

Research progress of PDGF-BB/ERK/HIF-1 α signaling pathway in hypoxic pulmonary hypertension

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Abstract: Hypoxic pulmonary hypertension (HPH) is a refractory disease. The main symptoms of HPH are pulmonary vascular remodeling and persistent increase in pulmonary vascular resistance, which can lead to progressive right ventricular hypertrophy and even death. The role of platelet-derived growth factor-BB/ERK/hypoxia-inducible factor-1 α signaling pathway in the occurrence and development of hypoxic pulmonary hypertension has become the focus of attention. The hyperbaric treatment provides new ideas. This review mainly studies the research progress of the PDGF-BB/ERK/HIF-1 α signaling pathway in pulmonary hypertension in recent years and conducts related research.

Keywords: PDGF-BB; ERK; HIF-1 α ; signaling pathway; pulmonary hypertension

1. Introduction

HPH (Pulmonary arterial hypertension) is one of the causes of neonatal morbidity and death. Heart failure with limited treatment and high mortality [1-3]. Pulmonary vascular remodeling mainly manifests as excessive proliferation and Migration of PASMC (pulmonary arterial smooth muscle cell) and inhibition of PAEC (pulmonary arterial endothelial cells) apoptosis, which causes extracellular matrix increase, tube wall thickening and lumen narrowing and inhibits its abnormal proliferation and Migration may be effective in reversing pulmonary vascular remodeling, thereby reducing pulmonary artery pressure [4-5]. Currently, the essential treatment is mainly to improve ventilation and inhaled nitric oxide (iNO) and other pulmonary vasodilators[6], and there is still no specific treatment method. The pathogenesis of HPH involves multiple cell types, multiple factors, and joint effects of multiple signaling pathways[7]. The pathogenesis is still unclear—an important role in progress.

2. The relationship between PDGF-BB and pulmonary hypertension

Platelet-derived growth factor PDGF is a dimeric glycoprotein consisting of two PDGF-AAs, two PDGF-BBs, or each PDGF-AB. PDGF is a major growth factor that regulates cell growth and division. PDGF-BB is a vital mitogen acting on vascular smooth muscle cells. Studies have shown that PDGF-BB is highly expressed in the blood and lung tissue of experimental animal models and HPH patients and plays an essential role in pulmonary vascular remodeling [8-9]. PDGF-BB was extracted initially from human platelets and can also be produced by SMCs (smooth muscle cells), fibroblasts, osteoclasts, macrophages, etc. It plays an essential role in wound healing, angiogenesis, tumor growth, and airway remodeling play an essential role in process [10]. The PDGF signaling pathway is mainly composed of four ligands and two receptors in organisms. Different ligands and different receptors have different affinities. The primary ligand expressions are PDGF-AA, PDGF-BB, PDGF-CC, PDGF-DD, and PDGF-AB. PDGF-BB can bind to PDGFR- $\alpha\alpha$, PDGFR- $\alpha\beta$, and PDGFR- $\beta\beta$. After binding to the ligand, PDGFR (platelet-derived growth factor receptor) will dimerize, phosphorylate, and start the signaling pathway[11]. Studies have shown that PDGF-BB is a potent mitogen and chemoattractant of PASMC. This significant growth factor causes PASMC proliferation and Migration, and participates in vascular remodeling in the development of pulmonary arterial hypertension [12-14]. Studies have shown that PDGF-BB stimulation can promote the proliferation of PASMC. The growth rate of PASMC in PAH patients is faster than that of non-PAH patients. The expression of PDGF-BB mRNA

in small pulmonary arteries of PAH patients is higher than that of non-PAH patients [15-16]. Likewise, the PDGF signaling pathway has also been shown to be involved in pulmonary vascular remodeling [17]. CAPE (Caffeic acid phenethyl ester) significantly inhibited MCT-induced pulmonary vascular remodeling and improved correct ventricular systolic function in rats by reducing the expression of HIF-1 α and the production of PDGF-BB. It can effectively prevent the thickening of the diameter and wall of pulmonary arterioles and improve the PASMC proliferation induced by PDGF-BB [18]. Blocking the PDGF signaling pathway can effectively inhibit the dysregulation of PASMC, thereby alleviating the progression and symptoms of pulmonary arterial hypertension [19-20]. This study found that PDGF and PDGF receptors are highly expressed in the pulmonary artery wall of patients with pulmonary hypertension, and the activation of the PDGF pathway in PAH vascular lesions is related to PCNA, and confirmed the Migration and proliferation of PASMCs induced by PDGF in vitro, thus explaining the role of PDGF in PAH lungs. Play an essential role in vascular remodeling [21]. In recent years, tyrosine kinase inhibitors such as imatinib have been shown to inhibit PDGF receptor activity and can effectively reverse pulmonary hypertension. In addition, imatinib reversed monocrotaline-induced pulmonary hypertension in rats and improved hemodynamics in patients with end-stage PAH [22]. In this paper, a large amount of information was searched. It found that PDGF-BB down-regulated the expression of PMCA4 (calcium transporter ATPase 4) in PASMC through the MEK/ERK signaling pathway, which weakened the Ca²⁺ clearance in PASMC, thereby promoting the proliferation of PASMC, and in the absence of the model of oxygen-induced pulmonary hypertension in rats confirmed that it can increase right ventricular pressure and aggravate pulmonary vascular plasticity [23].

3. The relationship between ERK and pulmonary hypertension

ERK protein also has a bilobal structure formed by N-terminal and C-terminal coils, and its N-terminus is composed of 5 antiparallel β -sheet structures (β 1~ β 5), one α C helical structure, and a glycine-rich loop structure. The end is composed of 6 conserved α -helical structures and four shorter β -sheet structures (β 6~ β 9)[24]. Almost all mammals have ERK protein expression. So far, ERK protein has been identified as having two subtypes: ERK1 and ERK2 [25]. Studies have shown that under hypoxic conditions, the expression level of EC-SOD (extracellular superoxide dismutase) in pulmonary artery cells is reduced, and activation of ERK1/2 causes early growth response, leading to pulmonary vascular remodeling [26]. Studies have shown that Mir-455-3p-1 inhibits the expression of FGF7 through the RAS/ERK signaling pathway, inhibits the proliferation of PASMC, and alleviates pulmonary hypertension [27]. Plasminogen activator inhibitor-2 inhibits pulmonary artery smooth muscle cell proliferation in pulmonary arterial hypertension through PI3K/Akt and ERK signaling pathways. Researchers such as Xing J found that knocking out the expression of TRPM7 in human and rat PASMCs that were hypoxia-induced PAH inhibited the proliferation and apoptosis resistance of PASMCs, thereby exacerbating hypoxia-induced PAH. In addition, inhibition of TRPM7 activated the MEK/ERK pathway, suggesting that activation of the MEK/ERK pathway is the primary mechanism for exacerbating PAH [28]. In addition, atorvastatin inhibited pulmonary vascular remodeling and alleviated pulmonary hypertension by inhibiting the AKT/ERK-dependent PDGF-BB/HIF-1 α signaling pathway, down-regulating the expression of HIF-1 α and PDGF-BB.

Additionally, atorvastatin-induced apoptosis in hypoxia- or PDGF-BB-induced hPASMCs [29]. Professor Zhao Y and other researchers found that by cutting off the cervical sympathetic trunk, the concentration of noradrenaline in the lung tissue was reduced, thereby preventing noradrenaline from promoting the proliferation of PASMC mediated by the ERK-1/2 signaling pathway and inhibiting the induction of pulmonary arterial hypertension by monocrotaline. Remodeling and right heart failure [30]. Professor Feng and other researchers found that HMGB1 activates Drp1 phosphorylation and Drp1-dependent mitochondrial fission through extracellular signal regulation ERK1/2 signaling, which subsequently triggers autophagy activation, which further leads to bone morphogenetic protein receptor two lysosomal degradations and DNA binding inhibition. In addition, the pharmacological inhibition of HMGB1 by glycyrrhizic acid or the blockade of autophagy can inhibit the occurrence of monocrotaline-induced pulmonary hypertension in rats[31]. Professor Deng L and other researchers found that after PDGF-BB intervention, the expression of PMCA4 (plasma membrane calcium transporting ATPase 4) in PASMC was down-regulated, and MEK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase) was inhibited from eliminating it. Inhibition of PMCA4 attenuates Ca²⁺ entry into PASMCs, promotes cell proliferation, and enhances cell motility by mediating adhesion foci formation. In addition, MCT (monocrotaline) or hypoxia-induced decreased PMCA4 expression in the pulmonary arteries of PAH rats. Under normal conditions, down-regulation

of PMCA4 increases correct ventricular systolic pressure and pulmonary artery wall thickness in rats. The findings support the importance of the PDGF/MEK/ERK/PMCA4 axis in PASMCM intracellular calcium homeostasis and the functional role of PMCA4 in pulmonary artery remodeling and PAH development [23]. Studies have shown that using a monocrotaline rat pulmonary hypertension model through intraperitoneal injection of caffeic acid phenethyl ester reduces the expression of HIF-1 α and the production of PDGF-BB, significantly inhibits monocrotaline-induced vascular remodeling and improves Contractile properties of blood vessels in rats. In addition, phenethyl caffeate decreased the expression of HIF-1 α induced by hypoxia and PDGF-BB. It attenuated the proliferation of hPASCs (human pulmonary artery smooth muscle cells) by inhibiting the AKT/ERK pathway [32].

4. The relationship between HIF-1 α and pulmonary hypertension

Previous studies have shown that hypoxia is thought to exacerbate pulmonary vascular remodeling in animal models of hypoxic pulmonary hypertension [33]. One of the primary protein mediators of the cellular response to hypoxia is HIF (hypoxia-inducible factor), a heterodimeric transcription factor composed of HIF-1 α and HIF-1 β subunits. Under low oxygen levels, HIF-1 α and HIF-1 β subunits translocate to the nucleus, where the complex binds to hypoxia response elements and promotes the transcription of various target genes [34]. Previous studies have reported that under hypoxic conditions, the production of HIF increases, which participates in angiogenesis, cell metabolism, proliferation, apoptosis, and autophagy by inhibiting or inducing related genes [35]. HIF exists as the HIF1- α and cognate HIF2- α proteins, both of which are involved in the development of PH in models of chronic hypoxia [36-37]. Previous studies reported[38] that hypoxia can promote the overexpression of HIF-1 α in PASMCM, stimulate PASMCM cell cycle proteins, upregulate the expression of PCNA (Proliferating cell nuclear antigen), and lead to PASMCM proliferation. Studies have shown that under hypoxic conditions, the degradation pathway of HIF-1 α is blocked, and its expression increases. Combining with PCNA on its downstream proliferation target gene regulates the cell cycle, making its expression significantly increase in the late G1 period and reach a peak in the S phase, promoting cell growth. Proliferation. Previous studies by our research group found that hypoxia can increase the expression level of HIF-1 α in HPH neonates and animals[39-40]. In animal models of chronic HPH, pulmonary hypertension is partly caused by HIF activation in PASMCM (pulmonary vascular smooth muscle cells), causing PASMCM hypertrophy, suggesting that the development of HPH is related to HIF-1 α [41]. In addition, the activation of HIF-1 α during hypoxia leads to decreased potassium channel expression and increased Ca²⁺ concentration in PASCs, causing increased cytosolic calcium concentration and pulmonary vasoconstriction, with concomitant vascular remodeling leading to pulmonary hypertension [42-44]. The previous research of the research group of this paper found that the adenovirus-mediated overexpression of Hsp70 in HPH neonatal rats exogenously increased the expression of Hsp70 in PVEC, promoted the degradation of HIF-1 α and reduced the expression of ET-1 iNOS to constrict blood vessels Factor imbalance, attenuated pulmonary vascular remodeling, resulting in lower pulmonary arterial pressure [40]. Professor Chen and other researchers [45] found that HIF-1 α can regulate mitochondrial dynamics in pulmonary vascular remodeling under hypoxic conditions by directly regulating the expression of Drp1 (dynein-related protein 1), causing hypoxia-induced mitochondrial dysfunction and PASMCM proliferation and apoptosis. Researchers such as Luo have confirmed that the adhesion molecule CD146 and HIF-1 α can promote pulmonary vascular remodeling through the NF- κ B pathway. When the CD146/HIF-1 α axis is inhibited, vascular remodeling slows down, and PAH is improved. In addition, the hyperproliferation of PASMCM after exposure to growth factors such as epidermal growth factor, EGF, FGF2, and PDGF may also be mediated by HIF-1 α . Professor Cheng showed that phenethyl caffeate could significantly inhibit monocrotaline-induced vascular remodeling by reducing the expression of HIF-1 α and the production of PDGF-BB and improving the vasoconstriction ability of rats. In addition, phenethyl caffeate suppressed the expression of HIF-1 α induced by hypoxia and PDGF-BB by blocking the AKT/ERK pathway, thereby inhibiting the proliferation of human pulmonary artery smooth muscle cells and preventing the cells from resisting apoptosis.

5. Conclusion

The occurrence and development of the PDGF-BB/ERK/HIF-1 α signaling pathway in pulmonary hypertension are not completely clear in recent years. However, many studies have shown that PDGF-BB/ERK/HIF-1 α signaling pathway plays an essential role in pulmonary hypertension. There will be some results in the animal model. However, the HPH animal model is different from the

complex situation of the human body, and it isn't easy to push the experimental results in the animal model to the human body. In the future, relevant studies are still needed to verify the mechanism of action of regulators targeting the PDGF-BB/ERK/HIF-1 α signaling pathway in humans. Through a deeper understanding of the mechanism of this signaling pathway, new solutions will be provided for the study of the pathogenesis and treatment of pulmonary arterial hypertension.

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