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Could Pin1 help us conquer essential hypertension at an earlier stage? A promising early-diagnostic biomarker and its therapeutic implications for the disease

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ABSTRACT

Essential hypertension is a major risk factor for cardiovascular morbidity and mortality, and the early-diagnosis is very important for the prevention of essential hypertension. Previously, we found that Pin1, the only known enzyme isomerizing pSer/pThr-Pro motifs in proteins, may gradually become inactive under conditions of stress such as intracellular acidification and fever. Interestingly, essential hypertension and the dysfunction of Pin1 often synchronously occur with the increasing age. Recent evidence indicates that Pin1 primarily increases the activity of endothelial nitric oxide synthase (eNOS) and the production of nitric oxide (NO) in multiple ways, significantly promoting the relaxation response of blood vessels and preventing the elevation of blood pressure. Further, the inhibition of Pin1 results in significantly increased blood pressure in rats. So, we hypothesized and evaluated the potential of Pin1 to be a new early-diagnostic biomarker as well as a therapeutic drug for essential hypertension. The unique activity of Pin1 and some epidemiological and experimental data evidence that the decreased activity of Pin1 may be closely associated with the development of essential hypertension. The factors that may impact the activity of Pin1 and correlate with the risk of essential hypertension were also discussed. These findings indicate that Pin1 plays a key and permanent role in efficiently preventing the development of essential hypertension, and that Pin1 may be a promising early-diagnostic biomarker as well as an effective therapeutic drug for the early-diagnosis, prevention, and treatment of essential hypertension, potentially decreasing the risk of cardiovascular morbidity and mortality.

Introduction

Hypertension is a worldwide public-health challenge. Nowadays, more than 25% of the world's adult people have hypertension, which will increase to about 30% in 2025 [1]. Hypertension is a chronic medical condition with elevated blood pressure, and is a major risk factor for cardiovascular morbidity and mortality, endangering the worldwide healthcare [1,2]. These reliable information shows that hypertension is prevalent in many regions of the world, which determines the development of numerous health policies in order to prevent this serious condition. Especially, it is extremely important to identify individuals who are very susceptible to hypertension, and effective interventions should be carried out to prevent the disease at an earlier stage. Recent evidence suggests that biomarkers may greatly contribute to the early-diagnosis, prevention, and treatment of hypertension [3,4], although effective and efficient biomarkers for hypertension still need to be intensively exploited.

Essential hypertension, which has no identifiable cause, is the main form (for about 90%) of hypertension [5]. Many studies endeavor to illustrate the pathogenesis of essential hypertension, especially the early-diagnosis of it. However, the complicated pathogenesis of essential hypertension involves many genetic and environmental risk factors, and it has not yet been completely clarified until now [5,6]. For example, it is shown that genetic

Abbreviations: PPIase, peptidyl-prolyl cis–trans isomerase; NO, nitric oxide; eNOS and iNOS, endothelial and inducible nitric oxide synthase, respectively; VEGF, vascular endothelial growth factor; TGF-β, transforming growth factor-beta; Aβ, amyloid-beta; PBMC, peripheral blood mononuclear cells; AD, Alzheimer's disease.

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factors for essential hypertension involve many genes, such as endothelial nitric oxide synthase (eNOS) [7], vascular endothelial growth factor (VEGF) [8], transforming growth factor-beta (1) (TGF-β(1)) [6], and so on. Nevertheless, none of them can solely give a sufficient and satisfied precaution for essential hypertension, and the combination of two or more factors may be more reliable for the purpose. Recently, new factors that are correlating to the pathogenesis of essential hypertension are still increasing, and Pin1 may be one of the most unique and specific one among them.

We are focusing our research on the structural and functional stability of Pin1 in order to intensively reveal the role of Pin1 in the pathogenesis of age-related diseases. Under conditions of stressors such as heat, acidic pH, and mutations, some functional changes of Pin1 were recently identified [9–11]. These studies contribute to further understanding of Pin1-related diseases, including cancers, Alzheimer's disease (AD), and recently-discovered essential hypertension. So far, Pin1 is the only known peptidyl-prolyl cis–trans isomerase (PPIase) that specifically isomerizes the configuration of pSer/pThr-Pro motifs in many proteins, which is a key basis for the reversible phosphorylation of pSer/pThr-Pro motifs and plays a vital role in regulating many important proteins relating to kinds of cell signaling pathways, such as Cyclin D1, Raf-1, p53, p73, Tau, and so on [12,13]. Recently, emerging evidence shows that Pin1 is closely associated with the regulation of blood pressure, and Pin1 may be a promising early-diagnostic biomarker as well as a therapeutic drug for the treatment of essential hypertension, giving rise to efficient and effective approaches for the early-diagnosis, prevention, and treatment of essential hypertension.

Pin1 primarily prevents essential hypertension by regulating the production of nitric oxide

The association of Pin1 with essential hypertension is mainly due to its function of regulating the production of nitric oxide (NO). NO, which is mainly synthesized by eNOS in blood vessel endothelial cells, can promote the relaxation response of blood vessel and prevent the elevation of blood pressure, and the impaired bioactivity of NO is an important risk factor for essential hypertension [14,15]. Pin1 can modulate the production of NO in multiple ways, shown in Fig. 1. For example:

1. Chiasson et al. showed that Pin1 facilitated the dephosphorylation of pSer116 in eNOS in rats, leading to increased activity of eNOS, increased production of NO, and increased endothelium-dependent vasodilatation, which prevented the elevation of blood pressure [14,16]. Knockdown or inhibition of Pin1 resulted in decreased production of NO, decreased relaxation response of blood vessel, and increased blood pressure [14]. For instance, the mice treated with juglone (an inhibitor of Pin1) for 2 weeks exhibited the significantly increased blood pressure from 107 to 140 mmHg [14].
2. Erol et al. gave a reasonable explanation for the regulation of the production of NO by Pin1 [17]. Pin1 up-regulates the transcription of VEGF, VEGF activates the protein phosphatase 2B (PP2B), and PP2B facilitates the dephosphorylation of pSer116 in eNOS, leading to the increased activity of eNOS and the consequently increased production of NO [17–19]. By contrast, it is shown that the inhibition of VEGF by bevacizumab (Avastin, Genentech Inc.) may inhibit the production of NO and lead to endothelial dysfunction and hypertension [20].
3. TGF-β(1) can down-regulate the expression of eNOS as well as the production of NO, and significant inversely correlation between TGF-β(1) and NO is observed in some patients [21,22]. TGF-β(1) also has the potential of stimulating the expression and release of endothelin-1, renin, and angiotensin, as a result, the positive association between TGF-β(1) and blood pressure is often observed [6,23,24]. Interestingly, the recent evidence shows that Pin1 can inhibit TGF-β(1) signaling and TGF-induced transcription and gene expression [23,25], further indicating the unignorable role of Pin1 in promoting the production of NO and preventing the elevation of blood pressure.
4. Pin1 regulates the processing of amyloid precursor protein and inhibits the production of amyloid-beta (Aβ), and the inactivity of Pin1 can cause the over-production of Aβ [26–28]. Recent evidence reveals a new regulatory mechanism of eNOS by Aβ, suggesting that Aβ can decrease the production of eNOS as well as NO in human erythrocytes [29]. Consequently, it seems reasonable to conclude that Pin1 can inhibit the production of Aβ, and causes the increased production of NO, preventing the elevation of blood pressure.

Because of distinctive methodologies, cell lines, and animals, results obtained by Ruan et al. was not completely consistent with the above descriptions, but they also clearly confirmed that Pin1 facilitated the dephosphorylation of eNOS on pSer116, regulating the activity of eNOS [16]. Taken together, it is obvious that Pin1 is very important in the pathogenesis of hypertension by regulating the activity of eNOS and the production of NO. Moreover, the most findings listed above suggest that Pin1 enhances the activity of eNOS and the production of NO, playing a vital and permanent role in efficiently preventing the development of hypertension.

The hypothesis

World widely speaking, essential hypertension endangers the public health and causes many deaths every year. The demands for the early-diagnosis, prevention, and treatment of essential

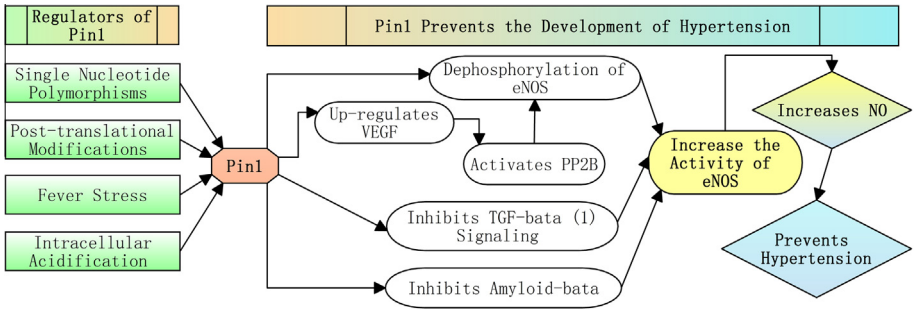

Fig. 1. Schematic representation of the role of Pin1 in preventing the development of hypertension. Pin1 can increase the activity of eNOS and regulate the production of endothelium-derived nitric oxide in multiple ways, preventing the elevation of blood pressure. The factors that may impact the activity of Pin1 are also shown, possibly contributing to the morbidity of essential hypertension.