Angiotensin II type-1 receptor regulates RhoA and Rho-kinase/ROCK activation via multiple mechanisms. Focus on “Angiotensin II induces RhoA activation through SHP2-dependent dephosphorylation of the RhoGAP p190A in vascular smooth muscle cells”

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Angiotensin II, a crucial regulator of the cardiovascular system, is not only required for physiological functions, such as maintenance of blood pressure and plasma sodium concentration but also is involved in pathophysiological conditions such as hypertension and atherosclerosis (26). Angiotensin II exerts its effect by mainly binding to the angiotensin II type-1 (AT1) receptor. As its seven transmembrane structure suggests, the AT1 receptor couples to several heterotrimeric G proteins including Gq. In addition, the activation of the AT1 receptor leads to increased reactive oxygen species; activation of various protein tyrosine and serine/threonine kinases; and of small G proteins such as Ras, Rac, and RhoA, which may require heterotrimeric G protein-dependent and -independent mechanisms (6, 7, 11, 19).

Among the downstream components involved in angiotensin II signal transduction, RhoA and its effector Rho-kinase/ROCK have attracted particular interest as novel therapeutic targets (18). RhoA, a member of the Rho family of small GTP binding proteins, is abundantly expressed in vascular smooth muscle (12) and is well known to participate in arterial smooth muscle contraction via Ca2+ sensitization (4). Moreover, the RhoA/ROCK pathway has been implicated in a wide variety of disease conditions in the cardiovascular system, including hypertension, atherosclerosis, arterial restenosis, myocardial ischemia, and cardiac hypertrophy/fibrosis in animal models as well as in humans (9, 15, 23).

The Rho protein functions as a molecular switch that cycles between the active GTP-bound form and inactive GDP-bound form. GDP/GTP exchange is facilitated by guanine nucleotide exchange factors (GEFs) that catalyze the exchange of GDP to GTP and by GTPase activating proteins (GAPs) that accelerate the hydrolysis of the GTP to GDP (21). In this regard, many G protein-coupled receptors (GPCRs) are believed to increase RhoA activity via the G12/13 family of G proteins through activation of their effectors, the RGS domain-containing RhoGEFs (p115 RhoGEF, PDZ-RhoGEF, and LARG are the known members) (20, 29). The presence of this “basic” mechanism of RhoA/ROCK regulation by a GPCR has been shown in the AT1 receptor activation of vascular smooth muscle cells (VSMCs) and cardiac myocytes in culture (14, 24) and in vivo for arterial contraction stimulated by angiotensin II (28). However, studies published recently (1, 27) also suggest that the regulation of RhoA/ROCK by the AT1 receptor is not limited to the G12/13/RGS domain-containing RhoGEF pathway.

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Fig. 1. Regulatory mechanism of the Rho/ROCK pathway activated by angiotensin II (ANG II) in vascular smooth muscle cells (VSMCs, see text). EGFR, epidermal growth factor receptor; ADAM17, a disintegrin and metalloprotease 17; NO, nitric oxide; MLCK, myosin light chain kinase; PKG, protein kinase G; ERK, extracellular signal-regulatory kinase; ROCK, Rho-kinase.
Bregéon et al. (2) identify SHP2, a tyrosine phosphatase, as a novel regulator of a RhoGAP, p190A in cultured VSMCs. In the resting state, SHP2 functions as a scaffolding protein that recruits a tyrosine kinase c-Abl to p190A and enables c-Abl to activate p190A by phosphorylating the Tyr1105 residue, thus maintaining a low basal activity of RhoA in VSMCs. Upon activation by angiotensin II, SHP2 dephosphorylates and inactivates the RhoGAP p190A (Fig. 1). This novel pathway is supported by experiments that involve small interfering RNA (siRNA)-mediated knockdown of the SHP-2 function and by expression of SHP2 mutants. It is interesting to note that it has been reported that Ser1150 phosphorylation of p190A and its subsequent inactivation by Rho-kinase/ROCK is required for sustained RhoA activation in VSMCs by another GPCR, endothelin type-A receptor (13). An inactive phosphorylation of p190A can also be induced by GSK3β (8). Taken together, these results suggest that not only is activation of an RGS domain-containing RhoGFP critical, but inactivation of the RhoGAP p190A is also a crucial aspect of the Rho-ROCK cascade activation by GPCRs. In addition, recent reports and the current study demonstrate that there are other regulatory mechanisms of the Rho/ROCK pathway that is activated by angiotensin II in VSMCs. The nitric oxide protein kinase G cascade (24) and the angiotensin type-2 (AT2) receptor signal transduction pathway (5) appear to be able to inhibit the RhoA/ROCK pathway at the level of G12/13 and RhoA, respectively. It is also interesting to note that all of these different types of regulation of RhoA/ROCK seem to be independent of the ERK1/2 cascade, which is activated exclusively through Gq, and of transactivation of the epidermal growth factor receptor in VSMCs (3, 16, 17, 24).

Although SHP2 appears to be a central player in this novel RhoGAP regulation by angiotensin II, the upstream signal transduction of the AT1 receptor linked to SHP2 has not been fully elucidated. Limited information implicates SHP2 association with the AT1 receptor (10) and an involvement of reactive oxygen species in SHP2 activation by angiotensin II (25). SHP2 has been shown to be required for VSMC proliferation induced by angiotensin II, whereas the effect of SHP2 has been explained through its participation in the JAK/STAT pathway (10). Moreover, investigation of the role of SHP2 in vascular physiology and pathophysiology in vivo has been very limited except for its preferential expression in neointima upon vascular injury (22). The roles of p190A RhoGAP in vascular biology are as-yet not clear. Therefore, further evaluation of SHP2 and p190A, especially in vivo, in relation to the vascular Rho-ROCK pathway, seem likely to help further understanding of signal transduction cross-talk and perhaps also lead to better treatments for cardiovascular diseases.

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REFERENCES

8050, 2005.


18441, 2005.


