensin II [43], TNF and interleukin-1β [39]. However, the functional significance of angiotensin II and proinflammatory cytokine mediated MAPK activation in the heart is not known.

Given that cell signaling pathways are different in neonatal and adult cardiac myocytes, we asked whether TNF was sufficient to provoke MAPK activation in adult cardiac myocytes. As shown in Figs. 6A–C, stimulation of isolated adult feline cardiac myocytes with 200 U/ml of TNF led to phosphorylation (activation) of ERK, JNK and p38 within 15 min, with a subsequent return towards baseline values within 60 min. TNF-induced MAPK activity was determined by measuring the degree of phosphorylation of specific transcription factors that are downstream from p44/42, p38 and JNK1/2, respectively, including Elk-1,

![Fig. 7. Dose-dependent effects of TNF on MAPK activity. Myocyte cultures were stimulated with diluent or 10–1000 U/ml TNF for 15 min, harvested, and analyzed by Western blotting as described above (Fig. 6). Panel A shows the dose dependent effects of TNF on Elk-1 phosphorylation. Panel B shows the dose dependent effects of TNF on c-Jun phosphorylation. Panel C shows the dose dependent effects of TNF on ATF phosphorylation. Data are expressed as the fold increase (mean ± S.E.) from control values, for myocyte cultures stimulated with diluent and 10–1000 U/ml TNF. The specificity of TNF-induced effects was determined using an anti-TNF antibody (Ab), which completely neutralized the effects of TNF on MAPK activity (left-hand hatched bar. *p < 0.05 compared with control values.](https://academic.oup.com/cardiovascres/article-abstract/63/3/433/344873)
ATF-2 or c-Jun. As shown by Figs. 6D and E, respectively, TNF (200 U/ml) stimulation led to increased phosphorylation of Elk-1, c-Jun and ATF-2. Peak levels of Elk-1, ATF-2 or c-Jun phosphorylation were observed within 15 min, and had returned to baseline values by 60 min. One-way analysis of variance (ANOVA) indicated that there was an overall significant increase in the level of phosphorylation of ERK, JNK, p38, Elk-1, c-Jun and ATF-2 ($P < 0.001$); post hoc analysis of variance testing (Dunnett’s) indicated that the level of ERK, JNK, p38, Elk-1, c-Jun and ATF-2 phosphorylation was significantly different ($p < 0.05$) from control values following 10–30 min of TNF stimulation, but was not significantly ($p < 0.05$) different from control values by 60 min.

Figs. 7A–C show that TNF-induced MAPK activity was dose-dependent. When the cells were stimulated with 10 U/ml TNF, there was no discernable effect on MAPK activity, whereas concentrations of TNF ≥ 50 U/ml produced a significant increase in the level of phosphorylation of Elk-1, c-Jun and ATF-2. Interestingly, the dose response relationship for TNF and MAPK activity was hyperbolic. That is, TNF induced MAPK activity increased progressively from 10 to 200 U/ml TNF and decreased significantly following stimulation with higher TNF concentrations (1000 U/ml). As shown by the left-hand hatched bar (Figs. 7A–C) a neutralizing anti-TNF antibody completely abolished the effects of TNF on increased levels of MAPK activity, thus confirming the specificity of the effects of TNF on MAPK activity. One-way ANOVA indicated that there were significant overall differences ($p < 0.001$) in the level of phospho-Elk-1, phospho-c-Jun and phospho-ATF-2; post hoc analysis of variance testing (Dunnett’s) showed that the levels of phospho-Elk-1, phospho-c-Jun and phospho-ATF-2 were significantly different ($p < 0.05$) from control values for 50–200 U/ml of TNF, but were not significantly different from control values following stimulation with 10 or 1000 U/ml of TNF.

4. TNF and angiotensin II induced oxidative stress provoke hypertrophic growth in cardiac myocytes

Several recent studies have implicated TNF and angiotensin II as a potent inducers of oxidative stress in a number of cell types, including cardiac myocytes [44–47]. As shown in Fig. 8, stimulation of cultured adult feline cardiac myocytes with TNF and angiotensin II resulted in increased ROI generation within 10 min, as demonstrated by the increase in fluorescence brightness in these cells. Moreover, the increase in fluorescence brightness could be quenched by administration of an antioxidant after TNF stimulation (10 mM N-acetyl-l-cysteine [NAC]). Thus, these experimental observations show that stimulation with angiotensin II and TNF leads to increased ROI in cardiac myocytes. Since previous studies have suggested that angiotensin II stimulation is sufficient to provoke MAPK activation in...
isolated cardiac myocytes [41,48], we sought to determine whether TNF-induced ROI was sufficient to upregulate MAPK activity in adult feline cardiac myocytes. Figs. 8B and C show that TNF-induced ROI was responsible for the increase phosphorylation of Elk-1, c-Jun and ATF-2. As shown, TNF induced activation of Elk-1, c-Jun and ATF-2 was completely suppressed when the cells were pretreated with NAC (10 mM for 30 min; Table 1).

Tumor necrosis factor-alpha and angiotensin II modulate heart failure by provoking hypertrophic growth in cardiac myocytes. Recent studies have suggested that ROI may be responsible, at least in part, for these hypertrophic effects. For example, a recent study in neonatal cardiac myocytes showed that TNF and Angiotensin II were both sufficient to trigger cardiac myocyte hypertrophy via generation of ROIs [47]. These investigators demonstrated that TNF (10 ng/ml) and angiotensin II (100 nmol/l) induced ROI generation in a dose-dependent manner, as well as an increase in cardiac myocyte size and increased [3H]leucine uptake. The antioxidant butylated hydroxyanisole (10 μmol/l) significantly inhibited the effects of TNF and angiotensin II, suggesting that TNF and angiotensin II provoke cardiac myocyte hypertrophy via generation of ROIs. In order to determine which MAPK's were involved in this hypertrophic response, we examined TNF-induced protein synthesis in the presence and absence of several different MAPK inhibitors. As shown by Fig. 9, stimulation with TNF led to an accelerated rate of general protein synthesis in isolated adult cardiac myocytes, consistent with previous studies from this and other laboratories [47,49]. Importantly, pre-incubation of the cells with antioxidant NAC (10 mM) completely abolished the effects of TNF on protein synthesis. Pretreatment of the cells with a p38 inhibitor SB 20350 (1 μM) blocked TNF-induced protein synthesis, whereas treatment with the ERK inhibitors PD 98059 (10 μM), or the JNK inhibitor SP 600125 (20 μM) had no effect on TNF-induced protein synthesis. Taken together these studies suggest that TNF provokes hypertrophic growth in cardiac myocytes through ROI dependent activation of the p38 pathway.

Table 1

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<td>124.9 ± 14.4</td>
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<td>TNF</td>
<td>127.67 ± 12.5</td>
<td>599.9 ± 19.5*</td>
<td>613.53 ± 19.7*</td>
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<tr>
<td>TNF + NAC</td>
<td>128.62 ± 12.8</td>
<td>575.7 ± 19.8*</td>
<td>263.97 ± 20.9**</td>
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<tr>
<td>Angiotensin II</td>
<td>138.9 ± 16.0</td>
<td>558.4 ± 23.2*</td>
<td>568.5 ± 22.9*</td>
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Data are presented as the mean fluorescence intensity in arbitrary units/cell (mean ± S.E.M.) for isolated adult cardiac myocytes that was loaded with 1 μM 5- (and 6)-chloromethyl-2′, 7′-dichlorodihydrofluorescein diacetate (CM-dH2DCFDA, Molecular Probes) for 15 min and then stimulated with diluent, TNF (200 U/ml), TNF stimulation for 10 min followed by NAC treatment at (10 μM) at 10 min, and angiotensin II (10–8 M). Fluorescence brightness was quantified per individual cardiac myocyte (n = 25 cells/time/group). *p < 0.05 compared to 0 min; **p < 0.05 compared to 15 min.

Fig. 9. Functional effects of TNF-induced MAPK activity. (A) To determine whether TNF induced activation of MAPKs was responsible for hypertrophic growth in adult cardiac myocytes, freshly isolated cardiac myocytes were exposed continuously for 24 h to diluent, 200 U/ml TNF, 200 U/ml TNF + NAC (10 mM), 200 U/ml TNF + PD 98059 (10 μM), 200 U/ml TNF + SP 600125 (20 μM) and 200 U/ml TNF + SB 203580 (1 μM). The cultures were then pulse-labeled for 24 h with 30 mCi/ml [3H]phenylalanine and the cardiac myocytes proteins processed as described [49]. Data are depicted as the fold-change in the phenylalanine incorporation in TNF-stimulated cells compared with diluent-treated cells. *p < 0.05 compared with control values.
5. Conclusion

In the foregoing discussion we have reviewed the evidence which suggests that there is functionally significant cross-talk between the renin–angiotensin system and inflammatory mediators in the adult mammalian heart. As summarized in Fig. 10, angiotensin II can provoke inflammatory responses through an NF-κB dependent pathway, whereas TNF can provoke activation of the renin–angiotensin system through increased ACE activity. Importantly, both of these pathways converge on one or more MAPK signal transduction pathways. While it is likely that these types of teleologically conserved interactions between proinflammatory cytokines and the renin–angiotensin system allow multiple stress signals in the heart to converge on common sets of transcription factors and genes that code for “acute-phase response” proteins [50–52], there is growing evidence that this type of cross-regulated network can lead to deleterious self-amplifying positive feedback loops that promote tissue damage and organ level dysfunction, particularly in the setting of chronic activation. And indeed, the results of studies in cardiac tissue [15], as well as studies in the kidney [50] suggest that the interaction between these two systems plays an important role in the resulting disease phenotype. Although speculative, one potential reason for the so-called phenomenon of “neurohormonal escape” [5], in which there is disease progression despite pharmacological blockade of renin–angiotensin system, may relate to the redundancy that exists between cross-regulated biological systems, such as the renin–angiotensin systems and proinflammatory cytokines. This statement notwithstanding it is also possible that a certain degree of cross-regulation of these biologically active systems is necessary to maintain homeostasis. For example, excessive blockade of cross-regulated biologically active systems, such as the renin–angiotensin system [53], the adrenergic system [54], endothelin and inflammatory mediators [55], may explain some of the untoward outcomes in a number of recent clinical trials in heart failure. Accordingly, one of the important unanswered questions that arises from the present review will be to delineate the downstream signaling pathways that are both unique and common to the renin–angiotensin system and inflammatory cytokines, with the intent of better understanding the important homeostatic, as well as the deleterious interactions that occur between these two teleologically conserved biological systems.

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References


