Angiotensin II Signal Transduction Through Small GTP-Binding Proteins

Mechanism and Significance in Vascular Smooth Muscle Cells

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Small GTP-binding proteins (G proteins) are monomeric G proteins with a low molecular weight of 20 to 40 kDa. A small G protein acts as a molecular switch that cycles between inactive GDP-bound and active GTP-bound forms. Thus far, >100 small G proteins have been identified in eukaryotes from yeast to humans. The small G proteins in this superfamily are structurally classified into ≥5 families: the Ras, Rho, Rab, Sar/Arf, and Ran families. In general, the Ras family mainly regulates gene expression, the Rho family regulates both cytoskeletal reorganization and gene expression, the Rab and Sar/Arf families regulate intracellular vesicle trafficking, and the Ran family regulates nucleocytoplasmic transport and microtubule organization during the cell cycle.

Multiple downstream effectors of small G proteins, some of them being protein kinases, have been identified. Ras mediates its effect on cell proliferation mainly by activation of its effector Raf to initiate the mitogen-activated protein kinase (MAPK/extracellular signal regulated kinase [ERK]) cascade. In addition, a variety of Ras effectors have been identified, such as a phosphatidylinositol 3-kinase (PI3K). The Rho family, such as Rho, Rac, and Cdc42, also has various effectors. One of the Rho effectors, Rho-kinase (ROCK), plays an important role in actin cytoskeleton reorganization and smooth muscle contraction. In addition, reduced nicotinamide adenine dinucleotide oxidase is known as a Rac effector and p70 S6 kinase (p70S6K) as a Cdc42 effector. Recently, small G proteins have been noted as novel therapeutic targets in cardiovascular medicine. In this regard, Ras and Rho G proteins are the most investigated molecules in the cardiovascular system. It has been shown that Ras is involved in growth of cultured vascular smooth muscle cells (VSMCs). Also, various vasoactive factors stimulate RhoA and ROCK, leading to enhanced vasoconstriction and migration of VSMCs.

Angiotensin II (Ang II), the major bioactive peptide of the renin–angiotensin system, is strongly implicated in various cardiovascular diseases, such as hypertension, atherosclerosis, restenosis after angioplasty, and heart failure. However, there still remains a huge void in the literature regarding the mechanistic insights by which Ang II contributes to each of these cardiovascular diseases. There are ≥2 transmembrane G protein–coupled receptors (GPCRs) known to mediate Ang II function, namely, the type 1 and type 2 (AT₁ and AT₂) receptors. The AT₁ receptor has been shown to mediate most of the physiological actions of Ang II, and this subtype is predominantly expressed in cardiovascular cells, such as VSMCs. Through this receptor, Ang II activates a number of cytoplasmic signaling pathways. AT₁ interacts with multiple heterotrimeric G proteins, including G_{q11}, G_{i3}, G_{12}, and G_{13}, and produces second messengers, such as inositol triphosphate, diacylglycerol, and reactive oxygen species (ROS). It also activates various intracellular tyrosine and serine/threonine kinases. Importantly, recent accumulating evidence highlighted the significance of these small G proteins as essential molecular switches that trigger many of the signal transduction and functions of Ang II. In this review, we describe detailed mechanisms of signal transduction pathways of Ang II involving small G proteins in VSMCs together with their functional significances in mediating vascular remodeling.

Activation of Ras by Ang II

The activation of Ras is induced by a number of peptide growth factors. Prototypically, the growth factor receptor on activation recruits a Ras guanine nucleotide exchange factor (GEF), Sos, via adaptor proteins Shc and Grb2. The best-characterized effector of Ras is Raf, a MAPK kinase kinase, in the MAPK/ERK cascade. Thus, Ras proteins are critical in stimulating cell growth and division. Moreover, recent accumulating evidence suggests that Ras is important in mediating cardiovascular remodeling, such as VSMC proliferation.

Upstream Mechanism of Ras Activation in VSMCs

In cultured VSMCs, Ang II stimulates the formation of Ras-GTP and Ras-Raf association. AT₁ was proposed to
activate Ras through Gq/phospholipase C–mediated intracellular Ca\textsuperscript{2+} elevation.\textsuperscript{10} However, Okuda et al\textsuperscript{11} suggested a role for Gi, because pertussis toxin partially blocked Ras activation by Ang II in VSMCs. A tyrosine kinase has been implicated in Ras activation by Ang II in VSMCs as well.\textsuperscript{10} For instance, c-Src may be involved, because c-Src antibody inhibited Ras activation by Ang II in VSMCs.\textsuperscript{9} However, among the various candidate kinases, epidermal growth factor receptor (EGFR) might be the most important.

It is now well recognized that Ang II activates EGFR, a receptor tyrosine kinase, although AT\textsubscript{1} receptor does not directly interact with EGFR, an event referred to as “trans-activation.” The EGFR transactivation induced by Ang II is required for ERK activation, a kinase downstream of Ras in VSMCs.\textsuperscript{12,13} EGFR transactivation induced by Ang II is mediated by a metalloprotease belonging to a disintegrin and metalloprotease (ADAM) family, such as ADAM17.\textsuperscript{14,15} ADAM cleaves a proform of EGFR ligand thereby producing a mature ligand to activate EGFR. In addition, Ca\textsuperscript{2+}, ROS, c-Src, c-Abl, and protein kinase C (PKC) have been implicated in EGFR transactivation by Ang II.\textsuperscript{8,12,16,17} EGFR transactivated by Ang II forms a complex with adaptor proteins Shc/Grb2, thereby recruiting Sos, a RasGEF in VSMCs.\textsuperscript{12} Also, Adachi et al\textsuperscript{18} demonstrated an additional Ras activation pathway by Ang II involving ROS. ROS stimulate S-glutathiolation of Cys\textsuperscript{118} on Ras to enhance its activity in VSMCs.

**Downstream Signal of Ras Activation in VSMCs**

The ERK pathway is a major downstream of Ras activation induced by Ang II (Table I, available online at http://hyper.ahajournals.org). Ang II induces the translocation of Raf to the membrane and the association between Ras and Raf-1 in VSMCs.\textsuperscript{19} Although a Ras-independent mechanism of ERK activation by Ang II has been proposed,\textsuperscript{20} we have confirmed that Ras is indispensable for ERK activation by Ang II reported in VSMCs by using adenovirus encoding a dominant-negative (dn) Ras mutant.\textsuperscript{13} Interestingly, Ras activation induced by Ang II leads to Akt activation,\textsuperscript{13,18} possibly by a Ras effector, PI3K, in VSMCs. Akt has been shown to be activated by ROS and required for VSMC protein synthesis by Ang II.\textsuperscript{21} p70S6K phosphorylates the ribosomal protein S6 and thereby participates in protein synthesis. Ang II–initiated activation of p70S6K requires Ras activation as well.\textsuperscript{13} A newly identified substrate for ERK, MAPK signaling–integrating kinase-1, is activated by Ang II through a Ras-dependent pathway in VSMCs. MAPK signaling–integrating kinase-1, in turn, phosphorylates eukaryotic initiation factor 4E (eIF4E).\textsuperscript{22} eIF4E is critical for translation initiation, the rate-limiting step for protein synthesis. Also, eIF4E is released from eIF4E binding protein/PHAS-I on phosphorylation of eIF4E binding protein/PHAS-I regulated through ERK and Akt activated by Ang II in VSMCs.\textsuperscript{23} In this regard, ERK activation induced by Ang II has long been implicated in vascular remodeling.\textsuperscript{3} Indeed, the blocking of ERK or EGFR results in inhibition of protein synthesis, DNA synthesis, and migration of VSMCs induced by Ang II.\textsuperscript{5,24} The current view of Ras activation, its upstream mechanism, and downstream significance by Ang II are illustrated in Figure 1.

**Activation of Rho by Ang II**

The Rho family consists of RhoA, RhoB, and RhoC. RhoA is a prototype for most studies. In general, Rho is activated by GPCR agonists of which the receptors are coupled to G\textsubscript{12/13}. The activated G\textsubscript{12/13} subunit of G 12/13 binds to the regulator of G protein signaling domain of a RhoGEF, such as p115RhoGEF, thereby stimulating the GEF activity.\textsuperscript{25,26} Rho has been shown to participate in the formation of focal adhesion and actin stress fibers, and it also mediates the redistribution of cytoskeletal components.\textsuperscript{1} Recently, Rho has been implicated in cardiovascular remodeling associated with hypertension and other cardiovascular diseases.\textsuperscript{4,25,26}

**Upstream Mechanism of Rho Activation in VSMCs**

In VSMCs, several GPCR agonists, including Ang II, stimulate RhoA activity.\textsuperscript{27} Ang II increases GTP-bound RhoA,\textsuperscript{27} as well as RhoA in particulate fraction.\textsuperscript{28} However, relatively little is known about the upstream mechanism by which Ang II activates RhoA through the AT\textsubscript{1} receptor (Table I). Because the AT\textsubscript{1} receptor is not only coupled to G\textsubscript{q} but also to G\textsubscript{12/13} in VSMCs,\textsuperscript{6,8} RhoGEFs sensitive to G\textsubscript{12/13}, such as p115RhoGEF, LARG, or PDZ-RhoGEF, may mediate Rho activation.\textsuperscript{25,26} Alternatively, tyrosine phosphorylation of a RhoGEF, Vav, may be involved in RhoA activation by Ang II.\textsuperscript{29} In HEK293 cells, β-arrestin 1, as well as G\textsubscript{q}, are required...
to activate RhoA by AT1.30 Interestingly, inhibition of Rho activity by AT2 receptor has been demonstrated in VSMCs.31

We have recently investigated possible upstream mechanisms of Rho activation by Ang II in VSMCs. By using a ROCK substrate, myosin-binding subunit of myosin phosphatase (MYPT) phosphorylation at Thr696 as a marker of Rho activation, we found that Ang II–induced Rho/ROCK pathway activation require a tyrosine kinase, PYK2, and its upstream PKC-δ activation in VSMCs. PYK2 may signal to Rho through phosphorylation and activation of RhoGEF. In fact, PYK2 was coimmunoprecipitated with PDZ-RhoGEF on Ang II stimulation. PDZ-RhoGEF was tyrosine phosphorylated as well.32 Thus, Ang II activates Rho in VSMCs through PYK2 and PDZ-RhoGEF (Figure 2).

**Downstream Signal and Function of Rho in VSMCs**

**In Vitro Evidence**

Functional analyses have revealed that Rho-dependent pathways are involved in contraction, migration, and proliferation of VSMCs.25 ROCK phosphorylates and thereby inhibits myosin light chain phosphatase activity, leading to the Ca2+ sensitization and vascular smooth muscle contraction.25,26 Thus, a ROCK inhibitor, Y-27632, may induce Ca2+ desensitization by inhibiting MYPT phosphorylation at Thr696 induced by Ang II.27 In this regard, Y-27632 attenuated Ang II–induced arterial contraction.33

Rho and ROCK may play an important role in Ang II–induced vascular hypertrophy and migration. ROCK inhibition has been shown to inhibit VSMC hypertrophy in vitro.28 The hypertrophy through Rho/ROCK is independent of ERK1/2 or p70S6K.28 Recently, c-Jun N-terminal kinase (JNK) has been shown to be indispensable for VSMC migration stimulated by Ang II.34 In this regard, dnRho and Y-27632 blocked Ang II–induced JNK activation.32 DnRho, Y27632 and dnJNK inhibited migration of VSMCs induced by Ang II as well. These data suggest that activation of Rho/ROCK is specifically required for Ang II–induced JNK activation and subsequent VSMC migration.32

Interestingly, dnRho was reported to suppress AT1 receptor mRNA expression in VSMCs, indicating that Rho contributes to enhance Ang II activity through AT1 induction.35 In addition, Y-27632 inhibits both Ang II–induced monocyte chemoattractant protein-1 and plasminogen activator inhibitor type-1 expression in VSMCs, suggesting that ROCK has a critical role in the progression of vascular inflammation in atherosclerosis.36,37

**In Vivo Evidence**

Recent studies have demonstrated the participation of Rho signaling pathways in several cardiovascular pathologies including hypertension, atherosclerosis, and restenosis.4,25,26 Ang II is known to upregulate ROCK mRNA expression in human coronary VSMCs.38 Thus, the enhanced ROCK expression together with the aforementioned AT1 receptor induction may further contribute to transducing the Rho-dependent pathogenic function of Ang II.

As expected by the role of Ca2+ sensitization, ROCK is reported to participate in Ang II–induced vasoconstriction through the AT1 receptor.39 In fact, Ang II infusion increases the activity of RhoA/ROCK, increases medial thickness, and promotes perivascular fibrosis in rat coronary arteries. Although oral treatment of fasudil, which is metabolized to a specific ROCK inhibitor, did not prevent Ang II–induced hypertension, these vascular alterations were ameliorated by its treatment.40 Recently, it has been demonstrated that activation of the Rho/ROCK pathway by ROS is required for the development of spontaneous tone in aorta from Ang II–infused rats.41 Taken together, these finding strongly indicate the critical role of Rho and ROCK in mediating vascular remodeling in hypertension associated with enhanced Ang II activity. In addition, fasudil inhibited the incidence of abdominal aortic aneurysm induced by Ang II infusion in apolipoprotein E–deficient mice. Fasudil attenuated aortic caspase-3 activity, DNA fragmentation, as well as matrix metalloprotease activity, indicating that aortic wall apoptosis and proteolysis was suppressed by ROCK inhibition.42 Also, perivascular fibrosis induced by Ang II was decreased in ROCK1 haploinsufficient mice.43

Other than Ang II/AT1 signal transduction, studies using ROCK inhibitors have further revealed that the Rho/ROCK cascade is critically involved in development of hypertension and the associated end organ damages. The ROCK activity seems to be enhanced in various rat models of hypertension.27 Upregulation of ROCK precedes the development of hypertension in SHR, and a ROCK inhibitor, fasudil, prevented the vascular lesion formation.44 Y-27632 inhibited spontaneous arterial tone in DOCA-salt rat aorta.45 Long-term treatment of fasudil also ameliorated renal damage in malignant hypertensive rats.46 Interestingly, treatment of fasudil in Zucker obese rats not only reduced blood pressure but corrected insulin resistance and endothelial dysfunction, suggesting the in-
volvement of Rho/ROCK in the metabolic syndrome.\(^47\) Moreover, the link between Rho/ROCK and hypertension has been confirmed in human studies. Fasudil significantly decreased forearm vascular resistance in hypertensive patients.\(^48\) ROCK polymorphism influencing blood pressure and systemic vascular resistance has been reported recently.\(^49\) Taken together these findings strongly suggest a potential therapeutic role for Rho/ROCK inhibition in hypertension.

**Activation of Rac by Ang II**

At the cellular level, Rac controls membrane protrusion and, thus, contributes to membrane ruffling and cell spreading, the processes involved in cell adhesion and motility. In addition, it is an important component of the reduced nicotinamide-adenine dinucleotide phosphate oxidase complex that produces ROS.\(^1,2\) Many investigations have placed Rac as a key mediator in cardiovascular physiology, including vascular reactivity and blood pressure regulation, as well as in pathological processes, such as cardiac and vascular hypertrophy, leukocyte migration, and platelet activation.\(^2\) In this section, we will describe the importance of Rac-mediated signaling induced by Ang II in VSMCs.

**Upstream Mechanism of Rac Activation in VSMCs**

Activation of Rac1 by Ang II in VSMCs has been shown by using p21-activated kinase (PAK)-protein binding domain binding assay.\(^16,50\) Rac1 is rapidly (within a minute) activated,\(^50\) and the activation is sustained \(\approx30\) minutes.\(^16\) Investigations attempting to define the upstream signaling components required for Rac activation by Ang II seem to be complicated possibly by the redundancy of the pathways (Table I). Seshiah et al\(^16\) demonstrated that Ang II–induced Rac1 activation was markedly blocked by a Src inhibitor, PP1, an EGFR kinase inhibitor, AG1478, and PI3K inhibitors. They demonstrated that AT\(_1\) receptor activation leads to a PKC inhibitor–sensitive ROS production, resulting in transactivation of the EGFR by a ROS-sensitive Src kinase. EGFR subsequently activates PI3K with resultant activation of Rac1. Thus, the Rac1 activation leads to phase 2 of sustained ROS production. In contrast, Schmitz et al\(^50\) demonstrated that Ang II–induced Rac1 activation was inhibited by a tyrosine kinase inhibitor, genistein, but not by PP1.\(^50\) This group also showed that Ang II activation of PAK1, a known Rac1 effector in VSMC, was insensitive to AG1478.

Interestingly, Ang II promotes trafficking of Rac1 into caveolae/lipid rafts associated with Rac1 binding to caveolin-1, suggesting that caveolin-like microdomains are involved in Rac1 activation by the AT\(_1\) receptor in VSMCs.\(^51\) In fact, caveolin-1 small interfering RNA significantly inhibits Rac activation, H\(_2\)O\(_2\) production, downstream ROS-dependent EGFR and Akt activation, and vascular hypertrophy.\(^52\) In addition, requirement of PI3K\(_\gamma\) for Rac activation and subsequent ROS production by Ang II has been demonstrated recently in murine vessels.\(^53\) However, further investigation may be needed to define the exact upstream components of Rac1 together with the identity of Rac GEF(s) responsible for Ang II activation in VSMCs.

**Downstream Signals and Functions of Rac in VSMCs**

As stated above, Rac1 is implicated in ROS production and subsequent ROS-sensitive kinase activation, as well as PAK activation by Ang II in VSMCs. Indeed, Ang II-induced ROS production was markedly attenuated by dnRac mutant overexpression in VSMCs.\(^16\) Pelletier et al\(^54\) showed that Ang II–induced Rac activation and subsequent generation of ROS is necessary for activating JAK/signal transducers and activators of transcription-dependent transcription in VSMCs. Also, we have demonstrated recently that dnRac significantly blocked PAK1 activation in VSMCs,\(^55\) and that dnJNK blocked Ang II–induced VSMC migration.\(^32\) In addition, ROS produced on Rac activation by Ang II could contribute to VSMC hypertrophy through Akt and p38MAPK.\(^31,56\) Thus, Rac1 may be involved in gene transcription, hypertrophy, and migration via the PAK/JNK pathway and ROS-sensitive protein kinase pathways in VSMCs (Figure 3).

**Activation of Other Small G Proteins by Ang II**

Cdc42 Activation by Ang II

Cdc42 regulates formation of filopodia in the reorganization of actin skeleton. Filopodia, fingerlike protrusions, are found primarily in motile cells and involved in directional migration of the cells.\(^1\) Ang II activates Cdc42 and induces filopodia formation in the intestinal cells through the AT\(_1\) receptors. Cdc42 then activates PAK and p38MAPK, which, in turn, causes transcription of the COX-2 gene.\(^57\) However, physiological roles of Cdc42 in Ang II–induced cardiovascular responses remain unknown.

Rap1 Activation by Ang II

Rap belongs to the Ras family of small G proteins. In pulmonary vein endothelial cells, Ang II was proposed to
activate PYK2 through Ca²⁺-dependent activation of g- 
anglygenarated Rap1.⁵⁸ Interestingly, Ang II activates Rap1 
through the AT₁ receptor leading to ERK activation in 
NG108-15 cells.⁵⁹ Based on these findings, it is possible to 
speculate that the Rap small G protein is one of the common 
effectors of the AT₁ and AT₂. However, the physiological 
significance of the activation of the Rap pathway by Ang II 
remains to be studied.

Ang II Pathway Through Rab Family
Rab small G protein family is one of the critical regulators of 
endocytic transport.¹ It has been shown that the AT₁a receptor 
carboxyl-terminal tail is associated with Rab5, and Ang II 
increases this association. Also, the AT₁ receptor activates 
Rab5 in COS7 cells. Rab5 binding to AT₁ protected the 
receptor from lysosomal degradation, whereas Rab7 and 
Rab11 overexpression increased the AT₁ receptor targeting to 
sylosomes and recycling to the plasma membrane suggesting 
that the Rab family regulate the trafficking of the receptor.⁶⁰ 
Furthermore, the AT₁ receptor is colocalized with Rab4 and 
Rab11 in addition to Rab5 in HEK293 cells.⁶¹ Interestingly, 
small interfering RNA against Rab1 decreased inositol phos- 
phate accumulation and ERK activation induced by Ang II 
in HEK293T cells.⁶² In cardiac myocytes, dnRab1 attenuated 
ERK activation and subsequent hypertropy induced by Ang 
II.⁶³ Thus, Rab G protein regulates AT₁ receptor transport to 
the cell surface and may further regulate AT₁ receptor signal 
transduction.

Ang II Pathway Through Arf Family
Phospholipase D (PLD) is a downstream effector of Arf 
proteins.¹ Many of the external agents that promote VSMC 
proliferation activate PLD. Ang II activated PLD, and this 
activation was blocked by the inhibitors of Arf proteins in 
A10 VSMCs.⁶⁴ Importantly, PLD activation has been shown to 
be required for Ang II-induced ROS production in VSMCs.⁶⁵ 
Thus, it is interesting to further define the role of Arf and its 
downstream effectors that possibly mediate VSMC remodeling induced by Ang II.

Perspectives
The importance of small G proteins in Ang II signaling is 
becoming clearer. Through activation of small G proteins, 
such as Ras, Rho and Rac, Ang II induces VSMC remodeling, 
including proliferation, migration, and hypertrophy. It is 
expected that small G proteins will be the target of therapy for 
cardiovascular diseases, such as hypertension, atheroscle- 
oris, and cardiac hypertrophy, where enhanced Ang II actions 
have been implicated. However, evidence of detailed mech- 
nisms of small G protein activation and their significance in 
vivo are still insufficiently characterized and need further 
investigation.

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