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Conundrum of Angiotensin II and TGF- β Interactions in Aortic Aneurysms

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Abstract

Angiotensin II (AngII) has been invoked as a principal mediator for the development and progression of both thoracic and abdominal aortic aneurysms. While there is consistency in experimental and clinical studies that overactivation of the renin angiotensin system promotes aortic aneurysm development, there are many unknowns regarding the mechanistic basis underlying AngII-induced aneurysms. Interactions of AngII with TGF- β in both thoracic and abdominal aortic aneurysms have been the focus of recent studies. While these studies have demonstrated profound effects of manipulating TGF- β activity on AngII-induced aortic aneurysms, they have also led to more questions regarding the interactions between AngII and this multifunctional cytokine. This review compiled the recent literature to provide insights into understanding the potentially complex interactions between AngII and TGF- β in the development of aortic aneurysms.

Overview of Aortic Aneurysms

Aortic aneurysms are a group of pathologies that have the common feature of permanent dilation, which occur in the thoracic (TAAs) and abdominal (AAAs) regions. Although TAAs and AAAs develop in the same “conduit”, they have distinctively contrasting characteristics. For example, TAAs occur in patients of all ages, are equivalent in both genders, and frequently have a known genetic basis. By contrast, AAAs are most prevalent in the aged male population without an overt genetic basis. Additionally, there are relatively greater roles of inflammation associated with AAAs than TAAs. Profound differences in pathological appearances of the aneurysmal tissues between TAAs and AAAs as described in our recent review article [1] also distinguish these two aortic aneurysms.

Although there are marked differences between TAAs and AAAs, activation of the renin angiotensin system (RAS) has been invoked in the etiology of both forms of aortic aneurysms [1]. Despite demonstration of the RAS contributing to aortic aneurysmal development, there are many unanswered questions on the mechanisms by which the RAS promotes TAAs and AAAs. Recent studies have illustrated potential interactions of AngII

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with a multifunctional cytokine, transforming growth factor- β (TGF- β), in the development of aortic aneurysms. While these have provoked interest in exploration of AngII and TGF- β interactions, these publications have also suggested an unexpected complexity of these interactions. The purpose of this brief review is to collate the recent literature regarding the effects of potential interactions between AngII and TGF- β in aortic aneurysms and discuss alternative interpretations that may provide insight into disparate conclusions in the literature.

Cellular and Intracellular Interactions of AngII and TGF- β

AngII exerts its bioactive effects on vascular physiology and pathology predominantly through binding to AT1 receptors. In rodents, chromosomal duplication leads to expression of two isoforms, termed AT1a and AT1b. AT1a receptors are the primary determinant of AngII effects in rodents. AngII-AT1 receptor interactions induce multiple signaling pathways in cell types resident in the aortic wall including smooth muscle and endothelial cells as well as infiltrating leukocytes [2]. Included in these signaling mechanisms are Smad and extracellular signal-regulated kinase (ERK) pathways.

TGF- β is a multifunctional cytokine with 3 isoforms in mammals that is essential for tissue morphogenesis and homeostasis. Upon activation, TGF- β transduces its signal across the plasma membrane by binding to its receptors including T β RI, T β RII, and T β RIII. It is well-established that T β RI and T β RII are abundant in the aorta and both are critical for normal aortic development [3].

There is accumulating evidence that AngII and TGF- β signaling have functional interactions. Many studies have reported that AngII increases TGF- β expression and release from cultured cells [4]. Accordingly, increases of TGF- β can be ablated by inhibition of either ACE or AT1 receptors [5]. There is also in vivo evidence that genetic disruption of TGF- β 1 in mice abolishes the development of cardiac hypertrophy and dysfunction induced by AngII [6]. This literature implicates TGF- β acting as a downstream mediator of AngII in pathological conditions. Although information is limited, some data support the converse effect of TGF- β regulating the RAS. These include TGF- β 1 inducing synthesis of ACE in rat cardiac fibroblasts [7], but downregulating AT1 receptors in vascular smooth muscle cells [8].

In addition to regulating each other, AngII and TGF- β also share common signaling pathways. Signal transduction of TGF- β is commonly considered to be primarily mediated by phosphorylation of the Smad family [9]. However, multiple nonclassical pathways (Smad independent) have also been implicated recently, for example, the mitogen activated protein kinase cascades (p38, ERK and JNK/p38) [10]. These pathways are also stimulated directly by AngII interaction with AT1 receptor signaling [2]. Although AngII and TGF- β share similar downstream signaling cascades, including the Smad pathway that has been considered the classic TGF- β signaling, the molecular details of AngII and TGF- β interactions remain unclear. Indeed, while both AngII and TGF- β promote vascular fibrosis, two recent studies have demonstrated that AngII promotes vascular fibrosis through activation of the Smad pathway independent of TGF- β [11,12].

Interactions of AngII and TGF- β in TAAs

Current literature is consistent with the premise of the RAS contributing to experimental and human TAA formation. Direct experimental evidence has been garnered from studies demonstrating chronic subcutaneous AngII infusion promotes TAAs [13]. These TAAs are predominantly localized to the ascending aortic region, although there are pathological changes that extend throughout the aortic arch. Dilation of the ascending aorta occurs

progressively during continued AngII infusion [14]. The pathological changes induced in the ascending aorta during AngII infusion are ablated in mice with AT1a receptor deficiency [15].

Only limited information regarding roles of TGF- β is available in the development of AngII-induced TAAs. This is restricted to a study in which two different TGF- β antibodies that neutralize the activity of TGF β 1–3 were injected into wild type C57BL/6 mice receiving AngII infusion [16]. Administration of TGF- β neutralizing antibodies in AngII-infused mice led to a high incidence of aortic rupture, which was mostly in the abdominal region. However, a few mice succumbed to rupture of the ascending aorta. A detrimental role of TGF- β neutralization was also demonstrated by expansion of ascending aortas of mice surviving co-administration with AngII [16].

TGF- β has been proposed to contribute to aortic aneurysms that develop in association with fibrillin-1 mutations. Mice with fibrillin-1 mutations were created to mimic features of individuals afflicted with Marfan's syndrome, which was considered to be provoked by increased TGF- β activity [3]. These manipulations in mice include expression of either a hypomorphic form of fibrillin-1 (Fbn1^{mgR/mgR}) or a mutant form of this protein derived from a C to G substitution at position 1039 (Fbn1^{C1039G/+}), which occurs at position 1037 in mice [17,18]. A single study provided evidence that inhibition of TGF- β attenuates ascending aortic dilation by administration of a polyclonal antibody that neutralizes the biological activity of all 3 isoforms of TGF- β [18], while in most studies the inferential role of TGF- β in the ascending aortic dilation is based on increased abundance of phosphorylated Smad2 in the dilated tissue [19,20]. However, there is evidence that dysregulation of Smad2 signaling exhibited in both Marfan and non-Marfan TAAs was attributed to epigenetic controls of smooth muscle cells independent of TGF- β 1 [21]. Additionally, in contrast to the proposed detrimental effects of TGF- β signaling in mice expressing mutated fibrillin-1, smooth muscle cell-specific T β R11 deficiency leads to embryonic lethality associated with vascular abnormalities including thoracic aortic rupture [22,23]. Therefore, the current literature has not provided consistent evidence on the role of TGF- β signaling in TAA formation.

The interpretation of several studies implicating a role of TGF- β in aortic dilation is based on the abundance of phosphorylated forms of Smad2 and ERK (Table 1). For example, measurement of aortic root dilation in fibrillin-1 mutated mice was accompanied by increased abundance of the phosphorylated forms of Smad2 and ERK (Table 1). Many studies have uniformly demonstrated increased abundance of pSmad2 [18–20,24,25]. Despite this being considered the canonical pathway for TGF- β , signaling through ERK has been dissected as the pathway responsible for aortic dilation [19,26]. Since Smad2 and ERK phosphorylations can be stimulated directly via either TGF- β or AngII, determinations of the abundance of these activated forms provide little information to discriminate the influence between TGF- β versus AngII, or their interactions. It is also worth noting that haploinsufficiency of Smad4 in fibrillin-1 mutated mice augments TAAs [26]. Although ex vitro data indicate enhanced Smad2 expression in these mice, direct evidence to answer whether TGF- β through Smad signaling (rather than Smad4) promotes TAAs would be blockade of TGF- β in fibrillin-1 mutated mice with Smad4 haploinsufficiency.

Some studies suggest that TGF- β promotes aortic aneurysms in fibrillin-1 mutant mice and humans via signaling pathways commonly associated with AngII. For example, several studies performed in mice expressing aberrant forms of fibrillin1 have manipulated the RAS. One approach has been administration of an AT1 receptor antagonist, losartan, to these mice. Losartan, the first of the sartan class of drugs, competitively antagonizes AngII interactions with the N terminal extracellular domain of AT1 receptors. It should be noted

that losartan is a prodrug with metabolites that have some properties beyond AT1 receptor antagonism [27]. However, the major actions of losartan are considered to be a result of specific interruption of AngII signaling. It was demonstrated that using this mode to antagonize AT1 receptors was highly effective in attenuating ascending aortic expansion in both the Fbn1^{C1039G/+} and Fbn1^{mgR/mgR} Marfan syndrome models as summarized in Table 1 [18–20,24,28,29].

The ability of losartan to prevent aortic aneurysm growth in fibrillin-1 mutant mice might be simply due to AT1 receptor blockade. However, there are other potential explanations. Antagonism of AT1 receptors may lead to increased availability of AngII. This has led to the proposal that some benefits derived from the AT1 receptor antagonism are augmented by increased stimulation of AT2 receptor. AT2 receptor stimulation may exert opposing effects to AT1 receptor stimulation, potentially via augmentation of opposing intracellular signaling pathways of AngII. Fbn1^{C1039G/+} mice have been generated with deletion of AT2 receptor to study effects on TAAs [19]. Deficiency of AT2 receptor led to increased aortic diameters in Fbn1^{C1039G/+} mice [19]. This study [19] also reported that inhibition of ACE (enalapril) in Fbn1^{C1039G/+} mice reduced aortic dilation to a lesser degree than AT1 receptor antagonism (losartan). These findings were interpreted as AT1 receptor antagonism augmenting AT2 receptor signaling, thereby resulting in inhibition of TGF- β mediated activation of ERK. Conversely, ACE inhibition reduced signaling for both AT1 and AT2 receptors. It is worth noting that the difference in size of aortic roots between AT2 receptor wild type and deficient mice was similar throughout the extended period of observation (2 – 12 months of age), indicating that the initial and persistent difference is attributable to events occurring early in life. Since AT2 receptor is highly expressed during fetal development, but dramatically diminishes after birth, this phenotype might be ascribed to embryonic deficiency of AT2 receptor expression. As speculated by the authors [19], increased availability of AngII for AT2 receptor stimulation has a potential benefit for TAA attenuation. However, it appears that increased stimulation of AT2 receptor was not responsible for the effects of losartan-induced reductions in TAAs in Fbn1^{C1039G/+} mice since the drug was equivalently effective in AT2 receptor deficient mice [19]. Additionally, there is no evidence that the single doses of the AT1 antagonist (losartan) and ACE inhibitor (enalapril) exerted equivalent effects on inhibition of the RAS [19]. A convincing interpretation could be provided by performing dose response curves to determine maximal effects of losartan versus enalapril, as demonstrated recently for multiple modes of the RAS inhibition in atherosclerosis [30].

Data from a retrospective clinical trial has also been cited to support a role for the RAS in aortic aneurysms associated with Marfan syndrome [31], whereas there is no direct evidence whether TGF- β inhibition is a mechanism for the beneficial effects of the RAS inhibition observed on aortic aneurysms. This analysis demonstrated that switching these patients from the standard care of β -adrenoceptor antagonism to a sartan was associated with significantly attenuated aortic expansion [31]. The concept that AT1 receptor antagonism attenuates aortic expansion is currently being evaluated by multiple double-blinded clinical trials [32]. We expect that these multiple double-blinded clinical trials will add to our understanding of TGF- β , AngII, and their interactions in genetically based TAAs.

Interaction of AngII and TGF- β in AAAs

There is uncertainty regarding the role of the RAS in human AAAs. Clarification of this role could be obtained through clinical trials that test pharmacologic approaches currently available for blocking the RAS, such as inhibitors of renin, ACE, or AT1 receptors. Despite the uncertainty regarding the role of the RAS in human AAAs, many animal studies have demonstrated that chronic AngII infusion promoted development of AAAs in both normo-

and hypercholesterolemic mice [1]. However, there are still major gaps in our knowledge on the basis for the mechanisms of the evolving disease.

There is a relative paucity of information on the role of TGF- β in formation of AngII-induced AAAs (Table 1). This includes the increased abundance of mRNA for TGF- β 1 and associated genes in aneurysmal tissues formed during AngII infusion [33]. Two studies directly determined the role of TGF- β in the development of AngII-induced AAAs. One study integrated the use of TGF- β neutralizing antibodies into studies that determined the increased formation of AngII-induced AAAs in apoE $-/-$ mice that were deficient in CXCL10 (a T-helper type 1 cytokine) [34]. A polyclonal neutralizing antibody to all 3 isoforms of TGF- β was injected at the time of AngII infusion. The presence of the TGF- β antibody had no effect on measurements of aortic area in CXCL10 $+/+$ mice, but decreased this parameter in CXCL10 $-/-$ mice [34]. In this study [34], AAA size was quantified by ratios of suprarenal/thoracic to infrarenal aortic area using aortic sections. It is unclear whether this measurement reflects the dilation of abdominal aortas, raising concerns over interpretation of the role of TGF- β in AngII-induced AAAs. Another study defined the role of TGF- β neutralizing antibodies in AngII-infused C57BL/6 mice [16]. Mice were infused with AngII while being injected with one of two neutralizing antibodies every 3 days. Although TGF- β inhibition led to reduced pSmad2 immunostaining in aortic wall and nearly ablated serum TGF- β concentration, co-administration of the TGF- β neutralizing antibodies with AngII provoked an AAA incidence greater than 80%, with the majority exhibiting rupture [16]. This study [16] used several well-accepted measurements to quantify AAAs including ultrasonic quantification, necropsy to identify aortic rupture specifically in abdominal regions, and ex vivo AAA severity classification. The detrimental effect of anti-TGF- β antibodies in AngII-induced AAAs was also confirmed in another study [35]. Taken together, the findings from these two studies [16,35] provide evidence that TGF- β inhibition augments AngII-induced AAAs.

The disparities in the literature on the role of TGF- β affecting AngII-induced AAAs may be attributed to many aspects of experimental designs such as different antibodies, variable doses, and different injection schedules. Clarity could be provided by using genetically manipulated mice. Unfortunately, deletion of many components of the TGF- β pathway leads to embryonic or fetal death. Therefore, an optimal approach would be the use of an inducible mode to deplete TGF- β in mature animals.

Conclusions and Perspectives

The current literature consistently demonstrates that AngII infusion promotes development of both TAAs and AAAs in mouse models. There is also consistency of the effects of AT1 receptor antagonism in reducing TAAs and AAAs induced by AngII infusion or genetic manipulations of fibrillin-1. However, the role of TGF- β in regulating these AngII provoked responses has results ranging from TGF- β neutralization being highly detrimental to beneficial. Given the current uncertainty for the role of TGF- β in development of aortic aneurysms, clarification of these conundrums is a dire need in order to develop therapeutic strategies for aortic aneurysms.

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Highlights

- The renin angiotensin system plays a critical role on aortic aneurysmal formation and development.
- Angiotensin II and TGF- β have potential interactions in the development of aortic aneurysms.
- The definitive roles of TGF- β in the development of aortic aneurysms need to be clarified.

Figure 1. Schematic summary of the main concepts discussed in this brief review
AngII and TGF- β have potential interactions in both Smad- and ERK-related signaling pathways [2,3]. While AngII plays a critical role in the formation of aortic aneurysms [1,13–16,33–35], there are also potential contributions of TGF- β to aortic aneurysmal development [3,16,18,19,26,34].

Table 1

Summary of TAA and AAA studies that have provided insight into potential interactions of the RAS and TGF- β .

Mouse model	Inhibition	Aortic dilation	Protein abundance in aortas		Reference
			pSmad2	pERK	
Fbn ^{C1039G/+}	ARB - losartan	TAA - decrease	decrease	ND	[18]
		TAA - decrease	decrease	ND	[24]
		TAA - decrease	decrease	decrease	[19]
		TAA - decrease	ND	ND	[28]
		TAA - decrease	decrease	decrease	[20]
	ACEI - enalapril	TAA - decrease	decrease	no effect	[19]
	AT2R -/-	TAA - increase	increase	increase	[19]
	AT2R -/- & losartan	TAA - decrease	decrease	decrease	[19]
	NAb - TGF-β	TAA - decrease	decrease	ND	[18]
		TAA - decrease	ND	decrease	[26]
TAA - decrease		ND	ND	[28]	
Fbn ^{mgR/mgR}	ARB - losartan	TAA - decrease	ND	ND	[29]
Fibulin-4 R/R	ARB - losartan	TAA - decrease	decrease	ND	[25]
AngII	NAb - TGF-β	AAA - increase	decrease	ND	[16]
AngII & CXCL10 +/-	NAb - TGF-β	AAA - no effect	ND	ND	[34]
AngII & CXCL10 -/-	NAb - TGF-β	AAA - decrease	ND	ND	[34]

ARB: angiotensin receptor blocker; ACEI: angiotensin-converting enzyme inhibitor; Fbn1^{C1039G/+}: one allele of fibrillin-1 gene contains C to G mutation at 1037 amino acid in mouse; Fbn1^{mgR/mgR}: fibrillin-1 contains a hypomorphic mutation (mgR), leading to ~15% of the normal amount of fibrillin-1; fibulin-4 R/R: 4-fold reduction of fibulin-4 expression; NAb: neutralizing antibody; ND: not determined.