

EDITORIAL

Checkpoint Kinase 1 Promotes the Development of Pulmonary Arterial Hypertension

Kimio Satoh, Nobuhiro Kikuchi, Ryo Kurosawa, Hiroaki Shimokawa

Pulmonary arterial hypertension (PAH) is characterized by histological changes in the distal pulmonary arteries, perivascular inflammation and fibrotic change, and right ventricular failure.^{1–5} In addition to genetic backgrounds, many environmental factors as well as volume overload because of heart disease and inflammation are involved in the development of PAH.^{6–8} In this process, pulmonary artery smooth muscle cells (PASMCs) will suffer epigenetic modifications by transcriptional factors.^{9,10} Recently, we have reported that SeP (selenoprotein P) is a pathogenic protein that induces the production of reactive oxygen species and promotes the proliferation of PAH-PASMCs (Figure).^{9–11} Moreover, it has been demonstrated that excessive reactive oxygen species (oxidative stress) will induce DNA damage in PAH-PASMCs.^{12–14} The characteristics of PASMCs in patients with PAH (PAH-PASMCs) are different from those of healthy controls.^{9,15} The abnormal features of PAH-PASMCs are based on their altered cellular functions similar to cancer cells.^{2,13} Thus, these features of PAH-PASMCs can potentially be a target to cure patients with PAH.

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CHK1 (checkpoint kinase 1) and CHK2 are serine/threonine kinases that serve as nexus between DNA damage sensors and components of the cell cycle machinery. CHK1 plays a crucial role in cell survival and cell response to DNA damaging agents. Once activated, CHK1 phosphorylates multiple proteins to temporarily halting the progression of cell replication and division, initiating DNA repair and triggering apoptosis in response to irreversible

DNA damage. Thus, CHK1 overexpression is a hallmark of many cancer-enhancing cell survival by preventing the accumulation of DNA damage. Therefore, it will be of great interest to elucidate the role of CHK in the development of PAH. In this issue of *ATVB*, Bourgeois et al¹⁶ challenged this issue. The authors demonstrated that hyperproliferating PAH-PASMCs exhibit increased levels of γ -H2AX and pRPA32, 2 markers of DNA damage/replication stress. In addition, the authors demonstrated that PAH-PASMCs display enhanced expression and activation of CHK1 and that its pharmacological or molecular inhibition induced further accumulation of DNA damage. More importantly, the authors showed that pharmacological inhibition of CHK1 improves established PAH in 2 clinically relevant PAH rat models. Interestingly, they provided evidence that decreased expression levels of miR-424 accounts for elevated CHK1 expression in PAH-PASMCs (Figure). The authors concluded that CHK1 exerts a proproliferative function in PAH-PASMCs by mitigating DNA damage and suggest that CHK1 inhibition may, therefore, represent an attractive therapeutic option for PAH patients.¹⁶ Why is this article so intriguing and important? First, they demonstrated that the CHK1 signaling is activated in PAH-PASMCs and that inhibition of this axis provides significant therapeutic effects in 2 complementary animal models mimicking PAH. This indicates that inhibition of CHK1 may represent a new therapeutic avenue for PAH patients by blocking or reversing pulmonary vascular remodeling. Next, the findings in this study set the ground for future studies deciphering the molecular mechanisms underlying MK-8776 action and exploring its ability to potentiate the effects of antiremodeling drugs in preclinical models of PAH. Finally, the authors provided the rationale to

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Correspondence to: Kimio Satoh, MD, PhD, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan. Email satoh-k@cardio.med.tohoku.ac.jp

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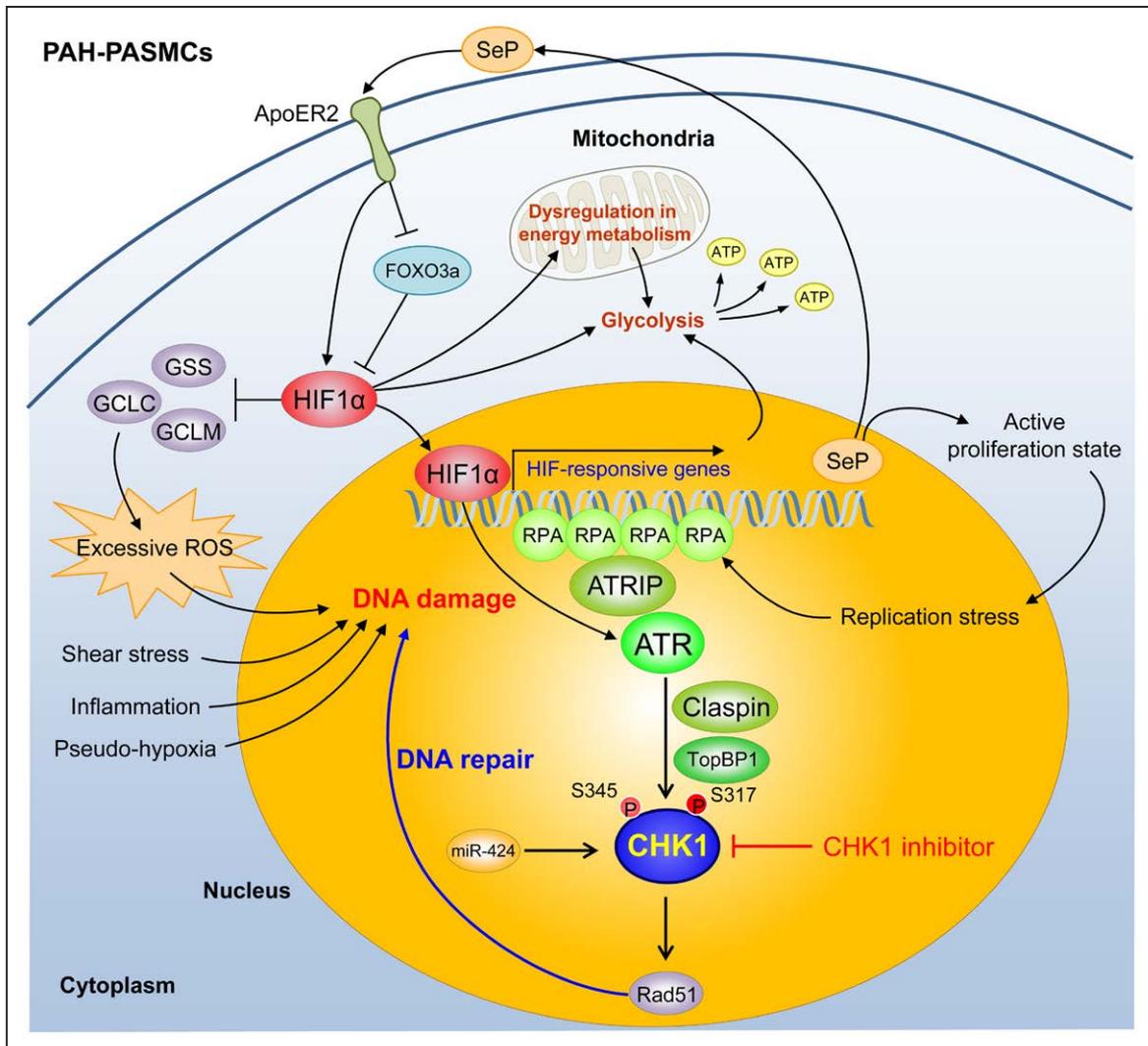


Figure. Oxidative stress-mediated DNA damage and roles of CHK1 (checkpoint kinase 1) in pulmonary arterial hypertension-pulmonary artery smooth muscle cells (PAH-PASMCs).

The characteristics of pulmonary artery smooth muscle cells harvested from patients with pulmonary arterial hypertension (PAH-PASMCs) are different from those of healthy controls, with mitochondrial dysfunction similar to cancer cells. This schema represents the molecular mechanisms promoting SeP (selenoprotein P) expression by HIF-1 α (hypoxia-inducible factor-1 α) activation and FoxO3a (forkhead box protein O3a) inactivation.⁹ Extracellular SeP induces oxidative stress, HIF-1 α activation, and FOXO3a inactivation via SeP-ApoER2 (apolipoprotein E receptor 2) signaling in PAH-PASMCs. Constitutively active HIF-1 α induces transcription of many genes and is closely related with the excessive reactive oxygen species (ROS), which is provoked by the lack of antioxidants such as glutathione (GSH). Here, the expression of GSS (glutathione synthase), GCLC (glutamate-cysteine ligase catalytic subunit), and GCLM (glutamate-cysteine ligase modulating subunit), all of which are responsible for GSH synthesis, are significantly reduced in PAH-PASMCs.⁹ In parallel, excessive production ROS (oxidative stress) results in DNA damage in PAH-PASMCs, which is similar to cancer cells. Here, overexpression of the serine/threonine-protein kinase CHK1 is exploited to counteract the excess of DNA damage insults in PAH-PASMCs. This schema represents an orchestrated response mediated by CHK1 to overcome DNA damage, allowing cell survival and proliferation, in PAH-PASMCs. In response to DNA damage and DNA-replication stress, CHK1 is phosphorylated by the ATR (ataxia telangiectasia and Rad3 related) kinase, which is facilitated by adaptor proteins DNA TopBP1 (topoisomerase 2-binding protein 1) and Claspin.

investigate the implication of CHK1 in other proliferative cardiovascular diseases characterized by DNA damage, such as carotid artery restenosis. Based on the present study and previous reports, CHK1 exerts a proproliferative function in PAH-PASMCs by mitigating DNA damage and suggest that CHK1 inhibition may, therefore, represent an attractive therapeutic option for PAH patients. These data will augment the possibilities of CHK1 inhibitors in PAH therapy.

CLINICAL SIGNIFICANCE

Several drugs and molecules target cell proliferation, all of which could be potentially protective against the development of PAH.¹⁷ In the present study, the authors have shown that CHK1 activation in PAH-PASMCs is a decisive event in the initiation of pulmonary vascular remodeling in PAH.¹⁶ These findings may have great therapeutic impact, leading to the development of novel therapeutic

strategies using CHK1 inhibitors against PAH. Thus, CHK1 may represent a novel therapeutic target against PAH-PASMC proliferation, pulmonary vascular remodeling, and PH.¹⁶ Thus, we expect the identification of potential predictive biomarker of CHK1 inhibitor sensitivity, which will define their potential use for PAH patient stratification and maximize their impact in the clinic.

ARTICLE INFORMATION

Affiliation

From the Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan.

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Disclosures

None.

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