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Multifaceted Role of Angiotensin II in Vascular Inflammation and Aortic Aneurysmal Disease

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1. Introduction

Aortic aneurysms and aortic dissections account for ~16,000 deaths in the United States annually (Kuivaniemi, et al., 2008). Recent evidence suggests that enhanced vascular inflammation underlies the progression of both abdominal aortic aneurysms and thoracic aortic aneurysms (Guo, et al., 2006a). Common pathologic features of vascular inflammation and aneurysmal disease include recruitment and activation of immune cells to the vessel wall, myofibroblast differentiation and extracellular matrix (ECM) remodeling. Recent preclinical work has implicated divergent signaling pathways downstream of the vasopressor angiotensin II (Ang II) peptide in controlling these activities. This work has elucidated two important paracrine signaling networks, one mediated by the NF-κB-IL-6 pathway controlling monocyte activation, and the second mediated by the TGF-β-Smad2 pathway controlling myofibroblast differentiation and T lymphocyte differentiation. Antagonism of Ang II signaling is being evaluated in the clinical management of patients with familial thoracic aneurysms. In this chapter, we will review the multifaceted role of Ang II in vascular inflammation in aortic aneurysmal disease.

1.1 Types of aortic aneurysms

Aortic aneurysms are primarily classified based on anatomic locations (Kuivaniemi, et al., 2008). Abdominal aortic aneurysms (AAA) primarily develop in the infrarenal segment of the abdominal aorta in humans or suprarenal aorta in rodent models. It predominantly affects elderly males, and is associated with hypertension, vascular inflammation and/or atherosclerosis (Guo, et al., 2006a). Initial pathological events in AAA involve recruitment and infiltration of leukocytes into the aortic adventitia and media, which are associated with the production of inflammatory cytokines, chemokine, and reactive oxygen species (ROS). Expression of macrophage activating cytokines is increased both systemically and locally in AAA. Importantly, as a major source of ECM-degrading matrix metalloproteinases (MMPs), recruited activated macrophages promote structural remodeling by degrading elastin and collagen in the vessel wall (Longo, et al., 2002). Moreover, in expanding aneurysmal tissues, increased infiltration of inflammatory cells may amplify MMP production by resident vascular cells (Pearce and Koch, 1996), facilitating aortic inflammation and structural remodeling.

In contrast, thoracic aortic aneurysms (TAA) are etiologically separable from AAA due to their strong genetic influence affecting areas including the ascending aorta, aortic arch,

and/or descending aorta. Common genetic disorders associated with TAAs include Marfan's Syndrome and Loeys-Dietz syndrome. Recent studies have also identified an inflammatory component in the etiology of TAA (Ejiri, et al., 2003). In TAA in patients undergoing surgical repair, enhanced expression of cytokines, such as interleukin-6 (IL-6) and interferon-γ (IFN-γ), as well as enhanced NADPH oxidase and reactive oxygen species (ROS) tone are found in aortic tissues. These events are spatially correlated with increased monocyte/macrophage accumulation and enhanced MMP production.

1.2 Cells and molecules implicated in inflammation in aortic aneurysms

The vascular inflammatory response involves complex interactions between recruited inflammatory cells (lymphocytes, monocytes, macrophages, neutrophils), vascular resident cells [endothelial cells (ECs), vascular smooth muscle cells (VSMCs) and adventitial fibroblasts] and the ECM. The ensuing inflammatory response increases expression of adhesion molecules, growth factors, cytokines and chemokines, that facilitates recruitment and local activation of inflammatory cells and matrix remodeling. Additionally, immune cells (macrophages, mast cells, B- and T- lymphocytes, neutrophils, along with VSMCs and adventitial fibroblasts) produce cytokines and enzymes, promoting an inflammatory reaction, extracellular matrix degradation, and neovascularization (Table 1).

Recruited CD68-expressing macrophages are found in both the adventitia and intima of aneurysms. They are attracted to the aortic wall by elastin degradation products, CC chemokines [e.g. monocyte chemotactic protein (MCP-1), RANTES, etc] and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Rizas, et al., 2009). MCP-1 produced by VSMCs and fibroblasts (Tilson, et al., 2000) induces monocyte chemotaxis by binding to CC-chemokine receptor 2 (CCR2). MCP-1 is an important mediator in early pathogenesis of aortic aneurysms because CCR2 deficiency prevents aneurysm formation in various mouse models (Daugherty, et al., 2010; Tieu, et al., 2009). Additionally, macrophages express 5-lipooxygenase (5-LO), which produces macrophage inflammatory protein 1α (MIP-1α) to recruit T-cells in a paracrine fashion. Locally infiltrated T-cells then magnify the inflammatory cascade by secreting various CC and CXC chemokines, attracting other inflammatory cells to the aneurysmal tissue (Zhao, et al., 2004).

CD3+ T-cells are abundant immunomodulatory and pro-inflammatory cells recruited to aneurysmal tissues, accounting for ~50% of local hematopoietic cells (Kuivaniemi, et al., 2008). Most T-cell subtypes have been identified, including helper T-cells (Th cells), cytotoxic T-cells and natural killer T-cells (NKT) (Kuivaniemi, et al., 2008). Recent studies to identify Th cell subtypes, which are predominant in aneurysms, reported controversial results. Some suggested Th2 was predominant, while other studies suggested Th1 (Galle, et al., 2005; Schonbeck, et al., 2002).

Aortic resident cells also potentiate inflammation via interactions with recruited immune cells. Adventitial fibroblasts produce cytokines and chemokines such as IL-6, MCP-1, VEGF, and TNF (Tilson, et al., 2000), contributing to leukocytic chemotaxis and activation. Work from our laboratory has found that Ang II stimulates aortic adventitial fibroblasts to recruit monocytes via fibroblast-derived MCP-1, and that the recruited monocytes further promote fibroblast proliferation, adventitial thickening, and additional cytokine production. This fibroblast-monocyte amplification loop may critically mediate adventitial inflammation (Tieu, et al., 2010; Tieu, et al., 2009). Upon stimulation with TGF-β, fibroblasts differentiate into α-smooth muscle cell actin-expressing myofibroblasts (Desmouliere, et al., 1993). Myofibroblasts play a role in wound healing and fibrosis, and are associated with development of aneurysmal disease (Sakata, et al., 2007).

Cells	Molecules	Roles in Aortic Aneurysms
Fibroblasts	MMP-1	Collagen degradation
	MMP-2	Elastin and collagen degradation
	VEGF	Angiogenesis
	MCP-1	Monocyte chemotaxis
VSMCs	MMP-2	Elastin and collagen degradation
	MMP-13	Collagen degradation
	MT1-MMP	Elastin and collagen degradation; ProMMP-2 activation; facilitate macrophage migration
	MCP-1	Monocyte chemotaxis
	IL-6	Macrophage differentiation; MCP-1 induction; systemic acute-phase response
Macrophages	MMP-3	Elastin and collagen degradation; VEGF activation
	MMP-9	Elastin and collagen degradation; dominant gelatinase in late pathogenesis; TGF-β, VEGF activation; macrophage migration
	MMP-12	Elastin and collagen degradation
	MT1-MMP	Elastin and collagen degradation; ProMMP-2 activation; facilitate macrophage migration
	Cathepsins	ECM degradation; angiogenesis
	MIP-1α	T-cell chemotaxis
	IL-8	Neutrophil chemotaxis
	LTD4	MIP-1α induction
	TGF-β	Angiogenesis; MMP induction; Th17 differntiation; myofibroblast differntiation
	IL-6	Macrophage differentiation; MCP-1 induction; systemic inflammatory responses
Mast cells	Chymases	ProMMP activation; VSMC apoptosis; Ang II induction
	Tryptases	ProMMP activation
	LTD4	MIP-1α induction
Netrophils	MMP-8	Collagen degradation
	MMP-9	Elastin and collagen degradation; TGF-β, VEGF activation; macrophage migration
	Cathespins	ECM degradation; angiogenesis
	Netrophil elastase	Elastin degradation
NKT cells	IFN-γ	Th1 differentiation; macrophage activation
	IL-4	Th2 differentiation; humoral immunity
Th Cells	IFN-γ	Th1 differentiation; macrophage activation
	IL-4	Th2 differentiation; humoral immunity
	IL-17	Macrophage chemotaxis

Table 1. Major cell types and secreted molecules involved in vascular inflammatory response in aortic aneurysms.

Among the different enzymes secreted by immune and stromal cells, MMP-2, MMP-9, MMP-12, cathepsins, and neutrophil elastase cause ECM degeneration (Table 1). Chymase causes smooth muscle cell apoptosis, and MMP-3, MMP-8, and MMP-13 cause adventitial collagen degradation, promoting abdominal aortic aneurysm rupture.

Cytokines and chemokines such as IL-8, MIP-1α, and MCP-1 facilitate recruitment and proliferation of inflammatory cells (Table 1). Cytokines include TNF, interleukins, interferons, colony stimulating factors, and transforming growth factors, etc. They are produced by diverse cell types including macrophages, T-cells and monocytes, VSMCs and fibroblasts. Circulating cytokines interact with specific receptors on various cell types to activate JAK-STAT, NF-κB, and Smad signaling pathways, regulating expression of various genes controlling inflammatory response involving cell adhesion, permeability and apoptosis. Cytokine signaling is also known to increase mitochondrial ROS production, induce integrins to facilitate cellular adhesion and activate MMPs to modify ECM composition. Further, increased local cytokine expression is implicated in aortic aneurysms.

Vascular inflammation is an ordered process producing recruitment of activated leukocyte subtypes into the vessel wall, initiating complex interaction with vascular residential cells and ECM. This process is initiated and amplified by local secretion of adhesion molecules, chemotactic factors and cytokines, whose inducible expression are signaled by vascular injury and modulated by vasoactive peptides (Ang II), CD40 ligands, oxidized cholesterol, and advanced glycation end products. Of these, the effects of Ang II have been implicated in vascular inflammation and have emerged as an important clinical target for the treatment of human aneurysms associated with Marfan's disease.

2. Ang II-induced vascular inflammation

Angiotensin II (Ang II) is the major effector peptide of the renin-angiotensin system. In addition to its potent vasoconstrictor actions, Ang II exert pro-inflammatory activity in the vascular wall, inducing production of inflammatory cytokines, adhesion molecules, and formation of ROS, resulting in macrophage accumulation, myofibroblast differentiation, and localized aortic dilation followed by dissections (Ejiri, et al., 2003).

Ang II is a potent inducer of vascular inflammation producing acute thoracic and suprarenal aortic aneurysms and dissections in many mouse models (Daugherty, et al., 2010; Tieu, et al., 2009). Chronic subcutaneous infusion of Ang II peptide into atherosclerosis-prone hyperlipidemic apolipoprotein E-deficient (ApoE-/-) or LDL receptor (LDLR-/-) deficient mice produces thoracic and suprarenal aneurysms (Reiner, 2007) . Also in aged C57BL/6J mice, Ang II produces both suprarenal and ascending thoracic aneurysms and dissections, albeit at a lower frequency than in the presence of hyperlipidemia (Tieu, et al., 2009). Moreover, Ang II type I receptor and ACE polymorphisms are associated with AAA in humans (Jones, et al., 2008), suggesting that Ang II is tightly associated with aneurysmal diseases. The mouse models of acute Ang II infusion showed significant vascular inflammatory responses in aneurysmal tissues, including enhanced aortic cytokine/chemokine production, early macrophage recruitment, elastin degeneration, and intramural hematoma formation.

Ang II stimulates inflammatory chemokine expression and ROS production in EC and VSCMs, events implicated in the pathogenesis of aortic aneurysms (Ejiri, et al., 2003; Longo, et al., 2002). In ECs, Ang II up-regulates expression of the leukocyte adhesion molecules vascular cell adhesion molecule (VCAM-1), intercellular adhesion molecule (ICAM-1), and selectins (Pueyo, et al., 2000), facilitating monocyte adhesion and recruitment into the vascular wall. Once

recruited, monocytes produce MMPs that mediate aortic wall remodeling in aneurysmal expansion, and migrate towards gradients of chemotactic cytokines (e.g. MCP-1, KC/Groβ, MIP-1α, etc). The actions of Ang II regulate many steps in these processes, inducing expression of chemokines MCP-1, KC/Groβ, and the cytokine IL-6 (Chen, et al., 2001; Han, et al., 1999). In VSMCs, Ang II is a potent inducer of cytokine and chemokine expression, including MCP-1 and IL-6. These molecules, in turn, cause more immune cell infiltration, further amplifying the inflammatory tone contributing to aneurysmal expansion.

The ability of Ang II to potently induce vascular inflammation involves the activation of two divergent signaling pathways important in the vascular stress response, the first being the nuclear factor-κB (NF-κB)-IL-6 signaling pathway, and the second, the transforming growth factor (TGF)-β-Smad pathway (Figure 1).

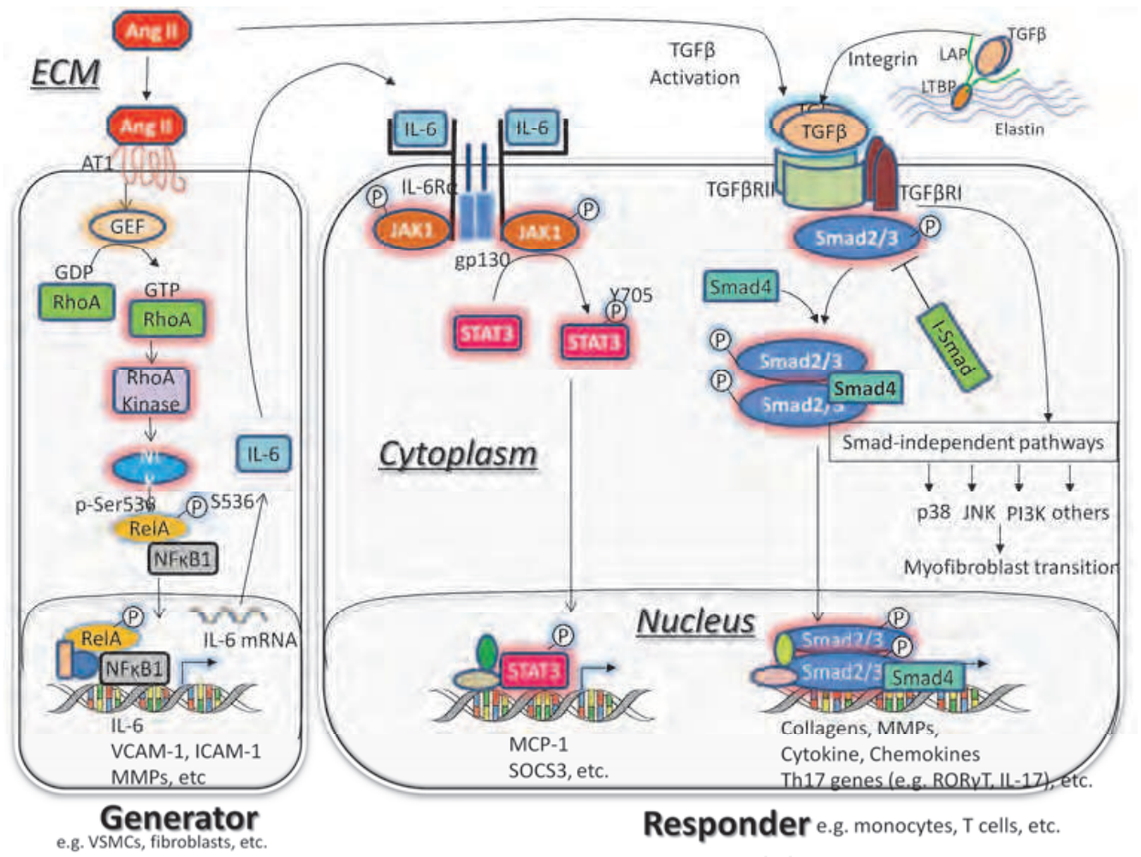

Fig. 1. Ang II-induced signaling pathways involved in vascular inflammatory events implicated in aortic aneurysms. The actions of Ang II involve cells directly responding to its actions schematically diagrammed as generators and downstream affected cells (responders) producing vascular inflammation and remodeling

3. The NF-κB-IL-6 pathway in Ang II-induced aortic aneurysms

A number of recent studies have demonstrated that NF-κB transcription factors play a central role in controlling the process of vascular inflammation. Responsive to vasoactive peptides such as Ang II, oxidized LDL, activated CD40 receptor, monocyte released

cytokines, or advanced glycation end-products, activated NF-κB is known to control leucocyte adherence and chemotaxis, key steps in the process of vascular inflammation. Recently, an additional role for NF-κB in controlling monocyte activation via the IL-6 pathway has also been discovered. Here, locally secreted IL-6 activates vascular monocytes and induces cellular protection from ROS-induced stress via signaling through the downstream effector signal transducer and activator of transcription 3 (STAT3). In this way, the NF-κB –IL-6 signaling pathway plays multiple roles in initiating and sustaining vascular inflammation.

3.1 Mechanism of NF-κB activation by Ang II in VSMCs

Ang II initiates intracellular signaling by binding to two types of heterotrimeric guanosine (G) -protein coupled 7-transmembrane receptors, termed the type I (AT-1) and type II (AT-2) Ang II receptors (Griendling, et al., 1997). AT-1 is the major receptor normally expressed on ECs, VSMCs, cardiomyocytes and monocytes (Murphy, et al., 1991). These receptors are activated by Ang II ligand binding in a G protein-dependent manner. The activation of G protein-dependent signals activates phospholipase Cβ to increase intracellular inositol trisphosphate and diacylglycerol, leading to increase in calcium and activation of protein kinase C (PKC) isoforms.

In vascular cells, although Ang II activates multiple second messenger pathways including phospholipase D, PKC, and the mitogen activated protein kinase/erk kinase (MEK/ERK) pathways, recent attention has been drawn to the Rho family of GTPases (Griendling, et al., 1997). The Rho family is a group of 20-21 kDa GTPases including RhoA, B, C, D and E; Rac1 and 2; Cdc42Hs and TC10. The three Rho family members primarily expressed in vascular tissues in humans include RhoA, Rac1, and Cdc42Hs. Under unstimulated conditions, the Rho proteins are cytosolic, bound to GDP and guanine nucleotide dissociation inhibitors (Van Aelst and D'Souza-Schorey, 1997). In response to Ang II stimulation, the ligand binding of the G-protein-coupled AT-1 activates guanine nucleotide exchange factors (GEFs), which in turn catalyze GDP-GTP exchange and activates the Rho GTPases (Figure 1). Activated RhoA affects ROS production and controls smooth muscle cell contractility by phosphorylating myosin light chain kinase (MLCK), enhancing DNA synthesis, inducing VSMC migration, stimulating cardiovascular fibrosis (Kobayashi, et al., 2002), and inducing hemostatic and inflammatory proteins (Kobayashi, et al., 2002).

NF-κB is a ubiquitously-expressed, highly inducible transcription factor complex composed of both latent cytoplasmic and activated nuclear components. One major activation NF-κB pathway that we and others have defined is referred to as the "canonical" pathway, a pathway that controls nuclear targeting of latent cytoplasmic Rel A•NF-κB1 heterodimeric complexes. Rel A•NF-κB1 is retained in a cytoplasmic location by association with the IκBα inhibitor (Beg and Baldwin, 1993). Stimuli inducing the canonical NF-κB pathway activate the IKK kinase complex, resulting in IκBα phosphorylation at specific N-terminal serine residues, ultimately targeting it for proteosomal degradation (Ghosh and Baltimore, 1990). As a result, sequestered Rel A•NF-κB1 complexes are then released to enter the nucleus. Nuclear translocated Rel A•NF-κB1 then binds to specific regulatory sequences in cytokine and acute phase reactant promoters, activating their transcription.

Although initially the Ang II signaling pathway was thought to induce the canonical NF-κB activation pathway in VSMCs, detailed studies have shown that Ang II induces cell type-

dependent activation of NF-κB pathways (Brasier, 2010). In non-vascular cells such as hepatocytes, PKC activation leads to cleavage of the IKK inhibitory TNFAIP3/A20 molecule and degradation of IkBα through the mechanisms as in canonical signaling induced by TNFα, resulting in activation of NF-κB translocation. In VSMCs, on the other hand, the Ang II-induced pathway is quite distinct from other cell types. A novel activation pathway independent of the well-recognized canonical pathway described above was identified by us and schematically diagrammed in Figure 1. In VSMCs, inactive NF-κB isoforms could be identified in unstimulated cells, and no significant changes in NF-κB abundance was observed in response to Ang II stimulation. Of importance, we found that Ang II stimulation rapidly induces phosphorylation of RelA at serine residue 536 in its COOH-terminal transactivating domain. Interestingly, we also found that phospho-Ser-536 RelA formation was blocked by RhoA inhibition, suggesting that Ser-536 phosphorylation was mediated upstream by RhoA. In addition, RhoA inhibition also blocked Ang II-induced IL-6 expression, indicating that Ang II-inducible phospho-Ser-536 RelA was required for IL-6 activation (Cui, et al., 2006).

Our studies in Ang II-stimulated VSMCs further showed that total RelA binding did not change on the native IL-6 promoter in response to Ang II, but fractional binding of phospho-Ser-536 RelA to the IL-6 promoter was increased (Choudhary, et al., 2007). These studies showed that Ang II induces NF-κB /RelA activation in VSMCs by increasing the relative abundance of phospho-Ser-536 RelA in the nucleoplasmic pool. We also confirmed Ang II-induced enhanced phospho-Ser-536 RelA formation in rat aortas treated with Ang II, establishing relevance to vascular signaling *in vivo* (Choudhary, et al., 2007; Cui, et al., 2006).

Our group further showed that Ang II-induced RelA Ser-536 phosphorylation is mediated by NF-κB-inducing kinase (NIK), the major regulated step controlling non-canonical NF-κB signaling. NIK inhibition prevented Ang II-induced Ser-536 phosphorylation and NF-κB-dependent transcription (Choudhary, et al., 2007), indicating that it is essential for RelA activation. We also found that NIK induced the activity of the RelA transactivation domain-1 and -2 in constitutively nuclear RelA proteins and that RelA formed an inducible nuclear complex with NIK in response to Ang II stimulation. The function and mechanism of this NIK·RelA complex in Ang II-induced vascular inflammation still requires further investigation.

Taken together, this data indicate that in VSMCs, where inactive NF-κB is constitutively nuclear, Ang II induces NF-κB -dependent transcription through an alternative pathway, being largely independent of IκB proteolysis, but mediated by the small GTPases Rac/RhoA, required for NIK·RelA complex formation and inducible phospho-Ser-536 RelA phosphorylation.

3.2 Vascular inflammatory actions of Ang II-induced NF-κB signaling

Ang II-induced NF-κB activation plays a central role in the development of aneurysms through regulation of gene expression of inflammatory molecules whose function broadly in the cascade of leukocyte recruitment and monocyte chemotaxis. These targets include pro-inflammatory cytokines (e.g. interleukins, etc.), chemokines (e.g. MCP-1, GM-CSF, etc.), adhesion molecules (e.g. E-selectin, ICAM-1, VCAM-1, etc.), and ECM-degrading MMPs.

A major target of Ang II-induced NF-κB activation is to activate expression of IL-6 by adventitial fibroblasts, recruited monocytes and VSMCs. Ang II induces rapid activation of

IL-6 transcription and translation (Han, et al., 1999). The transcriptional activation of IL-6 expression is mediated by NF-κB binding to its high affinity binding site in this proximal promoter of the IL-6 gene. This site is required for Ang II inducible expression since Ang II inducible activity is completely abolished by a promoter containing a point mutation that does not bind NF-κB (Han, et al., 1999). Together, these data suggest that NF-κB transcription factor is required for inducible expression of the IL-6 by Ang II.

IL-6 is a 26 kDa glycosylated cytokine that acts in a paracrine manner to signal through two distinct mechanisms, termed the classical initiated by membrane receptor binding, and the trans-signaling pathway mediated by soluble IL-6 Rα (Hou, et al., 2008). Classical IL-6 signaling is mediated via ligand binding to the IL-6Rα receptor on the cell membrane. The IL-6 trans-signaling pathway, on the other hand, involves circulating IL-6·IL-6Rα engagement with gp130 expressed on cells, enabling activation of the IL-6 signaling pathway in cells lacking IL-6Rα. In trans-signaling, proteolysis and/or alternative splicing lead to the generation of soluble IL-6 receptors (sIL-6R), which binds IL-6. The IL-6/sIL-6R complex can stimulate cells that only express gp130 but no IL-6R.

In IL-6-initiated classical signaling, the IL-6•IL-6Rα complex causes oligomerization with the ubiquitously expressed transmembrane gp130 β-subunit, inducing gp130 homodimerization, and subsequent formation of a hexameric IL-6•IL-Rα•gp130 complex (Boulanger, et al., 2003). This induces conformational changes of gp130, that trigger trans-autophosphorylation and activation of Janus tyrosine kinase JAK1, a specific Janus kinase mediating IL-6 signaling. JAK1 in turn induces tyrosine phosphorylation and activation of STAT isoforms STAT1 and STAT3 (Figure 1). As transcription factors, they then form homo- and heterodimers with each other, translocate to the nucleus, bind specific DNA sequences and enhance transcription of target genes via interactions with co-factors and co-activators such as p300/CREB-binding protein (CBP) and Positive Transcription Elongation Factor (PTEF-b) (Hou, et al., 2008).

IL-6 plays a major role in inducing systemic responses to the presence of vascular inflammation through the hepatic acute-phase response (Brasier, et al., 2002). IL-6 has diverse actions in multiple cell types of cardiovascular importance, including ECs, monocytes, platelets, hepatocytes and adipocytes. In the vessel, IL-6 promotes Ang II-induced ROS production because IL-6 deficiency protects against Ang II-induced endothelial dysfunction (Schrader, et al., 2007).

Importantly, a major action of IL-6 is to promote monocyte-to-macrophage differentiation, thus contributing to vascular inflammation. IL-6 stimulation increases esterase and phagocytic activities and enhances surface expression of Fc receptors, macrophage-colony stimulating factor (M-CSF) receptors, and the mature macrophage marker F4/80. Additionally, IL-6 induces expression of genes important for macrophage differentiation such as c-Jun, jun B, jun D, interferon-regulatory factor 1 (IRF1), JAK3, Egr-1 (Hou, et al., 2008). Moreover, IL-6 up-regulates MCP-1 expression (Biswas, et al., 1998; Tieu, et al., 2009) by vascular monocytic cells. MCP-1/CCR2 interactions are important in monocyte recruitment in the development of aneurysms (Boring, et al., 1998; Tieu, et al., 2009). Also, cell-cell interaction of monocytes and fibroblasts in cocultures induces IL-6 expression and macrophage activation, suggesting a role of IL-6 in monocyte-to-macrophage differentiation (Chomarat, et al., 2000; Tieu, et al., 2010). Recent studies demonstrated that IL-6-induced downstream gp130-JAK/STAT signaling pathway activation is also important for differentiation of monocytes (Hou, et al., 2008).

Recent studies indicate that enhanced IL-6 signaling is associated with vascular inflammation and aneurysm formation. IL-6 is elevated systemically and locally in patients and experimental models of aortic aneurysmal disease. IL-6 deficiency decreases aortic chemokine secretion and macrophage recruitment, and prevents aortic aneurysms and dissections in Ang II-infused mice (Tieu, et al., 2009). Conversely, in wild type mice, Ang II infusion potently induces IL-6 expression in the aorta, making IL-6 the most abundantly secreted cytokine that has yet been detected. IL-6 is predominantly expressed by fibroblasts and activated macrophages in the adventitia, with lesser amounts in the media and intimal layers (Recinos, et al., 2007). IL-6 signaling pathway was locally activated in Ang II-induced aortic aneurysms (Tieu, et al., 2009),where its action promotes monocytic activation and adventitial macrophage accumulation via a chemokine MCP-1-CCR2-based mechanism (Ishibashi, et al., 2004; Tieu, et al., 2009). These activated macrophages in the vessel wall produce pro-inflammatory cytokines, chemokines, ROS and MMPs, further facilitating local inflammation and remodeling.

4. The TGF-β-Smad pathway in Ang II signaling

The second pathway initiated by Ang II involves TGF-β receptor signaling pathway important in myofibroblast transition and vascular ECM remodeling, characteristic of aneurysmal disease. This cross-talk pathway is mediated by the effect of Ang II to upregulate TGF-β. TGF-β, in turn, induces the proliferation of adventitial fibroblasts and their phenotypic transition to myofibroblasts, that further promotes vascular remodeling with their enhanced mobility and secretory abilities. Additionally, Ang II-induced ECM decomposition and remodeling lead to monocytic chemotaxis and the release of latent TGF-β. TGF-β activation induces aortic Smad signaling, which further contributes to MMP production and macrophage recruitment. Finally, in conjunction with IL-6, TGF-β also modulates Th lymphocyte subsets by promoting Th17 cell differentiation via activation of Smad and STAT signaling.

4.1 TGF-β-Smad signaling mechanisms

TGF-β activates cells by binding to one of 7 type I TGF-β receptors (TGF-βRI) or 5 type II TGF-β receptors (TGF-βRII). In the cell, TGF-β signals through both Smad-dependent (Jones, et al., 2008) and Smad-independent (p38 MAP kinase-mediated) pathways (Funaba, et al., 2006). In the classic Smad-dependent pathway, ligand binding of TGF-β dimers leads to autophosphorylation and activation of a TGF-βRII homodimer, which in turn recruits and phosphorylates a TGF-βRI homodimer (Figure 1). TGF-βRI phosphorylates the appropriate receptor-activated Smad (R-Smad) (Jones, et al., 2008). Depending on the TGF-βRI that phosphorylates and activates them, there are 5 R-Smads in 2 groups (Smads 1, 5, 8; and Smads 2, 3). Once phosphorylated, R-Smad dissociates from TGF-βRI to form a complex with Smad4 (co-Smad), that translocates to the nucleus and regulates gene expression by binding to Smad binding elements. The signaling can also be regulated by inhibitory Smads (I-Smads), which attenuate the TGF-β response (Jones, et al., 2008).

4.2 Ang II and TGF-β interaction in TAAs

Recent studies have extensively focused on the role of TGF-β in the development of different forms of aortic aneurysms. Studies on TAAs caused by Marfan or Loeys-Dietz syndromes

suggested a critical pathogenic role for increased TGF-β signaling in promoting abnormal vessel remodeling, dilatation, and aneurysmal expansion. Enhanced TGF-β signaling was implicated in aortic dilatation and aneurysm formation in Loeys-Dietz syndrome caused by mutations in the genes encoding TGF-βRI and TGF-βRII (Loeys, et al., 2005). In Marfan syndrome caused by mutations in the fibrillin-1 gene, bioavailability of TGF-β1is dysregulated (Chaudhry, et al., 2007), which contributes to the pathogenesis of TAAs (Dietz, et al., 2005; Neptune, et al., 2003). Normally, fibrillin-1 in the extracellular matrix regulates TGF-β activation by sequestering it in a complex with latent TGF-binding proteins (LTBPs). LTBPs associate matrix microfibrils with latency-associated peptide (LAP), regulating TGF-β matrix association and activation (Figure 1). Recent studies of fibrillin-1 deficient ($Fbn1^{-/-}$) mice have shown that several cardiovascular pathologies are caused by abnormal up-regulation of TGF-β signaling. Enhanced formation of activated TGF-β and phospho-Smad2, a downstream signaling protein activated by TGF-β, are detected in cardiovascular tissues. Importantly, neutralizing antibodies to TGF-β administered to $Fbn1^{-/-}$ mice reduce pathological abnormalities, suggesting a critical role of TGF-β signaling in the development and progression of TAA (Neptune, et al., 2003).

Interestingly, enhanced Ang II signaling, which is a potent inducer of cytokines and chemokines, has also been implicated in Marfan syndrome. Aortic Ang II concentration is increased in aortas of mice with fibrillin mutations (Nagashima, et al., 2001). Also, the Ang II type I receptor antagonist, Losartan, prevents aortic aneurysm formation in patients with Marfan syndrome (Habashi, et al., 2006). The ACE inhibitor perindopril reduced aortic diameter in Marfan syndrome patients and significantly reduced TGF-β levels and plasma levels of MMP-2 and MMP-3. In addition, Ang II enhances TGF-β actions by activating Smad pathway in a TGF-β-independent manner (Carvajal, et al., 2008). It also induces the production of a potent activator of TGF-β, thrombospondin-1 (Habashi, et al., 2006). These data suggest that Ang II activates TGF-β signaling, contributing to aneurysm formation. Ang II may activate TGF-β signaling by regulating its transcription and/or its activation from the latent form (Habashi, et al., 2006). Previous studies have shown that in renal disease, Ang II regulates TGF-β signaling activation by activating tumor necrosis factor TNF-α-converting enzyme (TACE), which through the cleavage of vasorin, controls TGF-β-mediated epithelial-to-mesenchymal transition (Shah and Catt, 2006).

In a mouse model with fibrillin deficiency (mgR), an inflammatory-fibroproliferative response has been described in aneurysm formation. Homozygous mgR mice die between 3 and 6 months of age of dissecting TAAs, and adventitial inflammation may accelerate pathogenesis by stimulating unregulated degradation of elastic matrix. In this mouse model, enhanced monocyte/macrophage infiltration is also pronounced at late stages of disease progression (Pereira, et al., 1999). Additionally, aortas from these mice secrete a GxxPG-containing fibrillin-1 fragment that is able to induce macrophage chemotaxis (Guo, et al., 2006b). Together, these findings suggest that inflammation is important in extracellular matrix degradation associated with fibrillin deficiency-induced TAAs. Two recent reports by the Dietz's group of Johns Hopkins University suggested that the effects of Ang II on aneurysm progression in MFS was mediated through a noncanonical TGF-beta signaling pathway involving extracellular signal-regulated kinase (ERK). It was reported that ERK activation contributed to aortic aneurysm progression in MFS (Holm, et al., 20111). Using a mouse model haplo-insufficient for Fbn-1 ($Fbn1^{C1039G/+}$), this group found that ERK1/2 was activated and that ERK inhibition, but not Smad4 deficiency, eliminated aneurysm

development in MFS. It also was reported that AT1 receptor blocker losartan abrogated aneurysm progression by inhibiting TGF-beta-mediated ERK activation through AT2 (Habashi, et al., 2011).

Increased expression and activation of TGF-β are found in Ang II-induced AAAs. Preliminary studies from our group also demonstrated that Ang II induced Smad2/3 phosphorylation in mouse aortas. However, the precise role of TGF-β activity in inflammation in aneurysms remains contradictory. One study reported that TGF-β neutralizing antibodies afforded significant protection from Ang II-induced inflammatory aneurysms after Cxcl10 targeting (King, et al., 2009), while other studies showed that TGF-β played a protective role in AAA formation and TGF-β neutralization increased Ang II-induced aneurysm and monocyte invasiveness in C57BL/6 mice (Dai, et al., 2005; Wang, et al., 2010). Controversial results indicating the protective role of TGF-β in AAA formation may be explained by the concentration-dependent bipolar actions of TGF-β. With a higher dose of Ang II infusion in aged C57BL/6 mice (Tieu, et al., 2009), our preliminary studies showed that TGF-β neutralization decreased incidence of Ang II-induced aneurysm and adventitial thickening. Emerging evidence highlights the complex and context-dependent biphasic effects of TGF-β in the pathogenesis of aneurysm (Jones, et al., 2008), that can be partially explained by interaction with different receptors when TGF-β concentration changes (Goumans, et al., 2002). It may also be important to consider the variable roles of TGF-β during the dynamic transition from predisposition to terminal events. Thus, the detailed role of TGF-β in inflammatory aneurysms may be very complex and merits further exploration.

Also, we have recently demonstrated that co-culture of monocytes with adventitial fibroblasts resulted in enhanced expression of IL-6, MCP-1 and IL-6-dependent macrophage differentiation (Tieu, et al., 2009). It is interesting to speculate that TGF-β may play a role in this process as a paracrine factor (Dietz, 2010). TGF-β is known to induce IL-6 and MCP-1 expression (Seong, et al., 2009; Zhang, et al., 2009), monocyte recruitment and differentiation and myofibroblast formation, which in turn may amplify the process through secretion of TGF-β, MMPs, or even MCP-1 (Dagouassat, et al., 2010).

4.3 Effects of TGF-β-Smad signaling activation in aneurysms

TGF-β has both angiogenic and antiangiogenic effects (Goumans, et al., 2002), diametric actions thought to be controlled by the ratio of TGF-β signals via different receptors. Also, TGF-β produces opposing effects on mast cells to inhibit maturation or induce apoptosis, depending on their developmental stage and the TGF-β concentration (Rizas, et al., 2009).

Additionally, TGF-β controls both ECM synthesis and degradation (Jones, et al., 2008). TGF-β promotes ECM degradation by inducing MMP-2 and MMP-9 production (Kim, et al., 2007). On the other hand, TGF-β stimulates both fibroblasts (Varga and Jimenez, 1986) and myofibroblasts (Mishra, et al., 2007) to synthesize collagen I, that provides load-bearing characteristics, and collagen III, that provides tensile properties to the aortic wall (van Keulen, et al., 2000). TGF-β also induces α-smooth muscle actin expression in fibroblasts and promotes myofibroblast transdifferentiation (Vaughan, et al., 2000). The expression of α-smooth muscle actin was found to be significantly increased in adventitial fibroblasts of inflammatory aortic aneurysms, suggesting inflammatory remodeling in aneurysmal disease may be partly mediated by the proliferation of adventitial myofibroblasts (Sakata, et al., 2007).

It is also noteworthy that TGF-β engages in adaptive immunity by promoting the differentiation of naïve CD4+ T helper cells (Th0) to T helper 17 (Th17) cells via activation of Smad and STAT signaling, depending on the coinstantaneous presence of IL-6 or IL-21 (Reiner, 2007). TGF-β activation is critical and required for differentiation of Th17 cells (Melton, et al., 2010). It activates signature transcription factor RORγT (retinoic-acid receptor related orphan receptor gt) and cytokine IL-17 expression (Oukka, 2008). IL-17 mediates the production of inflammatory cytokines by stromal cells, which results in recruitment of leukocytes, thus creating a link between innate and adaptive immunity. Th17 cells and IL-17A have been implicated in the pathogenesis of autoimmune and inflammatory diseases (Tesmer, et al., 2008), and only recently in cardiovascular disease (Cheng, et al., 2008). Increased circulating Th17 cells and Th17 cell infiltration into the aorta are found in Ang II-induced hypertension, and IL-17 deficiency blunts these responses and prevents hypertension (Madhur, et al., 2010). Further, Th17 cells as well as IL-17 expression in atherosclerosis are increased, and blockade of IL-17A reduced aortic macrophage infiltration, cytokine secretion, and atherosclerotic plaque formation. Interestingly, IL-6 expression is induced by IL-17 and reduced by blockade of IL-17A signaling (Smith, et al., 2010), suggesting the proinflammatory effects of IL-6 could also be mediated by Th17 cells. Importantly, IL-17 and, by extension, Th17 cells, may contribute to inflammatory processes by promoting monocyte chemotaxis, adhersion and migration. It has recently been found that IL-17 mediated monocyte migration partially through MCP-1 induction (Shahrara, et al., 2010). IL-17A treatment of aortas from atherosclerotic mice promoted aortic CXCL1 expression and monocyte adhesion (Smith, et al., 2010). These studies highlight an important proinflammatory role for T cells, especially the Th17 subset, in vascular inflammation.

5. Conclusion

Recent preclinical research has indicated that Ang II influences development and progression of aortic aneurysmal disease in two important ways. First, Ang II affects the process of vascular inflammation by promoting macrophage accumulation, activation, local ROS production and aortic aneurysms in the suprarenal and thoracic aorta, followed by dissections through the NF-κB-IL-6 signaling pathway. Second, Ang II promotes myofibroblast transition and ECM remodeling - both characteristic of aneurysmal disease - by a TGF-β1-Smad pathway. Currently, there are still many important unresolved questions. For example, 1) the role of NF-κB RelA activation in the development of aneurysms; 2) the mechanism through which Ang II activates TGF-β in the vessel wall; 3) the precise role of TGF-β signaling in Ang II-induced aortic aneurysms; 4) the role of myofibroblast formation in the development of aortic remodeling and aneurysms; 5) the role of TGF-β signaling on Th17 cell differentiation and recruitment in the development of Ang II-induced aneurysms; and 6) clinical relevance of TGF-β neutralization in aneurysmal disease. Further elucidation of these issues will identify new targets for therapeutic intervention and biomarker development.

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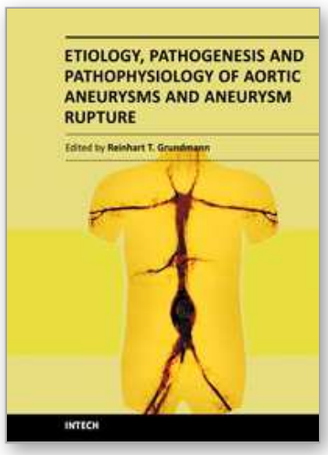

Etiology, Pathogenesis and Pathophysiology of Aortic Aneurysms and Aneurysm Rupture

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This book considers mainly etiology, pathogenesis, and pathophysiology of aortic aneurysms (AA) and aneurysm rupture and addresses anyone engaged in treatment and prevention of AA. Multiple factors are implicated in AA pathogenesis, and are outlined here in detail by a team of specialist researchers. Initial pathological events in AA involve recruitment and infiltration of leukocytes into the aortic adventitia and media, which are associated with the production of inflammatory cytokines, chemokine, and reactive oxygen species. AA development is characterized by elastin fragmentation. As the aorta dilates due to loss of elastin and attenuation of the media, the arterial wall thickens as a result of remodeling. Collagen synthesis increases during the early stages of aneurysm formation, suggesting a repair process, but resulting in a less distensible vessel. Proteases identified in excess in AA and other aortic diseases include matrix metalloproteinases (MMPs), cathepsins, chymase and others. The elucidation of these issues will identify new targets for prophylactic and therapeutic intervention.

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