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Understanding Angiotensin II Type1 Receptor Signaling in Vascular Pathophysiology

Satoru Eguchi[*], **Tatsuo Kawai**, **Rosario Scalia**, and **Victor Rizzo**

Cardiovascular Research Center, Lewis Katz School of Medicine, Temple University

Keywords

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Angiotensin II (AngII) is the most important endocrine ligand in the renin angiotensin system (RAS), contributing to the development of several cardiovascular diseases including hypertension [1]. AngII mediates its signal transduction and functions via the AngII receptors [2]. Historically, the presence of two subtypes of AngII receptors were pharmacologically recognized based on the sensitivity to the first orally-active non-peptide AngII receptor antagonist, losartan. The losartan-sensitive receptor was termed AT_1 receptor. It was assumed to be a heterotrimeric G protein-coupled receptor (GPCR) as it generates inositol triphosphate and diacylglycerol leading to intracellular Ca^{2+} elevation and protein kinase C activation, respectively. Most known physiological and pathophysiological functions of AngII including stimulation of vasoconstriction and salt and water reabsorption are mediated through the AT_1 receptor. The losartan-insensitive receptor was termed AT_2 receptor, whereas its G protein-coupling remains unclear [1, 3, 4]. In 1991, two research groups in the United States independently isolated cDNA (termed AGTR1) encoding the mammalian AT_1 receptor [5, 6]. Subsequently, rat AT_2 receptor cDNA (AGTR2) was cloned in 1993[7, 8]. These pioneer works revealed complete amino acid sequences of the AngII receptor subtypes belonging to the seven-transmembrane GPCR superfamily. In the early nineties, several studies reported that AT_1 receptor elicits tyrosine phosphorylation of multiple proteins as well as activation of mitogen-activated protein kinase (p42/p44 MAPK)/extracellular signal regulated kinase (ERK1/2) in various cell types including vascular smooth muscle cells (VSMC). The early nineties also saw the establishment of the concept that AngII via the AT_1 receptor has a direct action on cardiac myocytes, fibroblasts and VSMCs causing hypertrophic and fibrotic cardiovascular remodeling [9, 10]. The cardiovascular remodeling caused by AngII appeared to be at least partially independent from the hypertensive action of AngII [11]. These findings lead to identification of common signaling mechanisms shared by AT_1 receptor and a growth factor receptor which has an intrinsic tyrosine kinase activity [12–15]. Interestingly, AT_1 receptor can be activated by mechanical stretch contributing to cardiac hypertrophy [16, 17]. The mechano-sensor concept of the AT_1 receptor has been

[*]Corresponding author: Satoru Eguchi MD PhD FAHA, seguchi@temple.edu, Tel 215-707-8378, Cardiovascular Research Center, Lewis Katz School of Medicine at Temple University, 3500 N. Broad Street, Philadelphia, Pennsylvania 19140, USA.

Disclosures

None

expanded to mediate myogenic vasoconstriction [18–20]. Another key discovery from the early nineties is NAD(P)H oxidase-dependent reactive oxygen species (ROS) generation through the AT_1 receptor activation in VSMC [21]. This finding lead to a major (yet controversial) concept that ROS mediate cardiovascular pathophysiology including those involving the RAS. The finding was also significant as it is an important foundation for the well acknowledged concept established in the late nineties that AngII acts as a pro-inflammatory cytokine via the AT_1 receptor [22]. The basic understanding remains solid and unchanged that the AT_1 receptor signaling contributes to hypertension and various cardiovascular complications via activation of protein kinases, generation of ROS, and subsequent induction of remodeling and inflammation [2, 23]. However, there has been astonishing progress elucidating various novel components and pathways in the AngII/AT_1 receptor signal transduction for the past two decades. AT_1 receptor interacts and signals with G proteins and β-arrestin. In addition, AT_1 receptor communicates with growing numbers of AT_1 receptor-interacting proteins including other GPCRs (heterodimer formation). AT_1 receptor appears to activate several new signaling cascades including the Wnt/β-catenin pathway, Notch pathway and Hippo pathways. Moreover, AT_1 receptor mediates additional posttranslational protein modification including acetylation/deacetylation, S-nitrosylation, O-GlcNAcylation and SUMOylation (reviewed recently [2]). Crystal structures of the AT_1 and AT_2 receptors have also been recently demonstrated [24, 25]. However, further research is desired regarding the physiological and pathophysiological roles of these new components and signaling pathways. Here, based on the 2017 Lewis K. Dahl Memorial Lecture, we will describe noteworthy recent concepts of the AT_1 receptor signal transduction in mediating vascular pathophysiology. We will also discuss controversies, limitations and future directions of the AT_1 receptor research.

Transactivation of Growth Factor Receptor via a Disintegrin Metalloprotease 17 (ADAM17)

It has been demonstrated that AngII activates ERK1/2 via AT_1 receptor-mediated transactivation of epidermal growth factor receptor (EGFR) in VSMC *in vitro* [26]. The EGFR transactivation also mediates activation of other downstream kinases including Akt, p70 S6 kinase and p38 MAPK, and subsequent hypertrophic responses in VSMC [27–30] (Figure 1). Note that there are many other classical as well as novel pathways shown to potentially mediate vascular remodeling *in vivo* (reviewed in detail in the reference [31]). Moreover, while the EGFR transactivation cascade is well acknowledged in VSMCs, whether it has any significance in vascular pathophysiology linked to AngII had not been studied. Recently our group was able to demonstrate the critical roles the cascade play in AngII-induced hypertensive cardiovascular remodeling.

Upon 2 week AngII infusion in mice, activation of EGFR is mainly observed in coronary arteries in the cardiac section. Erlotinib is a clinically utilized selective EGF receptor kinase inhibitor. Treatment with erlotinib markedly attenuated vascular EGFR activation, vascular medial hypertrophy and perivascular fibrosis induced by AngII infusion, whereas AngII-induced hypertension was unaltered. Interestingly, AngII-induced cardiac hypertrophy was also prevented by the EGFR inhibitor [32]. These data suggest that vascular EGFR

transactivation mediate cardiovascular remodeling induced by AngII independently from hypertension. In addition, erlotinib prevented development of abdominal aortic aneurysm (AAA) induced by co-treatment of AngII and a lysyl oxidase inhibitor, β-aminopropianitrile [33]. Others also demonstrated that in EGFR inactivated mutant mice, AngII-induced cerebral arteriolar hypertrophy but not hypertension was attenuated [34]. In smooth muscle-targeted and inducible EGFR silencing mice, vascular hypertrophy and fibrosis induced by AngII infusion were also attenuated and development of hypertension was partially inhibited. However, AngII-induced cardiac hypertrophy was not prevented [35]. Taken together, these data suggest that EGFR transactivation is critical for AngII-mediated cardiovascular complications and that distinct cell types including VSMC and cardiac myocytes may be involved in the EGFR-dependent pathophysiology.

In vitro studies have demonstrated that a metalloprotease, ADAM17, mediates AngII-induced EGFR transactivation via generation of mature form of heparin-binding EGF-like growth factor [36, 37]. AT_1 receptor activates ADAM17 via Tyr^{702} phosphorylation through unidentified kinase [38]. Src family kinase is the potential candidate as it phosphorylates and activates ADAM17 in response to mechanical stretch in rat myoblasts [39]. In addition, several Ser/Thr kinases are implicated in ADAM17 activation in other cell systems [40]. We have utilized Sm22α-mediated conditional ADAM17 knockout mice to ask what role VSMC ADAM17 plays in hypertension and associated cardiovascular remodeling induced by AngII. Compared with wild type littermate control mice, vascular hypertrophy, perivascular fibrosis and cardiac hypertrophy but not hypertension induced by AngII infusion were blunted in the ADAM17 silenced mice. The phenotype is associated with inhibition of vascular EGFR activation. Systemic ADAM17 inhibition by neutralizing antibody also attenuated AngII-induced cardiovascular remodeling but not hypertension in wild type mice [41]. In addition, development of AAA induced by AngII plus β-aminopropianitrile was also blunted in VSMC ADAM17 silenced mice or wild type mice treated with ADAM17 antibody [42]. While Sm22α-mediated ADAM17 knockdown could partially reduce cardiac myocyte ADAM17 expression [41], others have reported that AngII-induced cardiac hypertrophy was not altered in cardiomyocyte-targeted ADAM17 silenced mice [43]. These data further support the concept that the VSMC ADAM17/EGFR transactivation mainly mediates cardiovascular pathology including cardiac hypertrophy induced by AngII.

It should be noted that ADAM17 has many other substrates beside EGFR ligands including tissue necrosis factor α (TNFα) [44]. In TNFα knockout mice, AngII-induced hypertension and cardiac hypertrophy were blunted [45]. Transplant experiment with TNFα knockout mice suggest a partial involvement of TNFα produced in kidney in AngII-induced hypertension [46]. Smooth muscle-derived TNFα has been shown to positively contribute to blood pressure responses [47]. Another important substrate for ADAM17 is angiotensin converting enzyme 2 (ACE2). ACE2 cleavage by ADAM17 inactivates ACE2 leading to reduced Ang(1–7) generation and enhanced AngII retention. This concept has been shown to be involved in DOCA-salt induced neurogenic hypertension [48]. Subsequent study demonstrated neuronal AT_1 receptor mediating the ADAM17-dependent ACE2 inactivation [49]. Therefore, in addition to EGFR transactivation, it is important to further investigate the potential participation of TNFα generation and ACE2 inactivation as consequences of ADAM17

activation, leading to hypertension, cardiovascular remodeling as well as other types of pathophysiology associated with enhancement of the RAS (Figure 2).

Involvement of Caveolin 1 in AngII-induced Vascular Remodeling

Caveolae are a specific type of small lipid raft at the plasma membrane and serve as important signal transduction platforms [50]. The roles of caveolin 1 (Cav1), a major component protein in caveolae in AT_1 receptor signal transduction has been extensively studied [51]. However, limited information has been available regarding the role of Cav1-mediated AngII signaling in vascular pathophysiology. It has been shown that in Cav1+/− mice, AngII-induced hypertension and decline in nitric oxide were partially blunted [52]. We have recently examined the involvement of Cav1 in AngII-induced vascular remodeling with Cav1 knockout (Cav1−/−) mice. In Cav1−/− mice, AngII infusion causes hypertension and cardiac hypertrophy similar to the control Cav1+/+ mice. However, AngII-induced vascular hypertrophy and perivascular fibrosis are attenuated in Cav1−/− mice. Protection of vascular remodeling seen in Cav1−/− mice may involve two mechanisms according to our *in vitro* analyses. Cav1 silencing in VSMC attenuated ADAM17 activation, EGFR transactivation, protein synthesis and collagen synthesis induced by AngII. In addition, Cav1 silencing in endothelial cells prevented induction of vascular endothelial cell adhesion molecule and leukocyte adhesion induced by TNFα [53]. We also reported that Cav1 knockout mice were protected from AAA formation induced by AngII, which were associated with reduced inflammatory cytokines and oxidative stress [54]. However, several problematic baseline phenotypes are also associated with Cav1−/− mice including cardiac hypertrophy and pulmonary hypertension [50]. Further experiments such as those with cell type specific knockout mice are needed before considering any intervention toward Cav1 function.

ER Stress and Cardiovascular Remodeling

ER stress is caused by adaptive responses to an excess of misfolded proteins leading to unfolded protein response (UPR). UPR mediates specific signaling pathways which lead to induction of protein chaperones and attenuation of protein synthesis to reduce misfolded proteins. Sustained ER stress also activates c-Jun N-terminal kinase and nuclear factor-kB causing inflammatory responses. Several disease conditions including those occurring in the cardiovascular system are associated with enhancement of ER stress [55]. It has been demonstrated that AngII stimulation causes ER stress/UPR in the target organs including vasculature, heart and brain [56–58]. CCAAT-enhancer-binding protein homologous protein (CHOP) is a critical transcriptional factor induced by UPR. CHOP−/− mice are protected from AngII-induced hypertension and cardiovascular pathology [59]. Our investigation has demonstrated that AngII mediated ER stress responses are attenuated if the Cav1/ADAM17/EGFR pathway is inhibited pharmacologically and or genetically [32, 33, 41, 42]. One potential interpretation is that ER stress causes ADAM17 gene induction and enhances EGFR transactivation as a positive feed-back mechanism, where inhibition of either ER stress or the transactivation cascade results in suppression of vascular remodeling induced by AngII [32]. Alternatively, suppression of protein synthesis and hypertrophic/fibrotic remodeling reduce the rate of protein misfolding [41]. In addition, whether the UPR in response to AngII stimulation is sufficient to attenuate misfolding to maintain protein homeostasis

(proteostasis) remains unknown due to a lack of study to directly evaluate protein misfolding. It has been well documented that imbalance among protein folding, UPR and clearance of misfolded proteins by proteasome pathway or autophagy lead to aggregation of specific sets of proteins causing neurodegenerative diseases. Enhancement of protein aggregates were shown in mice hearts infused with AngII as well as aged mouse hearts. Nearly a hundred proteins are identified as commonly enriched aggregated proteins [60]. It is interesting to speculate that these proteins cause specific proteotoxicity and "protein aggregate responses" thus enhancing cardiovascular pathophysiology induced by AngII.

Mitochondrial Signaling of AngII

Due to its significant contribution to mitochondrial ROS production, AngII-induced mitochondrial dysfunction has been strongly implicated in cardiovascular diseases, metabolic diseases and aging [61, 62]. Indeed, inhibition of mitochondrial ROS can attenuate vascular dysfunction and hypertension induced by AngII [63, 64]. Moreover, AngII-infused mice showed cardiac hypertrophy and diastolic dysfunction associated with reduced cardiac ATP production and glucose oxidation, suggesting a role for AngII signal transduction in mitochondrial dysfunction [65]. However, mitochondrial targeted treatment such as antioxidant peptide or mitochondrial catalase transgene have no effect on AngII-induced hypertension, whereas these interventions can inhibit cardiac hypertrophy [66, 67]. Regarding the molecular mechanism by which AngII increases mitochondrial ROS, the contribution of Nox2-derived cytosolic ROS has been demonstrated [64]. In addition, AngII has been shown to inhibit mitochondrial Sirt3 and SOD2 via S-glutathionylation and acetylation, respectively, thus enhancing mitochondrial ROS generation [68]. There are a few reports available regarding the relationship between AngII pathophysiology and mitophagy. An E3 ubiquitin ligase autophagy protein 5 (Atg5) mediates formation of autophagosomes and autophagy. AngII increases cardiac Atg5 expression, autophagy and mitophagy in infiltrated macrophages. In Atg5+/− mice, reduction in macrophage mitophagy is associated with enhancement of cardiac hypertrophy and oxidative stress [69]. However, in swine model of renovascular hypertension, AT_1 receptor blocker attenuated myocardial mitophagy and increased mitochondrial biogenesis [70].

Recent studies also demonstrated that AngII regulates mitochondrial morphology. Mitochondrial fission and fusion are key regulatory mechanisms required for mitochondrial homeostasis as well as quality control under stress. Accumulating evidence suggest the causal relationship between mitochondrial fragmentation/fission and cardiovascular/metabolic diseases. Mitochondrial fission and fusion are regulated by multiple distinct proteins distributed in cytosol, ER and mitochondrial outer and inner membranes, of which GTPases, dynamin-related protein 1 (Drp1) and mitofusion 1/2 are central mediators of fission and fusion, respectively [71]. In cultured VSMC and neuronal cell line SH-SY5Y, AngII stimulation caused mitochondrial fission which was associated with Drp1 Ser^{616} phosphorylation [72, 73]. Moreover, pharmacological inhibition of Drp1 by mdivi1 attenuated AngII-induced mitochondrial ROS production and VSMC proliferation [73]. However, it should be noted that mdivi1 is known to inhibit mitochondrial respiration at complex I and modulate ROS production [74].

During the lecture, our unpublished data utilizing both pharmacological and genetic manipulations including those obtained with conditional knockout mice were presented. These data support two novel signal transduction concepts regarding the mitochondrial dynamics dictating vascular pathophysiology induced by AngII or TNFα. 1) In VSMCs *in vitro* and *in vivo*, AngII activation of AT_1 receptor causes mitochondrial fragmentation via the EGFR transactivation. Mitochondrial fission appears to be an essential step for cardiovascular remodeling (but not hypertension) induced by AngII. 2) In endothelial cells *in vitro* and *in vivo*, TNFα induces mitochondrial fragmentation via a mechanism distinct from EGFR transactivation. Endothelial mitochondrial fragmentation significantly influences TNFα signal transduction. Moreover, inhibition of mitochondrial fragmentation prevents inflammatory responses induced by TNFα infusion in mice including leukocyte adhesion. Further research is warranted to answer several fundamental questions. Why do vascular pathogens cause mitochondrial fission and what is the consequence to mitochondrial homeostasis and cellular phenotype in cardiovascular diseases? What is the essential "forward grade" signaling mechanism utilized by the receptors that cause vascular mitochondrial fragmentation? Finally, we need to explore the other essential "retro grade" signaling mechanism by which mitochondrial fragmentation mediate vascular remodeling and inflammation.

Cell Type Specific AT_1 Receptor Signal Transduction

Although the literature presented here strongly suggests that VSMC (and perhaps partially via endothelial) AT_1 receptor signaling mechanisms mediate AngII pathophysiology in the vasculature including hypertension and vascular remodeling, there are noteworthy findings challenging these concepts. We are aware of the accumulating findings suggesting the importance of several distinct immune cell populations in mediating hypertension and endothelial dysfunction in response to AngII [75]. However, caution is required when interpreting the findings in this field [76]. Many of the strategies utilized manipulate a specific subset of immune cells by removing their presence in mice. As such it is difficult to specify if the outcomes are due to initiation of AngII signal transduction in the immune cell, if the immune cell's function lay downstream of AT_1 receptor signal transduction originally elicited in other cell types, or removing the specific immune cell type is affecting the phenotype independently from the RAS. Deletion of AT_1 receptor on bone marrow-derived cells augmented hypertension, renal inflammation and injury in mice [77]. Bone marrow AT_1 receptor appears dispensable for AngII-induced enhancement of atherosclerosis in apoE−/− mice [78]. A few studies are available utilizing immune cell targeted conditional AT_1 receptor knockout mice. In T cell AT_1 knockout mouse, no alteration was detected in hypertension induced by AngII. Moreover, AngII-induced renal injury was enhanced in the knockout mice [79]. Macrophage AT_1 receptor deletion also indicate the role of macrophage AT_1 receptor in renal protection [80]. These data thus challenge the concept that inactivation of the AT_1 receptor on inflammatory T cell or macrophage is protective against hypertension and end organ damage. The findings also indicate that while T cells and macrophages enhance AngII causing hypertension and end-organ damage, these actions are independent from immune cell RAS and likely regulated through the peripheral AT_1 receptor. However, additional

investigation is needed to explore the protective AT_1 receptor signal transduction in the immune cells.

Conditional AT_1 receptor knockout mice have also been utilized to study the requirement of AT_1 receptor in VSMC, endothelial cell and fibroblast to mediate hypertension and vascular remodeling (Table 1). Sm22α-Cre deletion of VSMC AT_1, Tie2-Cre deletion of endothelial (and hematopoietic) AT_1, or Eno2-Cre deletion of neuronal AT_1 did not alter hypertension or vascular medial hypertrophy induced by AngII infusion. In contrast, S100A4 Cre deletion of fibroblast AT_1 attenuated vascular hypertrophy but not hypertension induced by AngII [81]. However, there is a concern in the interpretation of these data. While these findings confirm no alteration of hypertension by "transgenic" Sm22α-Cre deletion of VSMC AT_1 in AngII-induced hypertension [82], more effective silencing of AT_1 receptor using Cre that is regulated by endogenous Sm22α ("knock-in") shows significant reduction in hypertension induced by AngII infusion [83]. However, whether AngII-induced vascular remodeling is attenuated in the mice remains to be studied. Expression of S100A4 in VSMC has been demonstrated [84]. Our mass spectrometry analysis of cultured rat VSMC lysates detected protein fragments derived from S100A4 (unpublished observation), thus Cre under control of S100A4 promoter may delete smooth muscle AT_1 receptors in addition to those on fibroblasts. In relation to these issues (insufficiency and non-specific targeting), a critical limitation common in these studies are lack of confirmation of AT_1 receptor "protein" silencing in the target cells/tissues. This is because reliable AT_1 receptor antibody has not yet been available [85, 86]. Therefore, further effort is desired to specify AT_1 receptor-expressing cell types involved in AngII-induced cardiovascular pathophysiology.

Perspectives

Here, we summarized the noteworthy novel concepts and progresses in AT_1 receptor signal transduction in mediating cardiovascular pathophysiology. The AT_1 receptor signal transduction appears to remain a central component in cardiovascular pathophysiology. To conquer cardiovascular complications and improve the prognoses of hypertensive patients, we have to further clarify the complexity of the AT_1 signal transduction. Better molecular tools should be developed, and additional effort is required in order to answer cell/tissue type specific roles that AT_1 receptor plays in cardiovascular and metabolic diseases. This seems particularly important in cardiac myocytes, fibroblasts, adipocytes and immune cell subsets. Organelle signal communication such as those involving ER, mitochondria and exosomes [87] as well as balance among protein synthesis, misfolding, aggregation and the "proteo"-toxicity are important questions to ask for their relevance in AngII pathophysiology. We also expect that unbiased system biology and bioinformatics approaches will further shed light on previously unrecognized AT_1 receptor signal transduction for the next decade. Finally, we strongly hope that this article helps the researcher to further explore novel molecular mechanisms that RAS plays in cardiovascular diseases and that these studies will lead to a remarkable translation into effective therapies.

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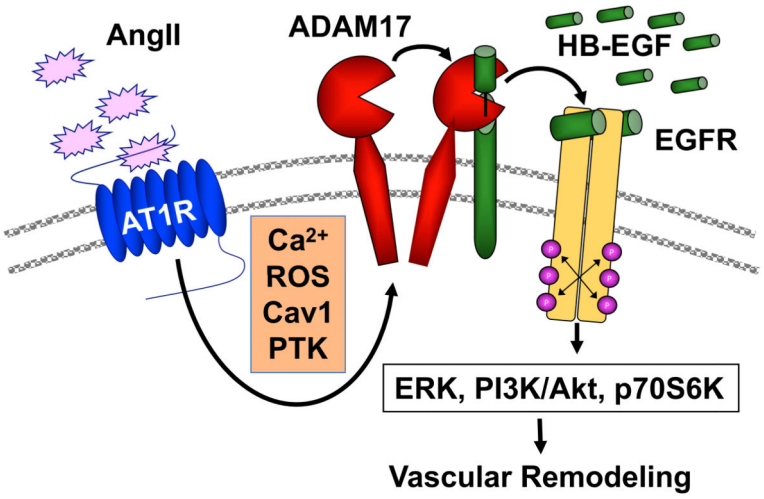

Figure 1.

Signal transduction mechanism of EGFR transactivation by AngII in vascular smooth muscle cells leading to vascular remodeling. PTK; protein tyrosine kinase, PI3K; Phosphoinositide 3-kinase, p70S6K; p70 S6 kinase. Please note that in addition to this cascade both classical and novel pathways have been shown to contribute to AngII-mediated vascular remodeling (reviewed in detail recently in the reference [31]).

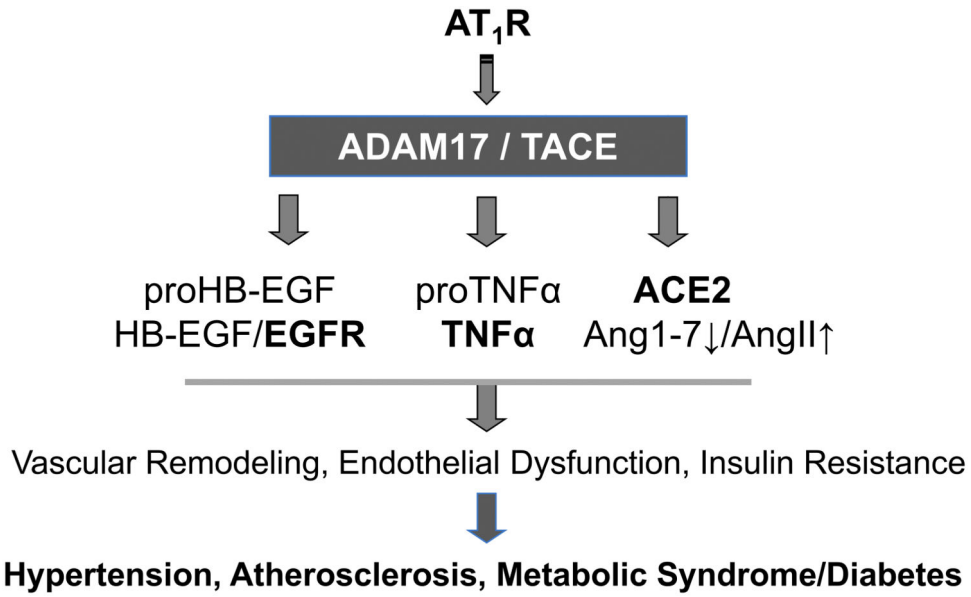

Figure 2.

Potential roles of ADAM17 activation in cardiovascular pathophysiology. In addition to EGFR transactivation, ADAM17 may contribute to endothelial dysfunction and insulin resistance by producing TNFα and inhibiting ACE2.

Table 1

Phenotype of conditional AT_1 receptor knockout mice infused with AngII

Target	Promoter	Phenotype	Reference
Smooth muscle	KI* Sm22α	Hypertension □	83
Smooth muscle	Sm22α	Hypertension ↔, Vascular hypertrophy ↔	81, 82
Endothelial cells	Tie2	Hypertension ↔, Vascular hypertrophy ↔	81
Neurons	Eno2	Hypertension ↔, Vascular hypertrophy ↔	81
Fibroblasts	S100A4	Hypertension ↔, Vascular hypertrophy ↓	81
T lymphocytes	CD4	Hypertension ↔, Kidney injury ↑	79
Macrophages	LysM	Hypertension ↔, Kidney injury ↑	80

*KI (Knock-in)