Arteriosclerosis, Thrombosis, and Vascular Biology

EDITORIAL

PIM1 (Provirus Integration Site For Moloney Murine Leukemia Virus) as a Novel Biomarker and Therapeutic Target in Pulmonary Arterial Hypertension

Another Evidence for Cancer Theory

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Pulmonary arterial hypertension (PAH) is characterized by histological changes in the distal pulmonary arteries, perivascular inflammation, and resultant right ventricular failure.[1–5] In addition to several specific genetic backgrounds, certain environmental factors, as well as volume overload due to heart disease and inflammatory disease, are involved in the development of PAH.[6–8] One of the important characteristics of pathological changes in pulmonary vasculature of PAH is an excessive proliferation and a resistance to apoptosis of pulmonary artery smooth muscle cells (PASMCs) like cancer cells.[9] Indeed, these cells exhibit many features common to cancer cells offering the opportunity to exploit therapeutic strategies used in cancer to treat PAH (cancer theory).[10] Although the primary trigger of such phenotypic changes of PASMCs from patients with PAH (PAH-PASMCs) still remains unclear, excessive oxidative stress and inflammation have been shown to play a key role in the development of vascular remodeling in PAH. These environmental changes surrounding pulmonary vasculature are known to cause DNA damage that might favor the emergence of the proproliferative and antiapoptotic phenotypes observed in PAH. Consistently, there is mounting evidence showing the importance of DNA-damage response (DDR) of PAH-PASMCs for the sustainability of such proproliferative phenotypic alterations.[11]

See accompanying article on page 783

Recently, we have reported that selenoprotein P is a pathogenic protein that induces the proliferation of PAH-PASMCs partially through dysregulation of oxidative stress and DDR.[12–15] We also have demonstrated that modulating DDR was associated with the amelioration of PAH-PASMC excess proliferation.[12,16,17] It has been demonstrated that excessive production of reactive oxygen species causes DNA damage through DNA base oxidation and deamination in variety kinds of cells associated with PAH.[18–20] It has been recently indicated that dysfunctional DDR facilitates the survival of PASMCs under such a harsh environment and enables them to become resistant to apoptosis and maintain proproliferative state, which is commonly seen in cancer cells.[10,11] Moreover, PAH-PASMCs have an upregulated critical enzyme implicated in DNA repair, poly (ADP-ribose) polymerase 1 levels, and subsequent downregulation of miR-204, which then results in overexpression of bromodomain protein 4, HIF (hypoxia-inducible factor)-1α, and NFAT (nuclear factor of activated T-cells), and finally promote their apoptosis-resistance.[18,21,22] These characteristics of PAH-PASMCs contribute to the cancer-like phenotype and are completely different from those of healthy controls.[12,23] Thus, these features of PAH-PASMCs explained by the cancer theory can potentially be a target to cure patients with PAH.

PIM1 (provirus integration site for Moloney murine leukemia virus) is a proto-oncogene encoding a serine/threonine protein kinase that is minimally expressed in healthy cells.[24] The authors have previously demonstrated a line of evidence on the crucial role of PIM1

Key Words: Editorials ■ apoptosis ■ DNA damage ■ hypertension ■ inflammation ■ phenotype

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Arterioscler Thromb Vasc Biol is available at www.ahajournals.org/journal/atvb

in the pathogenesis of PAH associated with an excessive proliferation and a resistance to apoptosis in PAH-PASMCs.[18,21,22] Furthermore, they took advantage of its specific expression in PAH and developed a novel concept of PIM1 as a powerful biomarker for discrimination of PAH patients from controls and their prognosis prediction.[25] Thus, it will be of great interest to elucidate the role of PIM1 in the molecular mechanism of PAH and translate it into future clinical use.

In this issue of the Journal, Lampron et al[26] designed an elegant study and provide strong evidence suggesting that PIM1 is a promising new target in PAH with a multifaceted role in regulating DNA damage repair signaling pathway in PAH-PASMCs. First, the authors demonstrated that PIM1 expression is increased in PAH, and its production is stimulated in response to DNA damage induced by DNA damaging agents, such as etoposide and X-rays irradiation. Pharmacological inhibition of PIM1 using several ways (potential drugs of SGI-1776 and TP-3654, and PIM1 siRNA) suggested that PIM1 might play a role in DNA damage recognition and in the primary events involved in DNA repair, which is clearly shown using detailed study of comet assay and quantification of 8-hydroxy-2'-deoxyguanosine for detection of DNA brakes and oxidative DNA damage, respectively. According to the previous studies and present results, the authors hypothesized that alteration of DNA damage repair by PIM1 inhibition could be accounted for a decrease in the canonical nonhomologous end-joining of double-strand break repair. They have successfully shown that pharmacological and genetical PIM1 inhibition prevented DNA damage repair through its direct target of KU70 (lupus Ku autoantigen protein p70) and its downstream molecule of DNA-PKcs (DNA-dependent protein kinase, catalytic subunit), which resulted in the decrease in PAH-PASMC proliferation and induction of the apoptosis (Figure). Moreover, the authors confirmed that PIM1 and the nonhomologous end-joining pathway of DNA repair are also activated in animal models of PAH. Importantly, pharmacological inhibition of PIM1 prevented pulmonary vascular remodeling and resulted in the reduction of pulmonary arterial pressure and improvement of right ventricular function in 2 rat models of established PAH (monocrotaline model and Fawn-Hooded rat). The authors concluded that PIM1 phosphorylates KU70 and initiates DNA repair signaling in PAH-PASMCs and that PIM1 inhibitors represent a therapeutic option for PAH patients.

CLINICAL SIGNIFICANCE

Despite the major progress in the therapy of PAH within the past decade, there is still no cure for this devastating disease. Our current therapeutic strategy consists mainly of vasodilators, which provide only modest improvement of quality-of-life and survival benefits to patients with

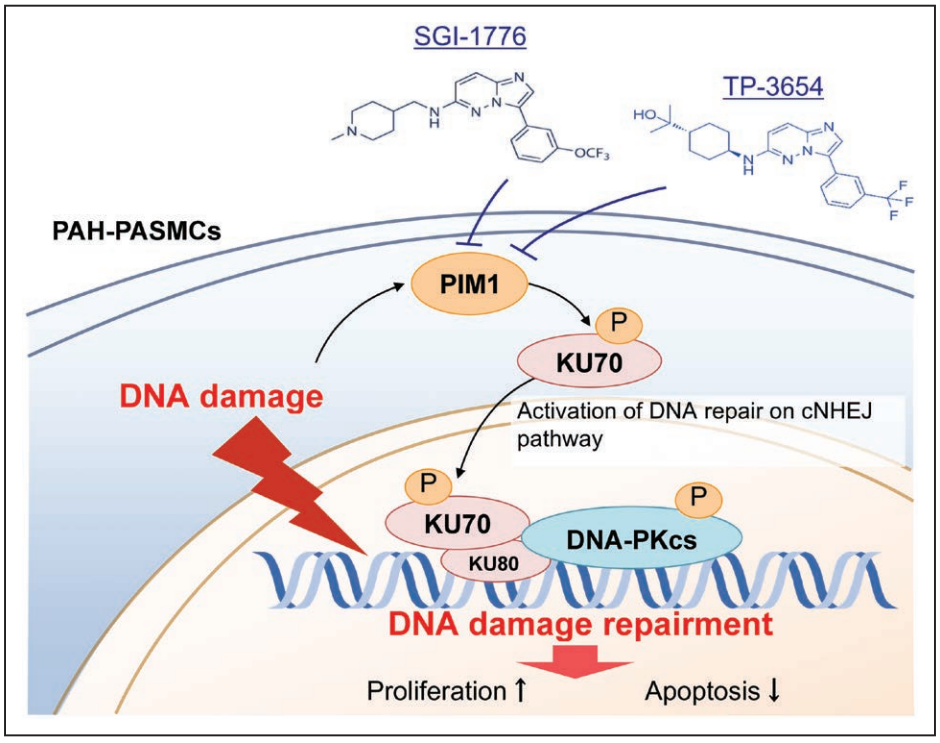

Figure. Roles of PIM1 (provirus integration site for Moloney murine leukemia virus) in pathogenesis of pulmonary arterial hypertension (PAH).
This schema represents the molecular mechanisms of PIM1 function in the context of DNA damage response and phenotypic change in PAH–pulmonary artery smooth muscle cells (PASMCs). cNHEJ indicates canonical nonhomologous end-joining; DNA-PKcs, DNA-dependent protein kinase, catalytic subunit; and KU70 and KU80, lupus Ku autoantigen protein p70 and p80.

PAH. This is largely attributable to the fact that various proproliferative, antiapoptotic, and inflammatory pathways additively and synergistically induce vascular remodeling that underlies PAH. Thus, deciphering the mechanisms governing pulmonary vascular remodeling and identifying novel targets and biomarkers of disease onset and progression have been more and more required in the research field on PAH. The present finding that several pathogenic pathways converge on PIM1 as a central hub molecule in DDR and resultant proproliferative PAH-PASMCs offers new options for biomarker development and therapeutic intervention based on the cancer theory of those cells. The preclinical evidence for the efficacy of the approach to inhibit PIM1 seems to be promising and will need to be assessed further in future clinical trials.

ARTICLE INFORMATION

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Disclosures

None.

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