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JAK-STAT and the renin-angiotensin system

The role of the JAK-STAT pathway in blood pressure and intrarenal renin-angiotensin system regulation

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Abbreviations: RAS, renin-angiotensin system; Ang, angiotensin; ACE, Ang converting enzyme; AT1R, Ang II type 1 receptor; AT2R, Ang II type 2 receptor; ROS, reactive oxygen species; PKC, protein kinase C; PI3, inositol-1,4,5-triphosphate; MAPK, mitogen-activated protein kinases; JAK, Janus kinase; IL-6, interleukin 6; IFN-γ, interferon γ; STAT, signal transducers and activators of transcription; SOCS, suppressor of cytokine signaling; TNF-α, tumor necrosis factor α; IL-1β, interleukin 1β; JGA, juxtaglomerular apparatus; APRE, acute phase response element

The renin-angiotensin system (RAS) plays important roles in blood pressure control and tissue disease. An inappropriate local angiotensin II elevation in the kidneys leads to the development of hypertension, tissue damage and chronic injury. Studies have demonstrated that the JAK-STAT pathway mediates angiotensin II-triggered gene transcription. The JAK-STAT pathway in turn, acting as an amplifying system, contributes to further intrarenal RAS activation. These observations prompt the suggestion that the JAK-STAT pathway may be of importance in elucidating the mechanisms RAS-associated tissue injury. Accordingly, this review provides a brief overview of the interactions between the JAK-STAT pathway and the RAS, specifically the RAS expressed in the kidneys.

Introduction

Hypertension is one of the most prevalent conditions affecting about 25% of adults worldwide and causing an estimated 7 million deaths every year.[1] The renin-angiotensin system (RAS) is a key player in blood pressure control and regulation of electrolyte and body fluids homeostasis.[2] According to its classical depiction, the RAS consists of an enzymatic cascade that begins with liver production of angiotensinogen, the precursor of angiotensin (Ang) peptides. Ang II, the main effector of the system, results from the successive enzymatic actions of renin and the angiotensin-converting enzyme (ACE). Ang II exerts most of its actions through the activation of Ang II type 1 and type 2 receptors (AT1R and AT2R, respectively). In the last few decades, novel components of the RAS including (pro)renin receptor, ACE2, other Ang peptides and their receptors have been discovered. These and other findings have provided us with knowledge of novel roles of the RAS in many fields that extend beyond blood pressure control.

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The observation that angiotensinogen, renin, ACE and the AT1R are expressed in multiple tissues have led to the suggestion of multiple local RAS that act as independent entities from the systemic RAS.[3-6] In particular, the finding that intrarenal Ang II content is elevated in many forms of hypertension supports a crucial role for the intrarenal RAS in the development of hypertension and RAS-associated injury.[7] Indeed, experiments in gene-targeted mice demonstrate that kidney-specific Ang II elevation induces high blood pressure,[8] the development of renal inflammation and fibrosis.[9] Further, renal RAS overactivity is associated with the development of various renal pathological processes including glomerular sclerosis, diabetic nephropathy and renal artery stenosis.[10-12] Thus, the elucidation of the regulating mechanisms of the intrarenal RAS is a potential new area for development of novel strategies for organ-specific intervention and treatment of hypertension and RAS-associated tissue injury.

The AT1R is a member of the G protein-coupled receptor family that physically associates with $G_{q/11}$, G_i, G_{12} and/or G_{13}.[13] Once Ang II binds to AT1R, various second messengers are activated via G protein-dependent pathways, resulting in the induction of vasoconstriction, generation of reactive oxygen species (ROS), changes in gene transcription and the induction of cell growth and migration.[13,14] Although the Ang II-mediated activation of second messengers is cell-specific, phospholipase C, A_2 and D have been identified as initial mediators in the G protein-dependent AT1R signaling pathways.[15] The activated phospholipases stimulate protein kinase C (PKC) activity and induce augmentation of intracellular inositol-1,4,5-triphosphate (PI_3), diacylglycerol, arachidonic acid, Ca^{2+} and ROS concentrations. These signaling factors subsequently activate Rho kinase and mitogen-activated protein kinases (MAPK) including p44/42 MAPK, p38 MAPK and c-jun N-terminal kinase.[13,16,17] Thus,

while stimulation of the AT1R signals has typically been explained as result of conventional G protein activation, G protein-independent pathways also play an important role in Ang II-induced physiological and pathophysiological actions.[18] In this context, it is worth mentioning that the number of transcripts stimulated by the G protein-independent pathways is lower than that stimulated by G protein-dependent pathways.[18]

A landmark finding in terms of Ang II signaling was the discovery that JAK and other non-receptor tyrosine kinases are elicited by Ang II in both G protein-dependent and -independent fashion as described in the next section.[19-22] After these initial reports, mounting evidence has supported the importance of JAK in the development of RAS-associated diseases. In consequence, JAK is now acknowledged as a key target for clinical and biochemical studies associated with this system. There are other indirect interactions between JAK and Ang II that are especially important in the context of hypertension. The RAS and inflammatory cytokines synergize to elevate blood pressure.[23] Ang II systemically and locally increases cytokine levels including interleukin 6 (IL-6) and interferon γ (IFN-γ), which lead to activation of the JAK-signal transducers and activators of transcription (STAT) pathway. Importantly, the activated JAK-STAT pathway is a potent stimulus to protein expression of angiotensinogen in different organs. In this way, JAK-STAT pathway contributes to the local synthesis of Ang II and the progression of hypertension and tissue injury in Ang II-dependent hypertension. As previously mentioned, recent studies have provided firm evidence that activation of intrarenal RAS leads to the progression of Ang II-dependent hypertension and renal injury. However, the importance of the Ang II-activated JAK-STAT pathway and contribution of the activated JAK-STAT pathway to RAS stimulation in the kidney are still unclear despite the fact that they have been relatively well established in vasculatures and the heart. This review provides a detailed overview of mechanisms underlying activation of the JAK-STAT pathway by Ang II and interaction between the activated JAK-STAT pathway and the RAS, specifically the RAS expressed in the kidneys.

Molecular Mechanisms Underlying JAK-STAT Pathway Activation by Ang II

In 1995, Marrero and colleagues showed that Ang II induces rapid phosphorylation of JAK2 but not JAK1 in aortic smooth muscle cells.[19] The study demonstrated that the JAK2 activation by Ang II immediately induces physical association of JAK2 with AT1R.[19] A further study by Frank and colleagues in 2002 elucidated that PI_3-Ca^{2+} and diacylglycerol-PKC axes are required for the Ang II-induced JAK2 activation in G protein-dependent fashion in vascular smooth muscle cells.[21] Although JAK2 does not have an SH2 domain to directly bind to AT1R, an adaptor protein such as Src homology phosphatase 2 (SHP2) mediates the physical interaction between AT1R and JAK2, in which C-terminus of AT1R serves as a docking site.[24,25] In this mechanism, SHP1 downregulates this Ang II-induced JAK2 activation via dephosphorylation of JAK2.[16,24] These findings suggest that JAK2 is activated by Ang II via a G protein-dependent pathway. Moreover, Doan and colleagues proposed that the G protein-independent pathway also mediates the activation of JAK-STAT pathway stimulated by Ang II.[22] In the study, activation of the JAK-STAT pathway was observed in AT1R overexpressing CHO cells, which lack Gq coupling and Ca^{2+} signaling, when the cells were treated with Ang II.[22] Therefore, the involvement of G protein-dependent and/or -independent mechanisms in Ang II-induced JAK2 activation may depend on a cell type-specific manner. This point should be addressed in further studies using other cells including renal cells.

Ang II-induced JAK2 activation triggers the stimulation of downstream signaling transducers and transcription factors, which has been well studied in vasculatures and the heart. JAK2 participates in Ang II-induced activation of Fyn, a member of the Src family of tyrosine protein kinases, in smooth muscle cells.[26] In addition, Ang II enhances a formation of c-Src-JAK2 complex suggesting that the Ang II-induced JAK2 activation contributes to elevation of other tyrosine kinase activities.[27] Ang II has been shown to activate STAT1α/β, STAT2, STAT3, STAT5a/b and STAT6 in the heart cells including myocytes.[28-33] In vascular smooth muscle cells, JAK2 activation by Ang II results in rapid STAT1 and STAT2 phosphorylation and a time-delayed STAT3 phosphorylation.[19,34] Furthermore, the AT2R, which exerts some opposing actions to AT1R, inhibits STAT1, STAT2 and STAT3 AT1R-mediated activation in vascular smooth muscle cells.[35] This inhibitory action of AT2R on STAT activation does not influence JAK activity. Ang II-induced activation of the JAK-STAT pathway has also been demonstrated in brainstem astrocytes,[36] hepatocytes,[37] renal proximal tubular cells[38] and mesangial cells.[39,40] Interestingly, it has been reported in mesangial cells that intracellular Ang II activates STAT3 in JAK2-independent pathway.[41] As a whole, these findings indicate that the JAK-STAT pathway participates in Ang II-stimulated gene transcription via diverse mechanisms in various tissues and cells including renal cells (**Fig. 1**).

Activation of the JAK-STAT pathway induces the suppressor of cytokine signaling (SOCS) expression, which acts as an internal suppressing mechanism of the JAK-STAT pathway.[42] Notably, it has been shown that Ang II increases SOCSs expression, and the augmented SOCSs limit the progression of Ang II-induced tissue injury as described in the next section.[43,44] SOCS3 expression is augmented by Ang II via JAK2 activation in hypothalamus, which in turn, blocks further activation of the pathway and consequently leads to desensitization to Ang II stimuli concerning its dypsogenic effect.[45] This Ang II-induced SOCS3 augmentation that counteracts any further JAK2 activation is also observed in ventricular myocytes.[46] In the kidneys of Ang II-infused rats, cultured mesangial cells and tubular epithelial cells, Ang II stimulates SOCS1 and SOCS3 expressions via AT1R activation in parallel with JAK2 and STAT1 activation.[10]

Physiological and Pathophysiological Roles of the JAK-STAT Pathway in RAS-Associated Diseases

Recent evidence indicates that the JAK-STAT pathway is crucial for the hypertensive response to Ang II infusion. Ang II-activated

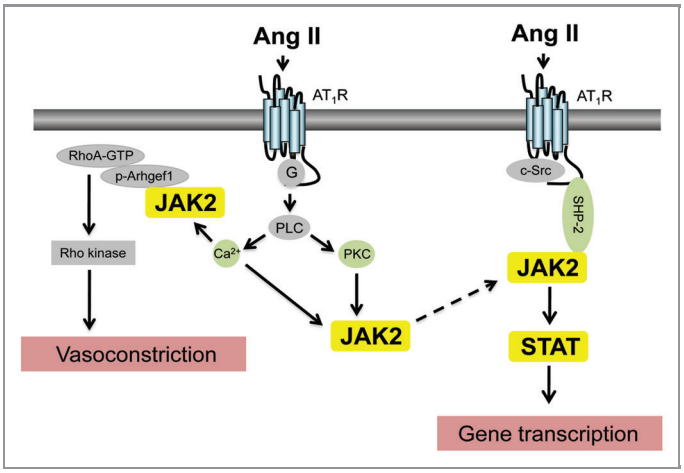

Figure 1. Scheme illustrating the activation of the JAK-STAT pathway by Ang II through AT1R. Ang II activates JAK2 via the G protein-dependent and -independent mechanisms leading to gene transcription and vasoconstriction. Various second messengers including PKC, Pyk2, Arhgef1 and SHP2 are involved in these pathways.

JAK2 induces phosphorylation of a RhoA guanine nucleotide exchange factor, Arhgef1 in vascular smooth muscle cells.[47,48] The activated Arhgef1 then stimulates the RhoA-Rho kinase axis resulting in augmentation of blood pressure, which was delineated by showing that Arhgef1 knockout mitigates Ang II-induced high blood pressure accompanied by attenuation of Rho kinase activation.[47] In line with this finding, recent studies show that JAK2 pharmacological inhibition attenuates the hypertensive response of Ang II-infused animals. Specifically, JAK2 knockdown in smooth muscle cells[49] and administration of a JAK2 inhibitor[50] prevent the development of hypertension by Ang II infusion supporting JAK2 crucial role in the development of Ang II-dependent hypertension.

In terms of renal injury, it is known that hyperglycemia, via Ang II, induces the JAK-STAT pathway in glomerular mesangial cells.[40] This in vitro finding goes in line with the in vivo observation that both AT1R blockage and JAK2 inhibition prevent the progression of proteinuria and hypertension in streptozotocin-induced diabetic nephropathy.[51] As another evidence of critical roles of the JAK-STAT pathway in the development of renal injury, administration of a JAK2 inhibitor ameliorated development of renal injury accompanied by suppression of JAK-STAT activity in renal ischemia/reperfusion model.[52] Further, SOCS1 and SOCS3 overexpression, that suppresses the intrarenal JAK-STAT pathway, abrogates the development of renal injury.[43,44] Importantly, when SOCS3 is knockdown, the unopposed Ang II induction of STAT activation and c-Fos/c-Jun expression results in more severe renal damage. Thus, these observations suggest that the JAK-STAT pathway activation by Ang II plays a crucial role and SOCS proteins serve as limiting factors in the progression of renal damage in the RAS-induced renal injury. On the basis of the evidence, new questions arise with regards to the potential contribution of the JAK-STAT pathway to the development of hypertension and renal injury. In particular, dissecting the contribution of STAT-stimulated gene transcription in such pathological settings is needed. It is also important to elucidate whether the JAK-STAT pathway participates in Ang II regulation of the renal microcirculation, glomerular pressure and sodium tubular transport.

RAS Components Regulation by the JAK-STAT Pathway

There has been substantial evidence of interactions between the RAS and pro-inflammatory factors. Ang II increases cytokine production via activation of nuclear factor-κB. In addition, Ang II increases infiltration of immune cells in tissues which in turn intensifies local cytokine production. Indeed, Ang II-infused animals and Ang II-treated tissues exhibit enhanced expression of plasma and tissue pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), IL-6 and IFN-γ. This is best characterized in Ang II-dependent hypertension.[53-58] In the following paragraphs we will address the impact of these interactions on the RAS expressed along the nephron because intrarenal RAS regulation as well as other local RAS is a key factor in the development of hypertension.[8]

Renin. Juxtaglomerular apparatus (JGA) cells in the kidney are the primary source of circulating renin. Although IL-6 is known to be a strong activator of STAT3, IL-6 decreases renin expression in As4.1 cells, an immortalized renin-producing renal tumor cell line.[59] Moreover, in the same cell line, IL-1β attenuates renin expression mediated via the p44/42 MAPK-STAT3 pathway.[60] Oncostatin M is an endotoxin-responsive pro-inflammatory cytokine that also downregulates renin expression via activation of STAT5 in As4.1 cells.[59] These results suggest that activation of the JAK-STAT pathway reduces renin expression in the kidney. However, other reports contradict this concept. Despite that IL-1β suppresses renin expression via STAT3 activation in As4.1 cells, it has been demonstrated that in vivo infusion of IL-1β increases plasma renin levels and blood pressure.[61] It is also known what while chronic Ang II infusion suppresses renin expression and secretion in JGA cells,[62] renin expression in principal cells of renal connecting tubules and collecting ducts is increased. This is an important observation, because the presence of all RAS components in the tubular fluid indicates that local intratubular Ang II contributes to the blood pressure elevation.[63] Thus, our knowledge regarding renin regulation via the JAK-STAT pathway is far from complete, but it is possible that the contradicting results may be explained on the bases of cell specificity.

Angiotensinogen. From the point of view of Ang production, renin is the rate-limiting processing enzyme in the RAS cascade.[64] However, because plasma angiotensinogen concentration is close to *K*m for the reaction with renin,[65] angiotensinogen level is also regarded as an important factor influencing RAS activity.[66,67] The major source of plasma angiotensinogen is the liver. In addition, angiotensinogen can also be synthesized in the kidneys.[68-70] Intrarenal angiotensinogen is mainly produced in renal proximal tubular cells.[71-73] The importance of this observation is supported by experiments showing that renal proximal tubule-specific overexpression of angiotensinogen in transgenic animals causes the development of hypertension and renal injury.[74] Importantly,

Ang II has been shown to promote intrarenal angiotensinogen augmentation.[73,75,76] This intrarenal Ang II-angiotensinogen amplification mechanism has been regarded as a facilitating system in the progression of hypertension and renal injury and several reports demonstrate that is an important component of the renal responses to chronic Ang II infusion.[76] This is not a direct effect; recent evidence indicates that inflammation and ROS are important mediators of such amplification. IL-6 is a well-known stimulator of systemic angiotensinogen. IL-6 stimulates the secretion of angiotensinogen protein in hepatocytes,[77-79] IL-6 increases DNA-binding activity of the St-domain, a STAT binding motif, in the rat *angiotensinogen* promoter.[32] Furthermore, Ang II also stimulates DNA-binding activity of the St-domain accompanied by activation of STAT3 and STAT6 in the cells.[32] In the kidney of IL-6 knockout mice, Ang II-induced activation of a STAT3 activity is substantially reduced.[23,80] This animals also develop a milder hypertension and less renal injury in Ang II-induced salt-sensitive hypertension.[81] In vitro, IL-6 via STAT3 contributes to angiotensinogen upregulation in human renal proximal tubular cells.[82,83] This observation is consistent with the identification of an acute phase response element (APRE) in the promoter region of the rat *angiotensinogen* gene.[84] Similar observations have been made in other species. Three STATs binding sites have been identified within three APREs located in human *angiotensinogen* promoter region.[85] Specifically, STAT3 binds to APRE1 and APRE3 and STAT1 binds to a region between -271 and -279 in human *angiotensinogen* promoter.[78,85,86] As a whole, these findings suggest that IL-6 and STAT3 augment angiotensinogen expression leading to further Ang II production in plasma and in local tissues.

There is also an association between IFN-γ and angiotensinogen. In hepatocytes, angiotensinogen expression is augmented by IFN-γ via activation of STAT1 but not STAT3.[86] In renal proximal tubular cells, IFN-γ decreased angiotensinogen expression at early phase of treatment (6 or 12 h), with strong STAT1 phosphorylation induction and STAT3 suppression. In contrast, longer exposure (24 or 48 h) increased angiotensinogen expression accompanied by increased STAT3 activity. Thus, angiotensinogen overexpression mirrors STAT3 activation. In addition, SOCS1 levels were negatively correlated with angiotensinogen expression during the IFN-γ treatment. Based on these observations, the authors concluded that IFN-γ biphasically regulates angiotensinogen expression in renal proximal tubular cells via STAT3 activity modulated by STAT1-SOCS1 axis. The time-dependent biphasic activations of STAT1 and STAT3 found in the angiotensinogen regulation have also been observed in Ang II-treated cardiomyocytes.[31] Furthermore, the opposing effects of STAT1 and STAT3 in the angiotensinogen regulation are supported by findings in other physiological phenomena such as cell apoptosis.[87,88] These observations suggest that STAT1 and STAT3 act as counteracting mechanisms on angiotensinogen regulation, and the balance of these transcription factors may be of importance for intrarenal RAS activity regulation, the development of hypertension and the establishment of renal injury (**Fig. 2**). Moreover, because participation of SOCSs in regulation of systemic and local RAS activity has not been established using in vivo settings, further animal and clinical studies may provide us with novel evidence that RAS is regulated by SOCSs.

TNF-α increases angiotensinogen expression in several tissues and reduces its expression in others.[89] In renal proximal tubular cells, TNF-α suppresses angiotensinogen expression through a p50/p50 homodimer formation.[90] In the setting of inflammation and intrarenal RAS activation, TNF-α may act as a counteracting mechanism to reduce intrarenal angiotensinogen production. In addition, TNF-α decreases renin expression in adrenal cells and juxtaglomerular cells. In a broader context, in the initial phase of the hypertension, TNF-α may serve as an important trigger for TNF-α-associated renal injury and NF-κB-associated activation of cytokines such as IL-6 and IFN-γ that lead to more angiotensinogen production. However, in later phases TNF-α would itself reduce angiotensinogen expression. Nonetheless, the establishment of temporal profiles of intrarenal cytokines during Ang II-dependent hypertension will be required to confirm this assumption.

Other RAS components. Regulatory roles of the JAK-STAT pathway in AT1R, ACE, ACE2 and (pro)renin receptor have not been studied. This is due to the lack of STAT binding sites in 5' flanking region of these RAS components. The expression of AT2R is upregulated by IFN-γ via STAT1 activation in fibroblasts.[91] This augmentation of AT2R expression is mediated by STAT1-induced stimulation of interferon regulatory factor 1. Hence, at least in fibroblast, the IFN-γ-STAT1 axis indirectly increases AT2R expression. This observation has not been replicated in the kidneys.

Conclusion and Perspective

Recent experimental evidence demonstrates that the JAK-STAT pathway plays an important role in the development of Ang II-dependent hypertension. However, these findings have also revealed the complexity of this mechanism. So far, it is clear that an inappropriate elevation of Ang II stimulates production of

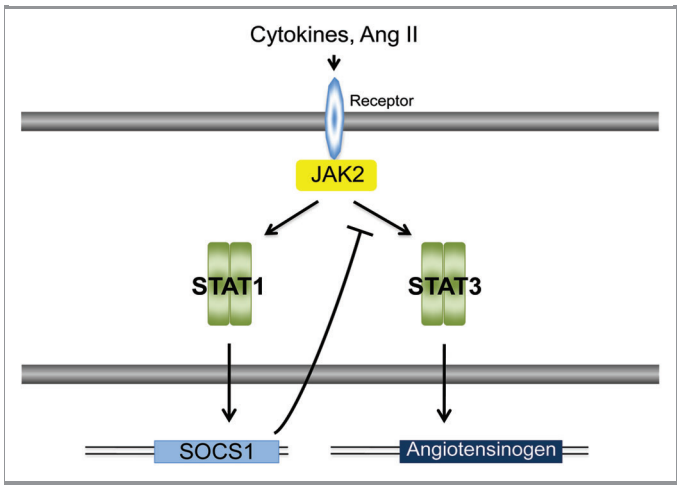

Figure 2. Schematic summary of the proposed angiotensinogen regulation by cytokines and Ang II in renal proximal tubular cells. These stimuli activate both STAT1 and STAT3; however, the activation of STAT1 induces SOCS1 augmentation, which suppresses STAT3 activation and angiotensinogen.

pro-inflammatory factors. Acting in concert, Ang II and cytokines activate the JAK-STAT pathway resulting in intrarenal RAS activation, the progression of hypertension and the establishment of renal injury. Considerable insight has been gain into the regulation of proximal tubule angiotensinogen by the JAK-STAT pathway. These observations may lead to new strategies to treat hypertension and diseases associated intrarenal RAS activation.

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