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Review Article

The Role and Regulation of Pulmonary Artery Smooth Muscle Cells in Pulmonary Hypertension

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Pulmonary hypertension (PH) is one of the most devastating cardiovascular diseases worldwide and it draws much attention from numerous scientists. As an indispensable part of pulmonary artery, smooth muscle cells are worthy of being carefully investigated. To elucidate the pathogenesis of PH, several theories focusing on pulmonary artery smooth muscle cells (PASMC), such as hyperproliferation, resistance to apoptosis, and cancer theory, have been proposed and widely studied. Here, we tried to summarize the studies, concentrating on the role of PASMC in the development of PH, feasible molecular basis to intervene, and potential treatment to PH.

1. Introduction

Pulmonary hypertension (PH) is a serious global health problem, which is characterized by progressing elevated pulmonary pressures and right heart failure, and mainly affects childbearing women [1]. The mean time from onset of symptoms to diagnosis is about 2 years, the mean survival time of idiopathic/heritable pulmonary arterial hypertension patients from treatment initiation is about 14.7 years, and the 10-year survival rates are 69.5% [2, 3]. Based on recent estimates, in the global population, the prevalence of PH is about 1%, while for individuals aged over 65 years, the number increases to 10%. What is more, about 80% of PH patients are living in developing countries [4].

The feature of PH is intense remodeling of small pulmonary arteries by myofibroblast and smooth muscle cell proliferation, and for familial pulmonary arterial hypertension, the bone morphogenetic protein type II receptor (BMPR-II) mutation in pulmonary artery smooth muscle cells contributes to abnormal growth responses to the transforming growth factor (TGF)-beta/bone morphogenetic protein (BMP) [5]. Compared to previous belief that vasoconstriction acts a vital role in PH pathogenesis [6, 7], there is a tendency to think that excessive proliferation and resistance to apoptosis of PASMC and pulmonary artery endothelial cells (PAEC) are the crucial components of pulmonary vascular remodeling [8]. PASMC has been widely proved to play an important role in the development of various types of pulmonary hypertension. Different mechanisms finally lead to uncontrolled proliferation of PASMC through apoptosis resistance, activated hypoxia-induced factor (HIF), HDAC modification, and inflammation, resulting in pulmonary hypertension [9, 10].

According to similar pathophysiological mechanisms, clinical presentation, haemodynamic characteristics, and therapeutic management, the clinical classification of PH is intended to categorize multiple clinical conditions into five groups [11]. Here, we mainly talk about WHO group 1 pulmonary arterial hypertension (PAH). To offer more suitable treatment and precisely evaluate patients' clinical outcome, the following parameters appear to have the greatest predictive capability: functional class, six-minute walk distance (6MWD), N-terminal pro-brain natriuretic peptide/brain natriuretic peptide (NT-proBNP/BNP) levels, cardiac index, right atrial pressure, and mixed venous oxygen saturation (SvO2) [12, 13]. Specific drug treatment of WHO group 1 PAH by targeting the nitric oxide, endothelin, and prostaglandin pathways has been the standard since

2003. Recently, based on different risk stratification, monotherapy or dual-combination therapies, including macitentan and sildenafil, riociguat and bosentan, selexipag and endothelin receptor antagonist (ERA) or phosphodiesterase inhibitor (PDE5i), or both, are recommended [14, 15].

2. Histopathology of Lungs in PH

2.1. Histology of Normal Lung Vessels. The major role of the right ventricle (RV) is to pump all the blood it receives per beat into the pulmonary circulation without elevating right atrial pressure. Normally, blood flow varies with minimum changes in pulmonary arterial pressure. Although the total compliance of the pulmonary circulation is about one-seventh that of the systemic circulation, it stores much less blood and has the ability to collapse pulmonary vessels as well as have them distended. Thus, the pulmonary circulation is able to accommodate increased blood volumes without increasing pulmonary artery pressure as much as would occur on the systemic circulation [16, 17].

2.2. Histopathology of PAH Lung Vessels. In 1958, Heath and Edwards [18] first described the histologic features of hypertensive pulmonary vascular structure changes into six grades in patients with congenital septal defects of the heart. The six grades included retention of fetal type pulmonary vessels, medial hypertrophy with cellular intimal reaction, progressive fibrous vascular occlusion, progressive generalized arterial dilatation with the formation of complex dilatation lesions (plexiform lesions), chronic dilatation with formation of numerous dilatation lesions and pulmonary hemosiderosis, and necrotizing arteritis. It is widely accepted that higher grade is related to worse pulmonary vessels and right heart function. Compared to the control groups, intima and intima plus media fractional thicknesses of pulmonary arteries were increased in the PAH group, in accordance with pulmonary haemodynamic measurements. There were remarkable perivascular inflammation in a mass of PAH lungs and correlated with intima plus media remodeling [19].

Pulmonary vasoconstriction caused by hypoxia was studied widely in PH [7]. As a result of global pulmonary hypoxic vasoconstriction, the right ventricular afterload could increase. Chronic hypoxia-induced PH is partly due to initial pulmonary artery contraction. Pulmonary artery pressures are higher in high-altitude dwellers with chronic mountain sickness, a syndrome including dyspnoea, fatigue, poor sleep, headache, and cyanosis. Hypoxic pulmonary vascular remodeling also contributes to PH and begins to develop within the first hours of hypoxic exposure. Hypoxia-induced PH in humans or animals is generally mild or moderate, but with a substantial afterload on the right ventricle during exercise. In vitro, hypoxia was reported to inhibit myocardial fibre contractility. Pulmonary vascular contraction plays an important role not only in hypoxic PH, but also in pulmonary arterial hypertension (PAH). Current pharmacological therapies for PAH mostly target pathways regulating endothelial factors with vasoconstrictive/vasodilatory and have made great achievements in improving the exercise capacity, haemodynamics, and time to clinical worsening of PAH patients.

It is increasingly believed that although vasospasm acts a role, pulmonary hypertension is an obstructive lung panvasculopathy and different forms of PH present with either a predominance of pulmonary arterial remodeling or vein remodeling or a variable contribution of both [20]. Obviously, there is medial and adventitial thickening of the pulmonary muscular and elastic vessels. The medial thickening is believed to result in hypertrophy and increased accumulation of smooth muscle cells as well as increased deposition of extracellular matrix proteins, predominantly collagen and elastin. The extent of structural changes, including SMC proliferation, hypertrophy, matrix protein production, and recruitment of adventitial or circulating cells, in the medial compartment of the pulmonary arterial wall partly determined the severity of chronic hypoxic pulmonary hypertension [21].

3. The Alteration of PASMC in PH

Data from post-mortem studies demonstrated medial hypertrophy, PASMC hyperproliferation, and muscle extension into distal arterioles, with important variability between individuals [22–25]. The accurate regulation of the balance between PASMC proliferation and apoptosis is significant in maintaining the normal integrity of structure and function in the pulmonary vessels. However, in severe angioproliferative PAH, this balance seems to be broken, following increased PASMC proliferation and decreased apoptosis, resulting in vessel wall thickening and vascular remodeling [26–31]. Contrast to previous belief that the relationship between pulmonary artery endothelial cells (PAEC) and PASMC is a simple one-way interaction from the endothelium to the PASMC, now it is more likely to believe that more complicated interactions exist between them [32–34]. Under abnormal or irritant conditions, the intricate interaction of PAEC and PASMC can be altered in the long term so that vascular proliferation and vasocontractility are enhanced further, which leads to PAH and right heart failure [35–38]. Owing to the characteristics of hyperproliferation and resistance to apoptosis of PASMC in PAH, there is an argument that PAH has something to do with cancer. At the molecular level, PASMC of PAH exhibits many features similar to cancer cells, which gives the chance to explore potential therapeutic treatments used in cancer to cure PAH [8, 39, 40].

4. Possible Pathways to Act on PASMC

4.1. Role of Ion Channels. It is well known that ions play many important roles in cell potential, cell contraction, and pH homeostasis, which can influence the proliferation and apoptosis of PASMC. Some studies demonstrated that decrease of K^+ channels affected the PASMC depolarization, then facilitated vascular remodeling, and inhibited PASMC apoptosis. In PAH rat models, restoration of K^+ channels activity and expression, using dehydroepiandrosterone or

dichloroacetate, reduced pulmonary vascular remodeling. However, the exact mechanisms by which K^+ channels act on PASMC are still controversial [41–51]. Lv et al. found increased expression of MicroRNA-206 suppressed potassium voltage-gated channel subfamily A member 5 (Kv1.5) and promoted the PASMC proliferation [52].

The elevated concentration of intracellular Ca^{2+} was found in PAH animal models and patients. This kind of phenomenon was not realized through activation of voltage-gated calcium channels (VGCC), but by increase of canonical transient receptor potential (TRPC) proteins, which involved Ca^{2+}-permeable nonselective cation channels (NSCCs). Increased abundance of NSCCs was detected in PAH rat models and patients and inhibition of NSCCs, either pharmacologically or by RNA silencing, effectively decreased the concentration of intracellular Ca^{2+} and proliferation of PASMC [53–61]. Song et al. reported that stromal interaction molecule 2 (STIM2) protein, a Ca^{2+} sensor in the sarcoplasmic reticulum (SR) membrane, may contribute to elevated intracellular Ca^{2+} [62]. What is more, Ca^{2+} could activate nuclear factor of activated T-cells (NFAT), then suppress K^+ channels expression, and lead to PASMC hyperproliferation [63]. It was also proved that hypoxia can cooperate with intracellular Ca^{2+}, which increased the expression of aquaporin 1 (AQP1), a membrane water channel, indispensable for PASMC migration. Increased AQP1 upregulated β-catenin and its target genes (such as c-Myc and cyclin D1), which accelerated the proliferation and migration of PASMC [64–66].

The normal operation of Na^+/H^+ exchange (NHE) is essential to keep pH homeostasis of PASMC [67, 68]. Studies showed that increased expression of NHE isoform 1 (NHE1) can promote the exchange, elevate the pH, and induce the proliferation and migration of PASMC. Although the specific mechanisms are still unclear, it may have something to do with p27 (a cyclin-dependent kinase inhibitor), E2F1 (a nuclear transcription factor), and cytoskeletal re-arrangement [69–75].

4.2. Crucial Molecules. When we talk about PAH, we should never miss hypoxia and hypoxia-inducible factors (HIF). Under the circumstances of hypoxia, increased expression and decreased degradation result in accumulation of HIF-1α. A lot of studies proved that HIF-1α can influence the PASMC proliferation and mediate pulmonary vascular remodeling, by acting on Ca^{2+}, pH homeostasis, endothelin-1 (ET-1), vascular endothelial growth factor (VEGF), and Warburg effect [76–84].

Endothelin is secreted by endothelial cells and has three isoforms, among which endothelin-1 (ET-1) is the most widely expressed and mediates vascular contraction, cell migration, and proliferation. In terms to PASMC, ET-1 binds to ET_A or ET_B and then has an impact on decreased K^+ channels, elevated intracellular Ca^{2+}, and activation of NHE1 and Rho kinase (ROCK) signaling, leading to the migration and proliferation of PASMC [85–88].

5-Hydroxytryptamine (5-HT) is well known in depression mechanism and it also takes part in the development of PAH. 5-HT enters PASMC through serotonin transporter (SERT). The signaling cascades caused by 5-HT include increased reactive oxygen species and activation of mitogen-activated protein kinase (MAPK) and ROCK pathway, which regulate the expression of genes targeting cell growth and influence PASMC [89–93].

4.3. Important Pathways

4.3.1. Rho Kinase. Rho kinase (ROCK) signaling pathway plays an indispensable part in vascular contraction and remodeling. Exposed to hypoxia, activation of ROCK in PASMC through Rho B (upstream activators of ROCK) could augment the proliferation and migration of PASMC, resulting in increased pulmonary vascular resistance. There were studies stating that long-term use of ROCK inhibitors could ameliorate vascular remodeling [94–103]. Abe et al. reported that PDGF activated ROCK, suppressed the translocation of Smad1 originally induced by bone morphogenetic protein 2 (BMP 2), and increased PASMC proliferation [104].

4.3.2. BMP Signaling. Bone morphogenetic protein receptor type 2 (BMPR2) mutations are present in patients with heritable and idiopathic PAH, which reminds us of BMP signaling's significant role in the development of PAH. The mutation of BMPR2 could inhibit the antiproliferation effect of BMP2, leading to PAH. BMP can exert its function in a way of Smad dependent or independent. BMP/BMPR1 interacts with Smad1/5/8, then increasing their binding with Smad4, finally leading to elevated related genes expression. In other ways, BMP activates MAPK, PI3K/AKT, or protein kinase C (PKC) to influence PASMC. The impaired control of BMP signaling may be a common characteristic of PH no matter what the pathogenesis is [105–110] (Figure 1).

4.3.3. Cancer Theories. As mentioned above, at the molecular level, PASMC of PAH exhibits many features similar to cancer cells, making it possible to explore potential therapeutic treatments used in cancer to cure PAH (reviewed in [40]). Studies showed increase of IL-6, monocyte chemotactic protein 1 (MCP-1), and tumor necrosis factor alpha (TNF-α) related to worse clinical outcomes in PAH patients. IL-6 knockout effectively ameliorated PAH in animal models. Platelet-derived growth factor (PDGF) mediated mitogenic signaling and thickening of the pulmonary vascular media. These growth factors and inflammatory mediators eventually have an impact on cell growth and survival by MEK/ERK, PI3K/AKT, or JAK/STAT3 pathways. In PASMC, it was reported that activation of STAT3 can upregulate the expression of proviral integration site for Moloney murine leukemia virus-1 (PIM-1) and then enhance NFAT-mediated transactivation, resulting in decreased K^+ channels and increased intracellular Ca^{2+}. In addition, activation of PI3K/AKT and JAK/STAT3 inhibited the transcription factor Forkhead box protein O1 (FOXO1), causing elevated Cyclin B1 and D1 and decreased p27, which promoted PASMC proliferation [48, 111–122].

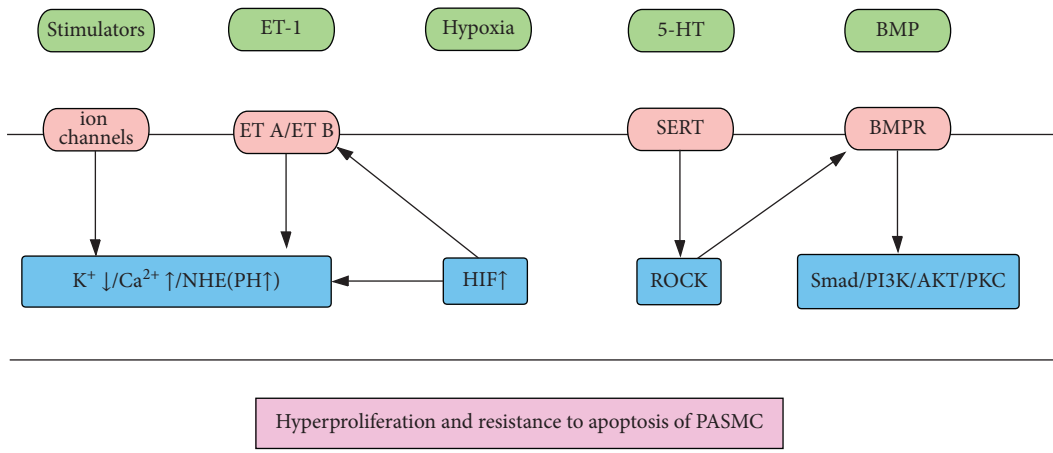

Figure 1: Molecular pathways in PASMC (1). ET-1: endothelin-1, 5-HT: serotonin, BMP: bone morphogenetic proteins, ET A/ET B endothelin receptor A/B, SERT: serotonin transporter, BMPR: bone morphogenetic proteins receptor, NHE: Na^+/H^+ exchanger, HIF: hypoxia-induced factor, ROCK: Rho kinase, PI3K/AKT: phosphatidylinositide 3-kinase/protein kinase B, PKC: protein kinase C.

Mammalian target of rapamycin (mTOR) signaling plays important roles in cell metabolism, cell proliferation, and survival. Together with other proteins, mTOR forms two independent complexes, mTORC1 (mTOR-Raptor) and mTORC2 (mTOR-Rictor). Activation of mTORC1 could enhance ribosomal protein S6 kinase beta-1 (S6K1) and suppress eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), which facilitates cell growth and proliferation. On the other hand, mTORC2 is more likely to respond to growth factors, increasing cell survival [123–125]. However, Tang et al. reported that mTORC1 and mTORC2 had different roles in the development of PAH. Inhibition of mTORC1 ameliorated pulmonary hypertension, while inhibition of mTORC2 facilitated spontaneous pulmonary hypertension and it may result from upregulation of PDGF receptors in PASMC [126].

The Hippo signaling pathway is believed to relate to controlling organ size. It is constitutive of a cascade of tumor suppressive kinases mammalian STE20-like protein kinase 1/2 (MST1/2) and large tumor suppressor homolog 1/2 (LATS1/2), while its downstream molecules include yes-associated protein 1 (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ). Inactivation of LATS1/2 leads to decrease of YAP and TAZ in cytoplasm and activation of HIF-1α and Notch3 pathways, which plays a deleterious role in the development of PAH [127–133].

Most cancer cells rely on aerobic glycolysis, instead of depending on mitochondrial oxidative phosphorylation to generate energy, a phenomenon termed "the Warburg effect." This effect also can be seen in PASMC and PAH. Driven by HIF activation, augmented glycolysis is characterized by elevated expression of pivotal proteins in its pathway, such as glucose transporters, hexokinase, pyruvate dehydrogenase kinase (PDK), lactate dehydrogenase (LDH), and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3). By interacting with PI3K/AKT, ERK1/2, and HIF-1α and altering the morphology and subcellular distribution of mitochondria, Warburg effect increases the proliferation of PASMC in PAH [10, 134–144].

4.3.4. Other Pathways. Peroxisome proliferator-activated receptor γ (PPARγ) regulates mitochondrial gene expression and biogenesis. Loss of PPARγ leads to derangement in mitochondrial structure and function, which has a harmful impact on PASMC and PAH [145]. Xie et al. stated that leptin effectively ameliorated pulmonary vascular remodeling and PAH, via activation of ERK1/2 and elevated expression of early growth response-1 (Egr-1), resulting in loss of PPARγ [146]. In addition, Li et al. reported that activating prostanoid EP4 receptor (EP4) also decreased the expression of PPARγ through protein kinase A (PKA) pathway and attenuated pulmonary arterial remodeling [147] (Figure 2).

Cyclin-dependent kinases (CDK) are crucial regulators of cell cycle and proliferation. Dinaciclib and palbociclib inhibited specific CDK and decreased PASMC proliferation via cell cycle arrest and interacted with the downstream CDK-Rb (retinoblastoma protein)-E2F signaling pathway, offering a potential strategy in PAH [148]. Sphingosine kinase 1 (SphK1) is a lipid kinase for phosphorylating sphingosine to generate sphingosine-1-phosphate (S1P). SphK1/S1P have been reported to relate to cell proliferation, migration, and survival. TGF-β1 could phosphorylate Smad2/3 and then elevate the expression of SphK1 and S1P, which activates Notch3 pathway to promote PASMC proliferation [149]. What is more, Sysol et al. reported that decreased micro-RNA-1 induced by hypoxia had an effect on the development of PAH via regulation of sphingosine kinase 1 [150].

5. Potential Treatment to PAH

While calcium channel blockers, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors and guanylate cyclase stimulators, prostacyclin analogues, and prostacyclin receptor agonists are the classical specific drug therapies for PAH, their effects still are limited and unsatisfactory. Based on the molecular pathways mentioned above, tyrosine kinase inhibitors (platelet-derived growth factor inhibitors) and serotonin antagonists are being explored, but present

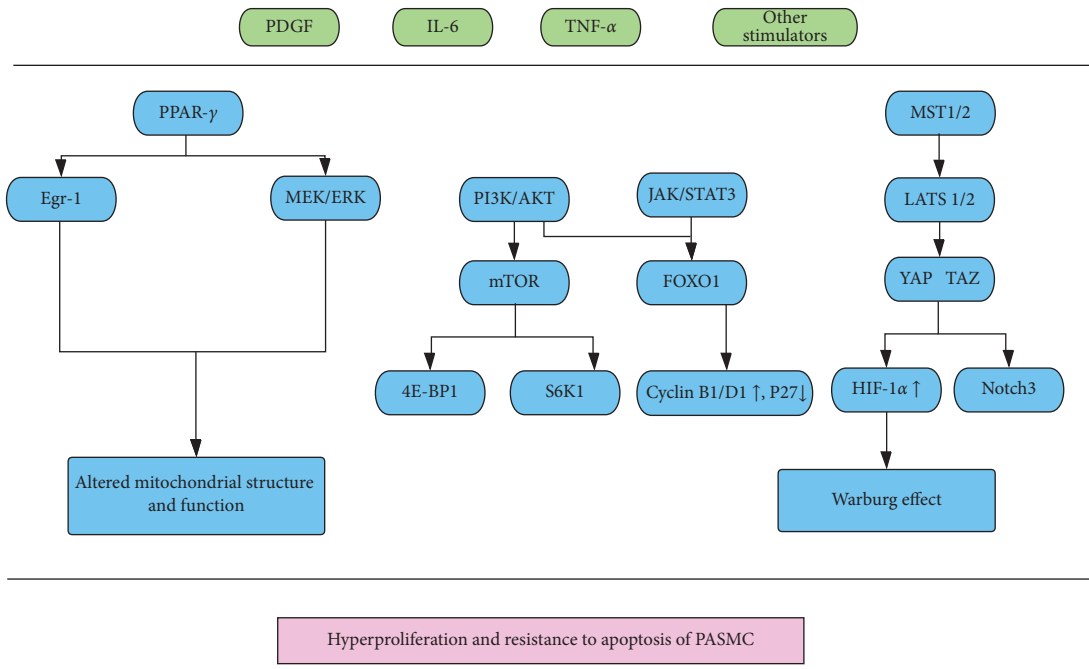

Figure 2: Molecular pathways in PASMC (2). PDGF: platelet-derived growth factor, IL-6: interleukin-6, TNF-α: tumor necrosis factor-α, PPAR-γ: peroxisome proliferator-activated receptor-γ, MST 1/2: mammalian sterile 20-like kinases 1/2, Egr-1: early growth response-1, MEK/ERK: mitogen-activated protein kinase/extracellular-signal regulated kinase, PI3K/AKT: phosphatidylinositide 3-kinase/protein kinase B, JAK/STAT3: Janus kinase/signal transducer and activator of transcription 3, LATS 1/2: large tumor suppressor kinases 1/2, mTOR: mechanistic target of rapamycin, FOXO1: forkhead box protein O1, YAP: yes-associated protein, TAZ: transcriptional coactivator with PDZ-binding motif, 4E-BP1: eukaryotic translation initiation factor 4E-binding protein 1, S6K1: ribosomal protein S6 kinase beta-1, HIF-1α: hypoxia-induced factor-1α.

outcomes are not ideal. Moreover, ROCK inhibitors, VEGF receptor inhibitors, stem cell therapy, mTOR inhibitors, PPAR-γ agonist, and strategies aiming at Warburg effect are all in the early phase of research [15, 142–144, 151, 152].

6. Summary

Although the treatment for pulmonary hypertension has achieved great improvement, it is still not that satisfactory. Owing to its indispensable role in the development of pulmonary hypertension, PASMC becomes the research hot spot in PH. Further elucidating the molecular basis of PASMC, including ion channels, HIF, ET-1, ROCK, BMP, PPAR-γ, and Warburg effect, could bring hope to PH treatment.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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