Letter to the Editor

In their recently published article in Hypertension, Chiasson and colleagues,1 in contrast to Ruan et al.,2 demonstrated that binding of Pin1 to endothelial NO synthase (eNOS) facilitates the dephosphorylation and activation of the enzyme. Thus, the activated eNOS increases NO production, leading to endothelium-dependent dilatation and blood pressure regulation.1 Although there seems an implication that Pin1 directly results in serine-116 dephosphorylation of eNOS, they clearly showed that Pin1 deficiency negatively affects eNOS-regulated endothelial functions. However, in an editorial commentary for this study published in the same issue,3 the authors consider Pin1 as a phosphatase. In addition, they accentuate this mistake clearly in their Figure. Furthermore, they state that the findings of this study are consistent with the previous study done by Ruan et al.,2 in contrast to the emphasis of Chiasson et al.1 in their article.

Pin1 is the only peptidyl-prolyl cis/trans-isomerase that specifically recognizes phosphorylated proline-directed serine/threonine peptide sequences.4 In other words, Pin1 can only bind to the phosphorylated proline-directed serine/threonine motifs of target proteins and just catalyzes the prolyl isomerization, leading a conformational change in the protein. If Pin1 catalyzes a cis- to trans-isomer change at the proline bond, it makes this target protein ideal substrate for protein phosphatases PP2A and PP2B.4,5 Altogether, Pin1 does not dephosphorylate, it just catalyzes the prolyl isomerization, leading a conformational change in the protein. If Pin1 catalyzes a cis- to trans-isomer change at the proline bond, it makes this target protein ideal substrate for protein phosphatases PP2A and PP2B.4,5 Hence, in contrast to the emphasis of Chiasson et al.1 in their article.

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In addition to these conflicting issues, Chiasson et al.1 have not demonstrated how Pin1 facilitates dephosphorylation of eNOS on serine-116, which causes NO increase and improves endothelial function. Here, I propose a working model to clarify the uncertainty. eNOS is a Ca2+/calmodulin-dependent enzyme, the activity of which is influenced by the phosphorylation at ≥3 sites in the enzyme: serine-1177, threonine-495, and serine-116. Akt and the AMP-activated protein kinase are the important regulators of eNOS serine-1177. The phosphorylation of threonine-495 is modulated by the agonist bradykinin, and phosphorylation of eNOS at serine-116 is subjected to hemodynamic shear stress.5 Vascular endothelial growth factor (VEGF), one of the key activators of eNOS in the vessel wall, promotes the activation of enzyme through the dephosphorylation of eNOS at serine-116 by inducing the activation of calcineurin, a Ca2+/calmodulin-dependent protein phosphatase (PP2B).6 On the other hand, Pin1 induces transcriptional upregulation of vascular endothelial growth factor.6 Taken together, Pin1-mediated increased activation of VEGF may result in dephosphorylation and activation of eNOS at serine-116. Thus, whereas Pin1 deficiency negatively influences endothelial function as demonstrated by Chiasson et al.,1 deficiency of this important isomerase could also lead to the attenuation of VEGF-mediated angiogenesis (Figure).

Disclosures

None.

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References


Figure. Pin1 upregulates the expression of vascular endothelial growth factor (VEGF) that, in turn, activates the phosphatase PP2B. Increased VEGF influence in the vessel wall and dephosphorylation of endothelial NO synthase (eNOS) at serine-116 (S116) by PP2B activates eNOS toward the protection of endothelial homeostasis.
Pin1 as a Protector of Vascular Endothelial Homeostasis
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