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Review

The molecular functions of SHP2 in angiotensin II mediated signaling pathways

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ABSTRACT

The Src homology 2-containing phosphotyrosine phosphatase (SHP2) is a ubiquitously expressed tyrosine phosphatase with two N-terminal SH2 domains, one tyrosine phosphatase domain and two tyrosine phosphorylation sites at the C-terminus. This unique structural organization suggests that SHP2 plays a regulatory role in various Angiotensin II-induced signaling pathways that contribute to normal vascular function and subsequent disease progression. This review discusses the various Ang II signaling pathways involved in maintenance of hemodynamics and SHP2's involvement in that balance, suggesting that SHP2 may serve as an important therapeutic target for the intervention of signaling pathways associated with cardiovascular diseases.

KEYWORDS: SHP2, angiotensin II signaling, tyrosine phosphatase, cardiovascular diseases

INTRODUCTION

Angiotensin II is a biologically active peptide that acts both as a hemodynamic regulator and as a growth factor. Growth factor properties of Angiotensin II (Ang II) have been demonstrated in a variety of cell types including mesangial cells, endothelial cells and vascular smooth muscle cells (VSMCs). The mitogenic effects of Ang II in VSMCs have been linked to pathophysiological conditions such as hypertension, atherosclerosis and restenosis [1, 2]. The cellular responses to Ang II are directed by specific G-protein-coupled receptors. There are two major classes of Ang II receptors that have been pharmacologically defined and are now commonly referred to as the AT_1 and AT_2 receptor subtypes. The use of non-peptidic inhibitors for each of these receptor subtypes has demonstrated that the hemodynamic manifestations of Ang II are mediated by the AT_1 receptor [2]. The AT_1 receptor contains the structural features of the seven transmembrane G-protein-coupled receptor superfamily and is structurally different from cytokine or growth factor receptors.

The biological effects of Ang II are due to unique signaling cascades downstream of the receptor-ligand interaction. Like cytokine receptors, the AT_1 receptor lacks intrinsic tyrosine kinase activity. However, the ligand binding to the receptor activates several receptor and non-receptor tyrosine kinases. A substantial amount of AT_1 receptor signaling occurs via the activation of several non-receptor tyrosine kinases including Jak2, Tyk2, Src, Fyn, Pyk2, and focal adhesion kinases [3]. By phosphorylating multiple downstream substrates, these protein tyrosine kinases trigger signaling along several distinct signaling pathways, cause the activation of transcription factors, and ultimately facilitate increased expression of early response genes. The net result is cell proliferation, or mitogenesis.

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Tyrosine phosphorylation represents a critical control mechanism for Ang II-induced mitogenesis in several cell types. Protein tyrosine phosphorylation is regulated by the opposing activities of protein tyrosine kinases and protein tyrosine phosphatases. Among the tyrosine phosphatases activated by Ang II are SHP-1 [4], SHP2 [5], PRL-3 [6] and MAP kinase phosphatase-1 [7]. Several laboratories have reported that Ang II activates SHP-1 solely through the AT_2 receptor, whereas the Ang II-dependent activation of SHP2 is specific for the AT_1 receptor [8, 9]; which is associated with the hemodynamic effects of Ang II.

Several recent reports have indicated a clinical relevance of SHP2 to some human diseases such as Noonan Syndrome [10], neutropenia [11], diabetes [12], gastric ulcer [13], and carcinoma [14, 15], further emphasizing the importance of studies on the physiological functions of SHP2 and their impact on cardiovascular disease. The present review will focus on the tyrosine phosphatase SHP2 in Ang II-mediated tyrosine kinase signaling pathways.

Role of tyrosine phosphatase SHP2 in angiotensin II-mediated signaling

JAK-STAT and MAP kinase pathways, known to be activated by Ang II, are important for the expression of early response genes, cell growth, cell differentiation, and cell death [1]. Several investigators have shown that, similar to cytokine receptors, activation of the AT_1 receptor by Ang II promotes 1) STAT tyrosine phosphorylation, 2) STAT nuclear translocation, 3) STAT-DNA binding activity, and 4) STAT-dependent transcriptional activation. Electroporation experiments with neutralizing anti-Src homology phosphatase-1 (SHP-1) and anti-SHP2 antibodies suggest that the tyrosine phosphatases, SHP-1 and SHP2, have opposite roles in Ang II-induced JAK2 phosphorylation. SHP-1 appears to be responsible for JAK2 dephosphorylation and termination of the Ang II-induced JAK/STAT cascade. In contrast, SHP2 appears to have an essential role in JAK2 phosphorylation and initiation of the Ang II-induced JAK/STAT cascade leading to cell proliferation [4]. Consistent with these results, Godney *et al*. [16] demonstrated that the N-terminal SH2 domain of SHP2 interacts with the Tyr^{201} of Jak2. In this scenario, SHP2's role is that of an adaptor protein to bring Jak2 to the AT_1 receptor. The functional consequence of this interaction is to activate the JAK-STAT pathway. These results suggest that activation of the JAK-STAT pathway is positively regulated by SHP2.

Previously, we reported that Ang II induces SHP2 tyrosine phosphorylation and the formation of a SHP2-containing complex with IRS-1 [5]. Subsequently, our work established that SHP2 regulates Ang II-induced activation of the MAP kinase pathway by inactivating c-Src in VSMCs [17]. There are two working models by which SHP2 may regulate MAP kinase activity. One mechanism involves a SHP2 C-terminal phosphotyrosine residue that serves as a docking site for Grb2, which then facilitates complex formation with mSos [18]. This potentially important post-translational modification in SHP2 may thus allow Ras and ultimately the MAP kinase pathways to become activated. The second mechanism, instead, relies on SHP2 phosphatase activity for MAP kinase regulation. Because our studies indicated that Ang II failed to induce any detectable complex formation between SHP2 and Grb2, SHP2 functioning as an adaptor protein in upstream signaling that leads to activation of MAP kinase is excluded. Our results strongly suggest that SHP2 regulates Ang II-induced MAP kinase pathway by deactivating c-Src activity instead. This is supported by the observation that wild type (wt) SHP2 promotes a significant reduction in the extent of phosphorylation of the positive regulatory Tyr^{418} within c-Src. The consequence of the dephosphorylation of this critical tyrosine residue within the c-Src catalytic domain appears to be the inhibition of Ang II-induced ERK activation in VSMCs. Therefore, we hypothesize that the biological effects of SHP2 in Ang II-stimulated cells depend on its phosphatase activity [17]. Our hypothesis is further supported by Tang *et al*'s observation that SHP2-mediated dephosphorylation of the calcium-sensitive tyrosine kinase Pyk2 correlates with the inactivation of MAP kinase and c-jun (NH2) terminal kinase signaling pathways in endothelial cells [19].

SHP2 is a ubiquitously expressed protein, and a critical component of several signaling pathways.

It has two SH2 domains, a protein tyrosine phosphatase domain, and two tyrosine phosphorylation sites, Tyr^{542} and Tyr^{582}, at the carboxy terminus [20, 21]. In addition, Mitra *et al*. [22] reported that Tyr^{63} and Tyr^{279}, which are sites of germline mutation in LEOPARD Syndrome and Noonan Syndrome, are phosphorylated by Abl kinase. Crystal structural analyses revealed that the amino terminal SH2 domain of SHP2 is inserted into the catalytic cleft of the SHP2 phosphatase domain, inferring that the enzyme maintains an autoinhibitory normal state [21]. However, when the SH2 domain is occupied by bound ligand, the phosphatase activity of SHP2 is stimulated [23]. Thus, the molecular structure of SHP2 suggests that signaling proteins might interact with SHP2 to accomplish signaling tasks within the cell. This hypothesis is supported by the observation that several receptors, including PDGF, EGF and growth hormone, interact with SHP2 [20]. Their interactions are mediated through the phosphotyrosine residue of the receptor and the SH2 domains of SHP2. The net effect is either positive or negative, depending on the specific type of signaling network. For example, SHP2 acts as a negative regulator in both PDGF receptor mediated signaling [24], and in Toll-like receptor signaling [25]. In FGF and insulin signaling pathways, SHP2 acts as a positive regulator in the activation of MAP kinase pathway and in mitogenic signaling, respectively [26, 27]. SHP2 has also been shown to play both a negative and positive role in the Jak/STAT pathway when activated by different cytokine receptors [28, 29]. Similar to growth factor receptors, Ang II binding to the AT_1 receptor leads to SHP2 interacting with IRS-1 [5], Jak-2 [16] and PLCβ1 [30] in response to Ang II, although the precise interactive site has not yet been elucidated. These SHP2 interactions have been shown to be essential for AT_1 receptor signaling.

The classical signaling pathway for the AT_1 receptor is to couple and activate heterotrimeric G-proteins. The ultimate biological consequence(s) of G-protein-coupling, in the context of SHP2 activation, however, has yet to be determined. SHP2 is tyrosine-phosphorylated at Tyr^{542} and Tyr^{580}, in response to growth factor receptors, with concomitant increases in phosphatase activity [23]. Araki *et al*. [31] demonstrated that phosphotyrosine residues are required for the activation of the MAP kinase pathway, in response to PDGF and NGF, but not EGF. These results suggest that tyrosine residue(s) might be responsible for Ang II-dependent SHP2 catalytic activity. It is important to address whether different phosphotyrosine residues of SHP2 mediate different Ang II signaling pathways.

In recent years, the critical role of SHP2 in the regulation of various genes has been reported. These include interferon α/β-induced gene transcription [32], the β-casein promoter [33], the vasoactive intestinal peptide gene [34], *c-fos* gene [35] and p53 target gene expression [36]. Guillemot *et al*. [37] have demonstrated the possible involvement of SHP2, downstream of the AT_1 receptor, in regulating cyclin D1 promoter activity to control the cell cycle progression. The results of this study suggest that SHP2-mediated regulation of genes might contribute to normal vascular functions and disease progression.

Tabet *et al.* [38], using the VSMCs cell preparation from spontaneously hypertensive rats (SHR), showed that Ang II induced activation of various signaling pathways in VSMCs derived from SHR was due to the oxidation/inactivation and blunted phosphorylation of SHP2. These data suggest the importance of reactive oxygen species in SHP2 signaling by Ang II. Interestingly, a new function of SHP2 has been reported by Langdon *et al*. [39]. Their study demonstrated that SHP2 activity is associated with heart development and differentiation. Further evidence in the role of SHP2 in heart development has been highlighted by showing that SHP2 functions along the FGF/MAPK pathway to maintain survival of proliferating populations of cardiac progenitor cells.

Hypertrophic cardiomyopathy (HCM) is typically characterized by marked left ventricular hypertrophy and interstitial fibrosis. HCM is a genetic disorder and frequently occurs as a result of mutations in SHP2 in pediatric patients with Noonan Syndrome [40]. Cardiomyocyte specific deletion of SHP2 in mice causes dilated cardiomyopathy, leading to heart failure and

premature mortality [41]. SHP2-deficient primary cardiomyocytes are defective in MAPK pathway activation in response to a variety of agonists and pressure overload. Recently, Marin *et al.* [42] demonstrated that SHP2 tyrosine phosphatase activity controls the size of cardiomyocytes by down regulating FAK/Src and mTOR signaling pathways. Chang *et al.* [43] reported that up regulation of several tyrosine phosphatases, including SHP2, is associated with neointima formation following rat carotid artery injury, thus suggesting a crucial role of SHP2 in restenosis and atherogenesis. As reported by Lee *et al.*, Ang II is a key proapoptic factor in fibrotic tissue diseases [44]: Ang II-induced apoptosis requires SHP2 to regulate the activation of the anti-apoptic protein, Bcl-xl, in primary lung endothelial cells. Together, these observations suggest that SHP2 might be an important molecule that integrates signal along numerous signaling pathways, contributing to Ang II-mediated cardiovascular diseases, including cardiac hypertrophy, endothelial dysfunction, vascular remodeling/atherosclerosis, and nephropathy.

Role of SHP2 in angiotensin II-induced cytoskeleton organization

Vascular remodeling, or the alteration of vessel structure, is one of the pathophysiological conditions promoted by Ang II. Rearrangements of the VSMCs cytoskeleton and focal adhesions are potential key events that might contribute to vascular remodeling. Protein tyrosine phosphorylation and dephosphorylation were shown to play critical roles in the remodeling of vessel structures [45]. It is well established that Ang II induces actin reorganization in a variety of cell types including VSMCs, cardiac fibroblasts, and cardiomyocytes [46-48]. The actin network is regulated by a variety of actin binding proteins, tyrosine kinases, and tyrosine phosphatases. The Src family of tyrosine kinases, focal adhesion kinase (FAK), and the Abl kinase are major tyrosine kinases which regulate the cytoskeletal organization. Many of the signals resulting from Ang II binding to the AT_1 receptor are centered on the focal adhesion tyrosine kinase (FAK) and its interactions with Src family tyrosine kinases. The Src-FAK complexes mediate the phosphorylation of $p130^{cas}$ and paxillin. The recruitment Src-FAK complexes of other signaling molecules such as phosphotyrosine-dependent Crk binding to $p130^{cas}$ leads to the formation of a multi-phosphoprotein signaling complex localized in focal adhesions [49, 50]. There are several reports showing that FAK is a direct substrate of SHP2. For example, dephosphorylation of FAK was postulated to be the cause of migration and spreading defects in the SHP2 ($^{-/-}$) cells [51]. However, the molecular mechanism regulating the FAK phosphorylation and the role of SHP2 have never been addressed in Ang II signaling. Studies from our laboratory suggest that SHP2 is involved in the turnover of focal adhesions by mediating dephosphorylation of several focal adhesion proteins including $p130^{Cas}$, paxillin, and tensin which, in turn, influence the cytoskeletal architecture [52].

The Rho small G-protein family members regulate various forms of focal adhesion complexes and actin filament dynamics. There are at least 20 Rho family GTP proteins in the human genome, of which RhoA, Rac1, and Cdc42 have been the most widely studied members. RhoA regulates the formation of actin stress fibers. Rac1 induces broad plasma membrane extensions known as lamellipodia. Cdc42 induces the extension of finger like extensions called filopodia [53]. Like all small G-proteins, RhoA cycles between a GDP-bound inactive form and a GTP-bound active state. This protein is primarily regulated by two proteins: guanine nucleotide exchange factors (GEF), which catalyze the exchange of GDP for GTP, and GTP-ase activating protein (GAP), which hydrolyzes GTP to GDP. p190Rho-GAP possesses GTP-ase activity for Rho family members, with a particular preference for Rho A.

The involvement of Rho in the formation of actin stress fibers has been described in VSMCs and cardiomyocytes [46, 54]. Considerable evidence suggests that Ang II stimulates reorganization of actin cytoskeleton in which the Rho family of GTP proteins plays important roles. The most compelling evidence regarding the role of SHP2 in Ang II-induced actin dynamics stems from the observation that the expression of a dominant negative SHP2 markedly increases the formation of actin stress fibers in VSMCs [52], thus implying a down regulatory role for SHP2. Vav2,

a Rho GEF, functions as an effector for Rho A, and is tyrosine phosphorylated in response to Ang II. The tyrosine phosphorylation of Vav2 is associated with an increased guanine nucleotide exchange activity, leading to increased fiber formation. Our results suggest that SHP2 may negatively regulate the activity of RhoA through suppression of the GDP/GTP exchange activity of RhoA-specific Vav2. Thus, SHP2 tyrosine phosphatase activity appears critical in linking the AT_1 receptor with a capacity to remodel the actin cytoskeleton by virtue of its ability to modulate communication along a RhoA/Vav2 signaling axis. Our data provide a novel mechanism by which SHP2 regulates Ang II-induced actin cytoskeletal organization in VSMCs. Consistent with our observations, several studies have reported that cells lacking functional SHP2 have greater actin stress fiber density and exhibit increased numbers of focal adhesion complexes [55, 56], providing strong evidence that SHP2 plays a pivotal role in cytoskeletal remodeling processes.

Ang II has previously been reported to induce Rho-GAP activity [57]. Rho-GAP activity might therefore contribute to the SHP2- induced cytoskeleton disruption by antagonizing the stress fiber assembly function of Rho proteins via decreasing GTP availability. Of great interest, a study by Bregeon *et al.* [58] demonstrated that SHP2 regulates p190 Rho-GAP phosphorylation in VSMCs. SHP-2 maintains a low basal activity of Rho A by recruiting tyrosine kinase c-Abl and enables c-Abl to activate Rho-GAP by phosphorylating the Tyr^{1105} residue in resting state. In response to Ang II, SHP2 dephosphorylates Rho-GAP, thereby activating Rho A. The functional consequence of activation of Rho A has not been investigated in the context of actin cytoskeletal reorganization. Nor has the role of Rho-GAP in SHP2-induced cytoskeletal disruption been evaluated. However, the accumulated data provide evidence that, in most circumstances, SHP2 negatively modulates the RhoA, even though it can also function as a positive regulator, depending upon its binding partner and interactions with downstream signaling networks [55, 56, 59]. Furthermore, SHP2 dephosphorylates several other focal adhesion proteins in VSMCs, which may be another mechanism Ang II utilizes to promote stress fiber formation in VSMCs that over express wild type SHP2 [52]. Since all of the reported studies used overexpression approaches, the role of SHP2 needs to be readdressed in an *in vivo* animal model.

CONCLUSION

Angiotensin II tissue-specific effects include vasoconstriction and blood pressure regulation, inflammation, endothelial dysfunction, atherosclerosis, neointima formation, hypertension and congestive heart failure. Experimental evidence suggests that a myriad of signaling pathways exist in which Ang II influences cardiovascular physiology and disease progression. SHP2 can act as a positive and/or negative regulator in these processes. In this review article, we summarized the various mechanisms proposed to date as illustrations of SHP2's positive and negative role on the Ang II-mediated signaling pathways.

Based on previously published results from several laboratories, we propose a model to illustrate how SHP2 regulates the Ang II-induced signaling pathways (Figure 1). According to this model, Ang II binds to the AT_1 receptor and activates a specific tyrosine kinase that induces phosphorylation of SHP2, thereby increasing phosphatase activity. Alternatively, G-protein coupling to the AT_1 receptor may be responsible for the tyrosine phosphatase activity of SHP2. SHP2 regulates the Ang II-mediated signaling pathways in a cell-specific and pathway- specific manner. SHP2, by virtue of its interactions with JAK2, positively regulates the Jak-STAT pathway to activate early response genes (pathway A). The activation of early response genes lead to the development of cardiovascular diseases such as vasoconstriction and elevated blood pressure. In contrast, SHP2 phosphatase activity appears to be responsible for the failure of stress fiber formation along a RhoA/Vav2 signaling axis, thereby regulating vascular remodeling (pathway B). Several studies suggest that SHP2 activates the MAPK pathway by an unknown mechanism in cardiomyocytes and might be responsible for the development of cardiac hypertrophy (pathway C). While pathway C is cardiomyocyte specific, pathways A and B are specific for VSMCs.

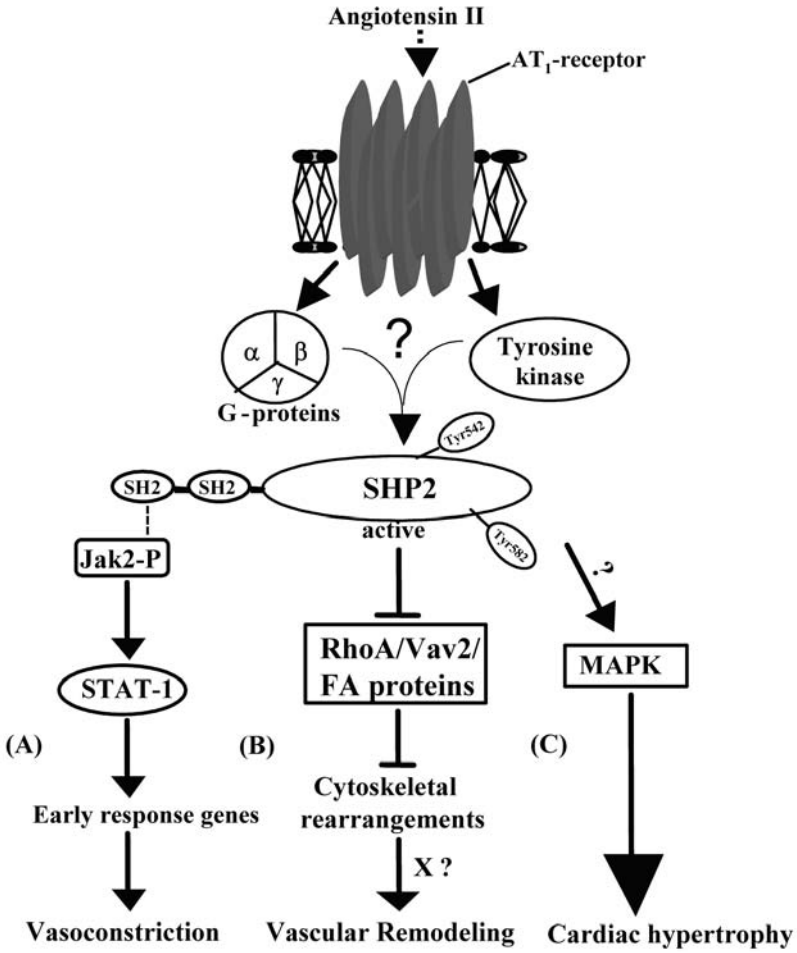

Figure 1. Schematic illustration of the potential signaling pathways controlled by tyrosine phosphatase SHP2. **(A)**: Ang II mediated phosphorylation of Jak2 in VSMCs leads to interaction with SHP2 via its N-terminus SH2 domain and modulates activation of Jak-STAT pathway. The result is activation of early response genes leading to blood vessel smooth muscle contraction. **(B)**: Activation of SHP2 phosphatase activity in VSMCs results in inactivation of RhoA/Vav2 activity and dephosphorylation of several focal adhesion (FA) proteins which in turn leads to failure of cytoskeletal rearrangements. **(C)**: SHP2 activates the MAPK pathway in cardiomyocytes through unknown mechanisms. The result is development of cardiac hypertrophy.

SHP2 is an important molecule that controls amplitude and duration of signaling along various pathways that might be associated with deregulated migration, differentiation and proliferation of cells which make up the vessel wall. Although, SHP2 has been shown to regulate VSMCs growth, neointima formation, atherogenesis, and the activity of tyrosine kinases associated with vascular remodeling, investigation of the role of SHP2 in vascular physiology and pathology *in vivo* has been very limited. The identification of the physiological substrate(s) of SHP2 using over expression studies, substrate trapping and gene targeting approaches, will bring future challenges to confer a definite role of SHP2 in cardiovascular biology. As such, these experimental approaches will provide new potential therapeutic targets for cardiovascular diseases.

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