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Pin1 in cardiovascular dysfunction: A potential double-edge role

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ABSTRACT

Backgrounds: Our lab focused on the structural and functional properties of Pin1, which is the only known *cis–trans* isomerase regulating pSer/pThr–Pro motifs in proteins and facilitates various signaling pathways. We are lucky enough to read the article, contributed by Costantino et al. in your esteemed journal, on the role of Pin1 in diabetes-induced vascular dysfunction. Pin1 regulates the production of nitric oxide (NO), which is a key physiological stimulator of blood vessels and promotes vascular relaxation responses significantly. However, the regulation of cardiovascular diseases by Pin1 is somewhat controversial.

Methods and results: We compared the recent studies that support the down-regulation, as well as up-regulation, of NO production by Pin1 and tried to explore the underlying molecular mechanisms. We especially compared the different regulations of endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) by Pin1, which is potentially the major reason leading to the controversial role of Pin1. Interestingly, the regulation of both eNOS and iNOS by Pin1 involves a double-edge effect, positively and negatively, contributing to paradoxical Pin1 functions in different animal models and cell lines. The extremely complex Pin1-regulated signaling networks might further exacerbate distinct cellular responses *in vivo* and influence NO production.

Conclusions: Pin1 plays a dual role, both positive and negative, in regulating NO production and in mediating the pathogenesis of cardiovascular diseases. Pin1 functions may vary a lot under different circumstances. Future investigations should focus on eNOS as well as iNOS in order to increase authenticity and accuracy of results.

1. Introduction

Diabetes and its complications are serious diseases causing a heavy social burden, and cardiovascular disorder is a main risk of death in patients suffering from diabetes [1–3]. Hyperglycemia induces cardiovascular complications and hinders the treatment of cardiovascular diseases [4,5]. Some key regulatory molecules have been discovered in the related studies until now, and emerging evidence gradually reveals that Pin1 plays an essential role in mediating the impact of diabetes on cardiovascular complications [6–8].

We are lucky enough to read the recent article contributed by Costantino et al. in your esteemed journal, which describes the regulation of diabetes-induced vascular dysfunction by Pin1 [8]. Costantino et al. demonstrated that high-concentration glucose attenuated the release of nitric oxide (NO) in human aortic endothelial cells (HAECs) contributing to vascular dysfunction, and juglone, a traditional inhibitor of Pin1, enhanced the production of NO and prevented glucose-induced impairment of NO bioactivity [8]. The result mainly indicates that Pin1 blocks the production of NO, however, some other studies evidence that the role of Pin1 in NO production and in cardiovascular diseases such as hypertension and atherosclerosis is somewhat controversial. Therefore, we wish to make a brief summary of the existing contradictory results and try to explain why these paradoxical phenomena occur.

2. Evidence to support down-regulation of eNOS and NO by Pin1

The impact of Pin1 on vascular function is mainly mediated by nitric oxide (NO), which promotes relaxation of blood vessels and guarantees normal physiological functions of blood vessels [9–11]. Impaired NO bioavailability potentially results in vascular dysfunction, cardiovascular diseases, and other complications [6,8,12,13]. Costantino et al. concluded that Pin1 prevented NO bioavailability by inhibiting the activity of endothelial nitric oxide synthase (eNOS), which is an important enzyme responsible for the synthesis of NO *in vivo* [8,14]. This conclusion is consistent with and is mainly based on the previous studies described by Ruan et al. and Paneni et al. [6,8,15]. Ruan et al. revealed that Pin1 interacted with pSer116 of eNOS in bovine aortic endothelial cells

Abbreviations: NO, nitric oxide; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; BAEC, bovine aortic endothelial cell; HAEC, human aortic endothelial cell; MPC, mouse primary cardiomyocyte; RAEC, rat aortic endothelial cell; VEGF, vascular endothelial growth factor; PDLC, human periodontal ligament cell; PCHC, primary cultured human chondrocyte; MAEC, murine aortic endothelial cell; Aβ, amyloid-β.

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(BAECs) and interacted with phosphomimetic Ser116Asp eNOS in COS-7 cells; Pin1 overexpression in BAECs suppressed cellular release of NO but juglone increased NO production, indicating that Pin1 negatively regulates the activity of eNOS [15]. Paneni et al. investigated the role of Pin1 in diabetes-induced vascular dysfunction and revealed that Pin1 promoted the interaction between Ser116-phosphorylated eNOS and its suppressor caveolin-1 in human aortic endothelial cells (HAECs) thus reducing NO availability; Pin1 gene-silencing in HAECs or Pin1 knockout in mice restored NO release and prevented vascular dysfunction, and blood Pin1 was enhanced in diabetic patients compared to healthy controls [6]. Alcohol consumption is a cause of left ventricular dysfunction, and recently Wang et al. found that alcohol stimulated the expression and activity of Pin1 in mouse primary cardiomyocytes (MPCs) and that Pin1 repressed the expression of eNOS and the production of NO in alcohol-treated MPCs [16]. Taken together, these results demonstrate that Pin1 inhibits the activity of eNOS and consequently hinders the synthesis of NO.

3. Evidence to support up-regulation of eNOS and NO by Pin1

eNOS is inactivated when Ser116 is phosphorylated, and Chiasson et al. illustrated that Pin1 bound with Ser116-phosphorylated eNOS and promoted dephosphorylation of eNOS in rat aortic endothelial cells (RAECs) and mouse aortas consequently enhancing eNOS activity and NO production; Pin1 knockdown by RNAi or Pin1 inhibition by juglone prevented pSer116-dephosphorylation of eNOS *via* the vascular endothelial growth factor (VEGF)-dependent pathway, resulting in hyperphosphorylation of Ser116, decreased eNOS activity, reduced NO production, and attenuated relaxation responses of blood vessels [17–19]. Consistently, Pin1-knockout mice and juglone-treated mice exhibited increased Ser116-phosphorylation of eNOS, vascular endothelial dysfunction, and hypertension [17,18]. Erol et al. have argued that the Pin1 serves as a protector of vascular endothelial homeostasis and presented an explanation of how Pin1 facilitates Ser116-dephosphorylation of eNOS: Pin1 up-regulates VEGF expression, VEGF activates the phosphatase PP2B, and PP2B dephosphorylates pSer116 of eNOS [14,19,20]. We also gave a comprehensive demonstration of the protective role and the potential prognostic value of Pin1 in cardiovascular diseases especially hypertension [14,21]. Besides, Cho et al. recently described that Pin1 inhibition by juglone or Pin1 knockdown by siRNA markedly attenuated NO production in human periodontal ligament cells (PDLCs) [22]. Sum up, these data support that Pin1 promotes Ser116-dephosphorylation of eNOS, enhances activity of eNOS, and maintains vascular function *via* increasing NO production.

4. Potential mechanisms leading to the seemingly contradictory dual role of Pin1

These contradictions above may have plagued a lot of scientists in the related research fields. Therefore, it is extremely necessary to evaluate the reasons why Pin1 has the seemingly contradictory functions in the pathogenesis of vascular diseases that are correlated with metabolic dysfunction of NO. Several possible reasons are listed below for the reader's reference, and we briefly illustrated the potential underlying molecular mechanisms in Fig. 1.

4.1. The regulation of eNOS by Pin1 may involve a double-edge effect

Phosphorylation/dephosphorylation is one of the most important regulatory mechanisms in cellular signaling transduction, and until now, Pin1 is the only known *cis–trans* peptidyl-prolyl isomerase specifically facilitating the dephosphorylation of phosphorylated serine/threonine linked to proline (pSer/pThr–Pro) in various proteins and thus promoting kinds of vital signaling pathways [23,24]. Phosphorylation of Ser116 (equivalent site in human is Ser114) is an inhibitory modification of eNOS activity, and dephosphorylation of eNOS at pSer116 enhances its activity. Chiasson et al. revealed that Pin1 promotes Ser116-dephosphorylation of eNOS and thus enhances eNOS activity and NO production [17,20,25]. However, Paneni et al. asserted that Pin1 regulates pSer116 of eNOS and promotes its interaction with caveolin-1 leading to blunted eNOS activity and reduced NO release [6,26]. These results seem contradictory but they may be both right, potentially reflecting that Pin1 has a double-edge role in regulating the activity of eNOS.

In order to assist this speculation, we would like to mention another similar example, the regulation of p53 by Pin1. When Pin1 activity is higher, it tends to stabilize p53 and enhances p53 activity; however, when Pin1 activity is lower, it tends to facilitates p53 ubiquitin-modification and promotes p53 degradation [27–29]. This further confirms the complexity of the cellular signaling networks regulated by Pin1. Hence, it is very hard to predict the relationship between Pin1 levels and eNOS activity or NO production, especially when there are some other factors that may disturb the prediction.

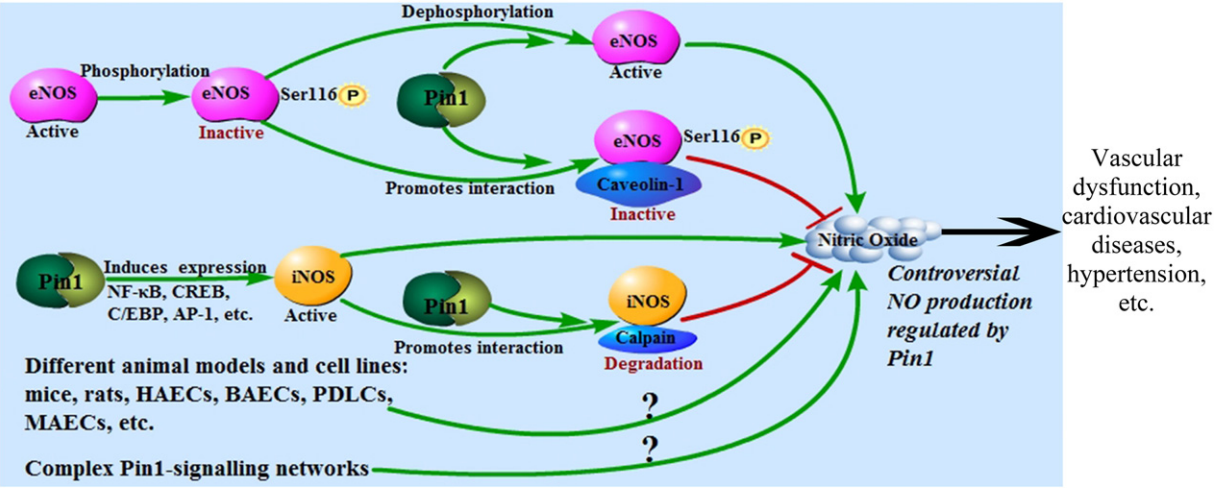

Fig 1. The multiple functions of Pin1 in the production of NO *in vivo*. Pin1 plays a double-edge role in regulating the activity of endothelial nitric oxide synthase (eNOS) as well as inducible nitric oxide synthase (iNOS). Different animal models and cell lines might have distinct NO metabolic pathways and regulatory mechanisms. Extremely complex Pin1-signaling networks, which regulate many phosphorylases, dephosphorylases, and transcriptional factors, may further exacerbate variations in NO production. All of these effects potentially contribute to the seemingly contradictory dual role of Pin1 in NO production and in the pathogenesis of cardiovascular diseases.