Hypertension Research (2025) 48:1684–1686
https://doi.org/10.1038/s41440-025-02170-7

EDITORIAL

Factors associated with blood pressure regulation in vascular smooth muscle cells

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Keywords Smooth muscle cells · transcription factors · circadian regulation · vasoconstriction

Received: 8 February 2025 / Accepted: 16 February 2025 / Published online: 7 March 2025

Functional abnormalities in vascular endothelial cells and smooth muscle cells (VSMCs), which influence vascular resistance, play a critical role in the regulation of blood pressure. It is also clinically known that arterial stiffness, particularly involving VSMCs, contributes significantly to blood pressure variability. A recent study published in Hypertension Research examined the relationship between brachial-ankle pulse wave velocity (baPWV) and long-term visit-to-visit variability in systolic blood pressure [1], accompanied by a commentary by Kajikawa et al. [2]. Blood pressure variability is influenced by numerous factors, and Faraci et al. recently published a comprehensive review discussing circadian biology [3]. Elevated nocturnal and early morning blood pressure are well-established risk factors for cardiovascular disease [4], and they remain particularly challenging to control [5].

Functional abnormalities in vascular components, such as endothelial cells and VSMCs, are crucial in the regulation of blood pressure and contribute to the development of cardiovascular diseases. As a result, substantial research has focused on elucidating the mechanisms underlying both blood pressure elevation and circadian variability, particularly with respect to endothelial dysfunction and VSMC proliferation and differentiation. This paper highlights two key transcription factors recently identified as influential in these processes (Fig. 1).

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Cui et al. reported that Zinc finger protein 36 (ZFP36), an RNA-binding protein that binds to adenylate-uridylate-rich elements in the 3' untranslated region of mRNA and regulates mRNA stability, is upregulated in hypertensive patients and rodent arteries [6]. Deletion of ZFP36 in a smooth muscle cell-specific manner results in reduced vasoconstriction and lower blood pressure. The authors suggested that ZFP36 could be a target for antihypertensive therapy, as it is expressed in vascular endothelial cells and has been reported to reduce inflammation by suppressing nuclear factor-κB-mediated transcriptional responses [7]. It has also been found that aldosterone levels increase with ZFP36 depletion [8]. Additionally, hyperosmolarity increases expression of the mRNA-destabilizing protein Tis11b, a member of the ZFP36 family, and reduces expression of the mineralocorticoid receptor (MR) in kidney KC3AC1 cells [9]. Although previous studies suggested that ZFP36 might have a hypotensive effect, the current report suggests that angiotensin II promotes ZFP36 transcription via poly(ADP-ribose) polymerase 1 (PARP1), impairing mRNA stability and increasing blood pressure through GPCR-mediated smooth muscle contraction [6].

Xu et al. demonstrated that the GLP-1/NCX1 pathway regulates cytoplasmic Ca^{2+} homeostasis, improving blood pressure variability [10], suggesting the involvement of intracellular signals and transcription factors. Recently, Wang et al. reported that PR domain-containing protein 16 (PRDM16), a transcription factor highly expressed in VSMCs, plays a key role in the circadian regulation of blood pressure [11]. VSMC-specific Prdm16 knockout (Prdm16-SMKO) mice exhibited significantly lower blood pressure during the active phase compared to control mice, and the mesenteric arterial rings in these mice showed a reduced response to phenylephrine. PRDM16 was also identified as a transcriptional target of the adrenergic receptor α1d (Adra1d), which regulates the expression of clock genes like Npas2, important for circadian rhythm regulation.

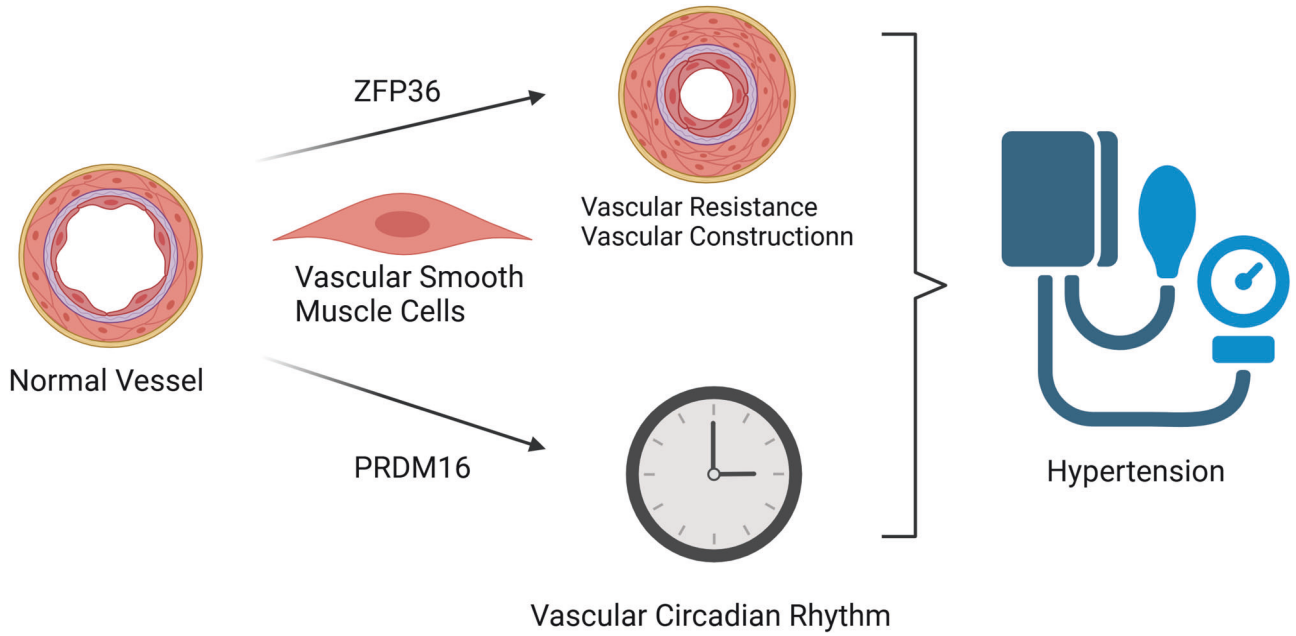

Fig. 1 Schematic presentation of the relation between blood pressure variability and vascular smooth muscle cells. The relationship between transcriptional factors in vascular smooth muscle and hypertension. Zinc finger protein 36 (ZFP36) has recently been reported to be related to blood pressure by affecting vasoconstriction, and PR domain-containing protein 16 (PRDM16) has also been reported by affecting circadian rhythms

Regarding PRDM16, Wang et al. also found that PRDM16 expression is downregulated in human abdominal aortic aneurysm (AAA) lesions, and that AAA formation worsens in mice with vascular smooth muscle-specific PRDM16 deletion. PRDM16 deficiency increases inflammation and apoptosis, making it a key regulator in the development of AAA, with metalloproteinase 12 (ADAM12) being a target of transcriptional repression [12]. They also reported that PRDM16 is an attractive target for new therapeutic strategies for patients with peripheral arterial disease, as it is essential for restoring arterial blood flow by influencing structural remodeling and maintaining endothelial function [13]. Thompson et al. also reported that specific deletion of PRDM16 in vascular endothelial cells regulates arterial development and vascular integrity, including reducing VSMC mobilization around arteries [14]. Recently, the importance of PRDM16 in blood vessels has been highlighted, especially regarding circadian rhythms of blood pressure, which is an intriguing development.

To identify novel therapeutic targets for hypertension, it is imperative that future research expands beyond the conventional focus on mechanisms of blood pressure elevation and critically examines the underlying factors driving blood pressure variability. A deeper investigation into the role of VSMCs in modulating blood pressure fluctuations is essential to uncovering new and innovative therapeutic intervention strategies.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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