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Emerging insights into pulmonary hypertension: the potential role of mitochondrial dysfunction and redox homeostasis

Junming Zhang[1] · Huimin Yan[1] · Yan Wang[1] · Xian Yue[1] · Meng Wang[1] · Limin Liu[1] · Pengfei Qiao[1] · Yixuan Zhu[1] · Zhichao Li[1]

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Abstract
Pulmonary hypertension (PH) is heterogeneous diseases that can lead to death due to progressive right heart failure. Emerging evidence suggests that, in addition to its role in ATP production, changes in mitochondrial play a central role in their pathogenesis, regulating integrated metabolic and signal transduction pathways. This review focuses on the basic principles of mitochondrial redox status in pulmonary vascular and right ventricular disorders, a series of dysfunctional processes including mitochondrial quality control (mitochondrial biogenesis, mitophagy, mitochondrial dynamics, mitochondrial unfolded protein response) and mitochondrial redox homeostasis. In addition, we will summarize how mitochondrial renewal and dynamic changes provide innovative insights for studying and evaluating PH. This will provide us with a clearer understanding of the initial signal transmission of mitochondria in PH, which would further improve our understanding of the pathogenesis of PH.

Keywords Pulmonary hypertension · Mitochondrial dysfunction · Mitochondrial biogenesis · Mitophagy · Mitochondrial dynamics · Mitochondrial unfolded protein response · Mitochondrial redox homeostasis

Introduction

Pulmonary hypertension (PH) is characterized by excessive obliterative pulmonary vascular remodeling defining an abnormal elevation in mean pulmonary arterial pressure (mPAP) to ≥ 20 mmHg and the need for pulmonary vascular resistance (PVR) to ≥ 3 Wood units (WU) to define the presence of pre-capillary PH [1, 2]. World Symposium on Pulmonary Hypertension (WSPH) further divides PH into five clinical categories based on the latent etiology, and the 5-year survival rates of the first four types in newly diagnosed patients are 72.2%, 71.7%, 60.0%, and 43.8%, respectively, in the Registry to Evaluate Early and Long-Term PH Disease Management (REVEAL) [3]. The delay in curing PH arising from virus infection, hypoxia, congenital anomaly, and secondary disease associations may be related to the undefined pathological mechanism [1]. Recently, several lines of evidence suggest that the dysregulation of mitochondrial redox status also contributes to the pathogenesis of PH. Moreover, current treatments cannot reverse or prevent pulmonary vascular remodeling and vasoconstriction, leading to a progressive elevation of pulmonary arterial pressure (PAP) and subsequent right ventricular (RV) heart failure and mortality. Therefore, it will be urgent to develop new treatments that will be capable of addressing orchestrate these different types of PH, which would further alleviate the stress caused by PH in clinical treatment.

Mitochondria, often referred to "the power factory of the cell", are ubiquitous and crucial organelle in mammalian cells, driving reactions to produce core metabolites essential for the biosynthesis of fats, carbohydrates, nucleotides, and proteins [4, 5]. One of their primary functions is to facilitate the oxidative capacity of the electron transport chain (ETC), which consists of four linked membrane protein complexes, known as complexes I, II, III, and IV [6, 7]. Additionally, the release of reactive oxygen species (ROS) from mitochondria (mROS) stimulates neighboring mitochondria to release more ROS, a phenomenon known as "Reactive Oxygen Species (ROS)-induced ROS-release" (RIRR), creating a closed-loop redox signal in the cell [8]. In the context of PH, its pathological manifestations are largely linked to mitochondrial dysfunction, including imbalance mitochondrial membrane potential, misfolded mitochondrial proteins and

✉ Zhichao Li
lizhic@fmmu.edu.cn

[1] Faculty of Life Science & Medicine, Northwest University, Xi'an 710127, Shaanxi, China

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changes in mitochondrial morphology [9–13]. Against this backdrop, persistent mitochondrial dysfunction contributes to dysfunction of various pulmonary vascular cells (PVCs), such as the apoptosis of pulmonary artery endothelial cells (PAECs) and the proliferation of pulmonary artery smooth muscle cells (PASMCs), which are inexorably linked to key pathogenetic mechanisms [14–16].

PH could lead to induce right heart failure and vascular remodeling, highlighting the importance of finely controlling mROS production, overload of calcium ions (Ca^{2+}), and selective degradation and elimination of dysfunctional mitochondria through mitophagy. Simultaneously mitophagy could eliminate damaged misfolded mitochondrial proteins, or portions of the mitochondrial network, and updates components by adding proteins and lipids through biogenesis, which together lead to mitochondrial turnover. The turnover process led by mitophagy is also known as mitochondrial quality control (MQC). This means that MQC plays a crucial role in PH, and targeting their reversible functional suppression (Fig. 1) could be a therapeutic focus, improving energy deficits, tissue loss, and facilitating cell repair and cell replacement. In addition, clinical trials of antioxidant strategies against PH have been lackluster, which may be due to the uncontrolled involvement of mROS in cell signaling and reoxidation as the second messenger [17]. Therefore, the following sections will delve into discussions on mitochondrial biogenesis, mitochondrial fission/fusion, mitophagy, mitochondrial unfolded protein response and redox reactions related to mROS, elucidating the irreplaceable role of MQC and redox homeostasis in the lung vasculature as a potential cornerstone of novel PH treatments. By comprehending how PH leads to cell dysfunction and vasculopathy, researchers are uncovering the pathogenesis of PH and identifying new pathways in cell biology.

Mitochondrial biogenesis in pulmonary hypertension

Mitochondrial biogenesis adjusts mitochondrial mass, distribution, and phenotype involved a bi-genomic program of nuclear-and mitochondrial-encoded genes that are rapidly activated by decreased energy supply or augmented ATP demand [18]. This implies that mitochondrial biogenesis plays a key role in body homeostasis and proliferation, as well as acting as a rescue mechanism under stress conditions. It's demonstrated that mitochondrial biogenesis is served as an impetus for PAECs and PASMCs proliferation under ongoing stimulation of hypoxia in the pathological

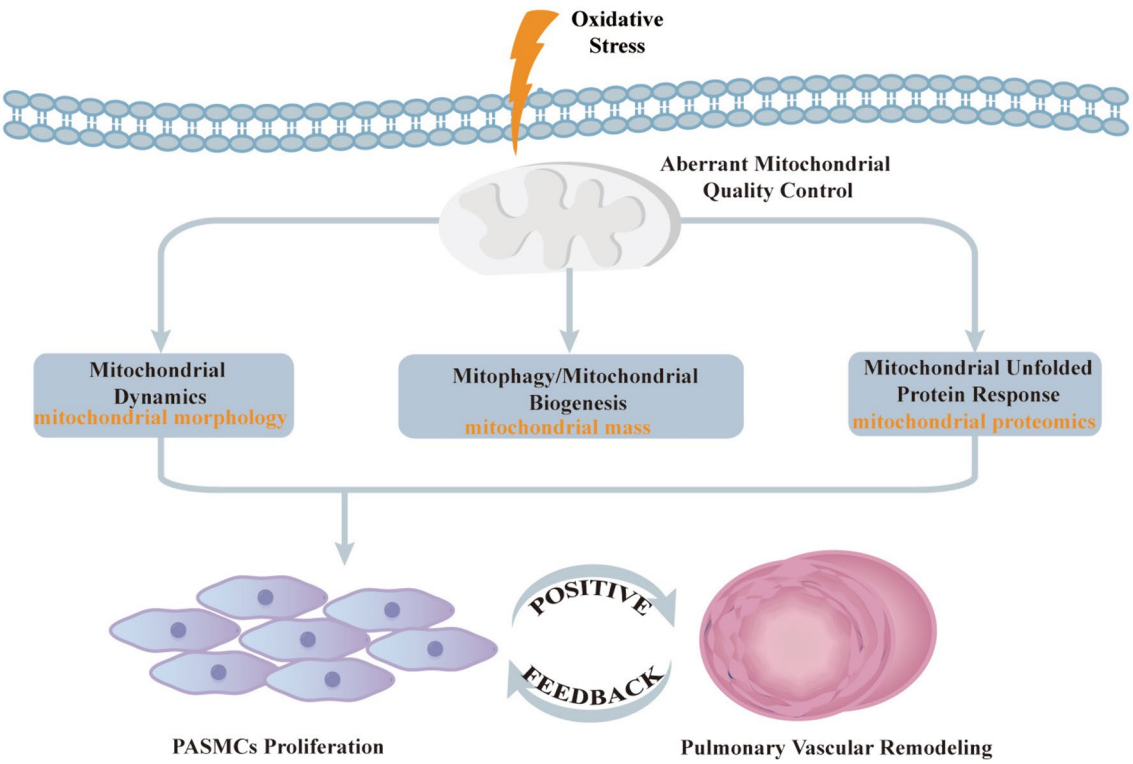

Fig. 1 Under oxidative stress conditions, mitochondrial dynamics could make mitochondria fragment, driving the change of mitochondria morphology. Following, mitochondrial biogenesis, mitopahgy and mitochondrial unfolded protein response are activated to govern mitochondrial content and mitochondrial proteomics, respectively. Unrepairable mitochondria would induce PASMCs proliferation, thus promote the process of pulmonary artery vascular remodeling

PH [19]. The widely regulated molecular in mitochondrial biogenesis is mainly the peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1α) family. PGC-1α of transcriptional co-activators play a major role in transducing and integrating pathophysiological signals controlling mitochondrial biogenesis that is followed by PASMCs proliferation, survival and pulmonary vascular remodeling [20]. Conceptually, therefore, PGC-1α related mitochondrial biogenesis is not only bonded up with energy production and compensated mitochondrial dysfunction dealing with the blows from the external.

PGC-1α-regulated mitochondrial biogenesis is generally accompanied by PASMCs proliferation phenotype and PAECs apoptosis phenotype, coming to regulate pulmonary arterial remodeling and right heart failure (Fig. 2). Coordinately, PGC-1α, independent of its own transcriptional activity, could be enabled to combine with the coordinated transcription of the majority of mitochondrial genes in the nucleus, such as peroxisome proliferator-activated receptor γ (PPARγ) and nuclear respiratory factors (NRFs) [21–24]. PPARγ, a member of the nuclear hormone receptor superfamily of ligand-activated transcription factors, activates the promoter of PGC-1α to ameliorate mitochondrial biogenesis and reverse metabolism derangements [25, 26]. The following scenarios by which reductions in PPARγ decreases the overall volume of mitochondria and increases fragmentation of existing mitochondria could contribute to the impaired mitochondrial biogenesis [23]. In addition, NRFs regulate the expression of proteins that make up the four respiratory complexes and regulate the expression of transcription factor A mitochondrial (TFAM), encoding mtDNA transcription and replication [27]. Although mtDNA only encodes certain mitochondrial proteins, fine-tuning the matching between mtDNA duplication and nucleus-encoded genes translation is contributed to mitochondrial biogenesis [28]. This means that the regulation of PGC-1α and its related factors could also control mitochondrial biogenesis and thus mitigate the pathological workload of PH.

The following would overview the protective mechanism of PGC-1α on PASMCs that mainly focus on curtailing

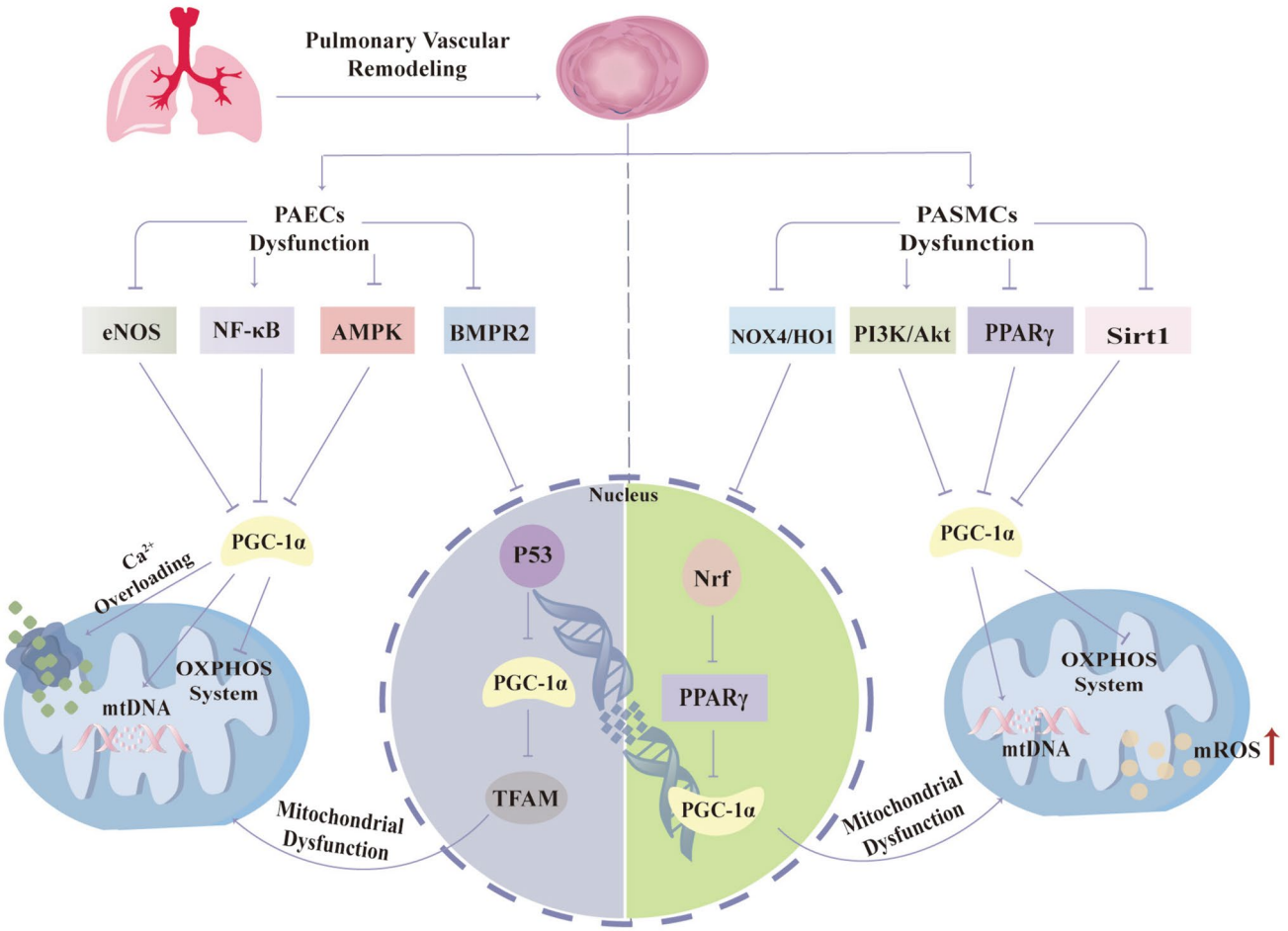

Fig. 2 The dysfunction of PASMCs and PAECs induced by vascular remodeling activate signaling cascades, leading to activate PGC-1α compensated regulation

proliferation properties. As an NAD^+-dependent deacetylase, nucleoprotein sirtuin 1 (Sirt1) could alter the balance between acetylation and deacetylation under hypoxia, as the result that it have also been implicated in significant role in pulmonary arterial hypertension (PAH) [29]. Sirt1 is a negative regulator of PASMC growth extracted in human PAH as well as in rat. Sirt1 activation leads to the tendency of PASMC phenotype normalization, the augmentation of PGC-1α and its downstream targets involved in the pathogenesis of PAH, which is essential for mitochondrial biogenesis and pulmonary arteries remodeling [30]. And Sirt1-specific activator Stac-3, induces a concerted upregulation of various factors controlled by PGC-1a that would contribute to abolishing the proliferation of PASMCs in rat. Mechanistically, as the center molecule of mitochondrial biogenesis, knockdown of PGC-1α could be also regulated by PI3K/Akt signaling pathway and further inhibit hypoxia-induced DNA synthesizing, cell viability, and PCNA expression of PASMCs in response to hypoxia stress [22, 31]. Also, ormeloxifene treatment improves NOX4/HO1 axis and attempted to recover hypoxia-induced mitochondrial membrane hyperpolarization, suggesting it has some positive effect on mitochondrial biogenesis in monocrotaline-induced PH in female rats [24]. Notably, PGC-1α appears to be as a potential biomarker of the progression of idiopathic pulmonary artery hypertension (IPAH), supporting its role in protecting pulmonary arteries [32]. Once the cascade reaction PPARγ and PGC-1α is reversed by short interfering RNA, PASMCs proliferation induced by mitochondrial function derangements could be improved [23], suggesting a feedback mechanism underlying PGC-1α-mediated mitochondrial biogenesis and hypoxia-stimulated pulmonary vascular relaxation.

Several potential operating mechanisms could be summarized to explain the molecular contributions of PGC-1α-mediated mitochondrial biogenesis to pulmonary artery endothelial protection (Fig. 2). This implies that regulated endothelial angiogenesis, vasoconstriction, inflammation, and energy relationships could ensure the opening of microvessels and provide anticoagulant action to avoid thrombosis. First, PGC-1α-related mitochondrial biogenesis controls angiogenesis and vascular integrity through multiple signaling pathway. Bone morphogenetic protein receptor II (BMPRII) have plays an irreplaceable role in different animal models of PAH pathogenesis, such as monocrotaline (MCT) and the SuHx rat models [33]. As a known regulator PGC-1α, P53 alters TFAM basing on the reduction of BMPR2, which mediates mtDNA replication as well as maintain and repair in PAECs from PAH patients [11, 34, 35]. On the side, a YAP1 mutant construct, YAP1S127A, stimulates the overexpression of PGC-1α to maximize angiogenic ability and minimize the potential toxicity [36]. Second, inflammation response, as evaluated by NF-κB activation as well as endothelial cells dysfunction, seems to have rectified by enhanced PGC-1α, which confers resistance to cellular derangements associated with mitochondrial biogenesis [37]. Third, vasodilator nitric oxide (NO) is initially identified as a vasodilator and inhibitor of SMC proliferation produced by NO synthetase (eNOS), but it has gradually been found to regulate mitochondrial biogenesis and function by binding to the mitochondrial respiratory chain [38–40]. It has been reported that excessive eNOS can improve mitochondrial dehydrogenase activity, number of pre-mitochondrial cells and mtDNA content in PH pathophysiology whereas sustained PGC-1α decreases mitochondrial swelling and increases eNOS phosphorylation [41, 42]. Furthermore, overexpressing PGC-1α improves endothelium-dependent relaxation and preserves eNOS coupling, suggested a feedback pathway between eNOS and PGC-1α [43]. Those would make to shed a new light on the link of eNOS, mitochondrial biogenesis and pulmonary vascular pathology. Fourth, the inter-cellular energy sensor AMP-activated protein kinase (AMPK) could converge on PGC-1α mainly regulated mitochondrial biogenesis. *Rana* et.al have reported that decreased angiogenesis contributes to persistent pulmonary hypertension of the newborn (PPHN), further abrogating AMPK-PGC-1α cascade reaction and curtail mitochondrial biogenesis in PAECs [44]. Similar results are seen in the animal model of hypoxia pulmonary hypertension (HPH) that hypoxia induces AMPK phosphorylation and decreases in PGC-1α protein levels. In the end, mitochondrial biogenesis is also affected by mitochondrial proteins. Artificially controlled upregulation of Tom70 level in PVECs results in the transfer of mitochondrial biogenesis marker TFAM to mitochondria, improving PVECs function and ultimately alleviated HPH. Given its fundamental role in mediating mitochondrial function and its ability to promote PVECs proliferation, abnormal mitochondrial biosynthesis represents an increasingly promising diagnostic and therapeutic target in PH.

It's summarized that some drugs or compounds affect mitochondrial biogenesis by the target PGC-1α and then alter PH physiological and pathological progression (Table 1). 15-Hydroxyeicosatetraenoic acid (15-HETE) is a product of arachidonic acid catalyzed by 15-lipoxygenase (15-LO), which stimulates angiogenesis and pulmonary vascular remodeling through PGC-1α-mediated mitochondrial biogenesis in PAH [45]. Estrogen-17, one of naturally occurring hormone in the human body, restores the expression levels of PGC-1α and fuels protective effects on mitochondrial density and oxidative capacity [46]. In the Sugen 5416/hypoxia rat model of severe PH, acetazolamide (ACTZ) treatment, similarity to chrysin, restores metabolic balance and improves RV function through the upregulation of PGC-1α [47, 48]. On the side, paeonol, a natural phenolic compound with bioactive constituents isolated from cortex moutan, could inhibit mitochondrial injuries and

Table 1 Drugs or compounds regulate mitochondrial biogenesis altering PH lesion by the target PGC-1α

Name	Target	Functions	References
15-Hydroxyeicosatetraenoic acid	Increase PGC-1α	Stimulate angiogenesis	[45]
Estrogen-17	Increase PGC-1α	Fuel protective effects on mitochondrial density and oxidative capacity	[46]
Acetazolamide	Increase PGC-1α	Restore metabolic balance and improves RV function	[47]
Paeonol	Increase PGC-1α	Inhibit mitochondrial injuries and cause mitochondrion-independent apoptosis	[50]
Pioglitazone	Increase PPARγ	Normalize epigenetic and transcriptional regulation primarily related to disturbed mitochondrial function in the failing RV	[51]
Oxymatrine	Increase Nrf-2	Activate the cellular endogenous antioxidant protection system	[52]
Pyrroloquinoline quinone	Increase PGC-1α	Attenuate cellular proliferation and promoted apoptosis via a mitochondrial-dependent pathway	[53]

cause mitochondrion-dependent apoptosis through PGC-1α in PASMCs in vitro [49, 50]. In parallel, reversing pulmonary hypertension and preventing RV failure are modified by pioglitazone, oxymatrine through the diversely underlying mechanism [51, 52]. And it's well-documented that pyrroloquinoline quinone (PPQ) improves integrative mitochondrial as well as metabolism by increasing mitochondrial PGC-1α and also prevent the development of PH in MCT treated rats [53]. It's worth noticing that more preclinical studies are expected to test the feasibility of strategy of targeting PGC-1α-related mitochondrial biogenesis for therapy in PH.

The occurrence of PH is not only due to the imbalance of mitochondrial biogenesis, there are other factors that could accelerate the process of PH pathological scenarios, such as fine-tuning mtDNA, Ca^{2+} overloading, energy depletion and inflammation overload [54]. Pulmonary artery obstruction, hypoxia, heart failure and other causes of PH Further researches are needed to investigate the biological function of mitochondria biogenesis in PH. The PH caused by hypoxia, pulmonary artery obstruction, the right heart failure and so on forces the mitochondrial biogenesis disorder, and with resultant triggers the corresponding physiological and biochemical reactions. In the event of sustained damage, the defense system briefly built up by mitochondrial biogenesis collapses after reaching the critical value. This means that mitochondrial biogenesis could partially reverse the impairment of right heart function from the direction of energy metabolism, control of key factors of vasoconstriction, and the environment as a precise therapy. Although there are still many shortcomings in mitochondrial biogenesis research, we are committed to opening new chapters and providing emerging insights for the treatment of PH.

Mitophagy in pulmonary hypertension

The mitochondria are regarded as "good actors" to keep the cellular metabolism and physiology running, and its components, subjected by oxidative damage, are eventually recycled through a specialized autophagic pathway known as mitophagy [55]. Mitophagy, a kind of selective autophagy, refers to the process that once mitochondria are damaged, intracellular signals would be activated to induce autophagy-related proteins to gather in the damaged mitochondria and form autophagosomes with bilayer membrane [56]. Subsequently, the autophagic membrane specifically recognizes and envelops the mitochondria that are energy-impaired or damaged and transports them to lysosomes for catalytic degradation, reducing the release of mitochondrial contents. During this process, damaged or redundant mitochondria in cells are removed, and intracellular ROS generation is reduced, which maintains intracellular mitochondrial homeostasis, normal physiological functions and mitochondrial fidelity. But this is only in the modest range, and once induced excessive mitophagy, its following effects could be devastating before intervention in PH. Three main mechanisms in PH have been summarized to explain the association between mitophagy and pathological characteristics of cells. First, some proteins inside and/or outside mitochondria coordinately or independently regulate mitophagy under oxidative stress. Second, mitophagy is linked with other related cellular biological activities to regulate PAECs apoptosis and PASMCs proliferation. Finally, mitophagy, as the opposite of mitochondrial biogenesis, could control mitochondrial mass, causing the broken oxidative respiratory chain and ATP exhaustion. Recent advances have led to the unraveling of characteristic of mitophagy, which could be divided mainly into receptor-dependent and non-receptor-dependent mitophagy in the ballpark (Fig. 3). Here, we discuss the inter-association between mitophagy and pulmonary vascular remodeling in PH, identifying those underlying molecular mechanisms of PH sensing mitochondrial damage and specific targets for clinical treatment.

Nonreceptor-dependent mitophagy in pulmonary hypertension

As for non-receptor-dependent mitophagy, it's mainly regulated by the phosphatase and tensin homologue

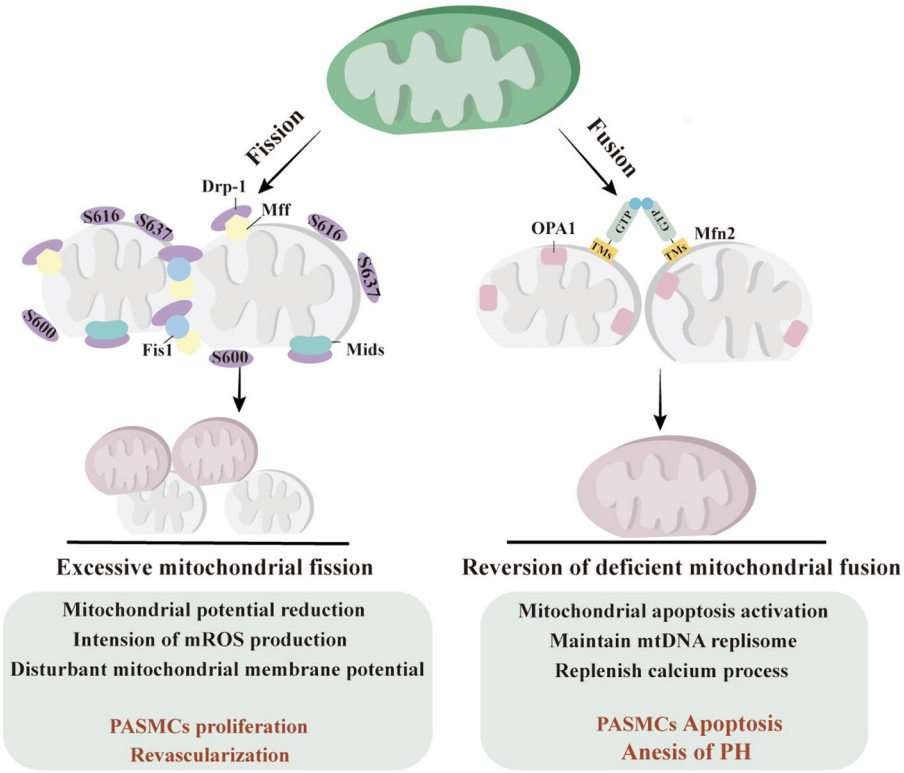

Fig. 3 Mitophagy can be divided into receptor-independent and receptor-dependent forms in general. When healthy mitochondria are stimulated, mitochondrial function is dysfunctional and mitophagy is initiated, forming mitophagosome and degradation by lysosome. Receptor-independent mitophagy is mainly mediated by PINK/Parkin. Meanwhile, Parkin itself binds to LC3 and P62/SQSTM1 initiating mitophagy. The latter activates mitophagy by binding with LC3 and/or Parkin through mitophagy receptors such as BNIP3, NIX and FUNDC1

(PTEN)-induced putative kinase 1 (PINK1), which codes for a mitochondrially localized kinase, and Parkin, whose is a cytosolic E3 ubiquitin ligase (Fig. 3). PINK1 phosphorylation recruits Parkin and accumulates on the OMM, making to ubiquitinate many membrane proteins such as VDAC1, mitofusin-1, mitofusin-2, TOM20, MIRO and hexokinase [57]. Signal connector proteins P62/SQSTM1, as the bridge between Parkin and autophagosome, recognize the phosphorylated polyubiquitin chain on the mitochondrial protein, which binds to autophagy-associated marker proteins LC3 with another specific area, initiating the formation of mitophagy [58]. In addition, there is also a way of PINK1 recruitment of Parkin that directly phosphorylates Thr175 and Thr217 within Parkin's linker region, making Parkin to locate on the mitochondria [59].

What's more, Parkin-mediated mitophagy requires the participation of autophagy core proteins such as ATG3, ATG5, ATG7, ect [60]. Recent studies have elucidated that both PINK1 and Parkin have the direct interaction with PI3K and Beclin-1 [61]. While mitochondria are depolarized, Ambral, an activator of Beclinl relied on Parkin, is recruited to the mitochondria, which may lead to the activation of the Beclin-1. Thus, Parkin's functions mainly contain ubiquitin of mitochondrial outer membrane proteins and the recruitment of Ambral, promoting mitophagy of damage mitochondria under oxidative stress. The role of PINK1/Parkin, belonged to the classical pathway of mitophagy, has not been thoroughly studied, but previous studies have shown PINK1/Parkin-related mitophagy is linked to the pathogenesis of cell proliferation and pulmonary vascular remodeling [62].

The above conclusion is further supported in knocking out PINK1$^{-/-}$and/or Parkin$^{-/-}$ from PASMCs, which is turned out to induce the excessive proliferation of PASMCs and promote the progression of pulmonary vascular remodeling in HPH [63]. In accordance with the aforementioned point, the model of PINK1$^{-/-}$ mice attenuates the degree of pulmonary vascular remodeling and ameliorates RV dysfunction after hypoxic exposure [64]. In addition, *Asish* et al. have certified that "protective mitophagy" during PAH is mediated by the commitment step of PINK1/Mfn2 [65]. Phosphorylated Mfn2 at Ser442 by PINK1 promotes the dissociation of its proteasomal degradation and make normal PASMCs resent to a hyper-proliferative phenotype. Increased mitophagy and disruption of mitochondrial biogenesis are verified in PAECs isolated from PH patients. Meanwhile, Parkin-induced mitophagy also plays a tanglesome role in hypoxia-induced pulmonary vasculature injury model. Utilizing the donor of si-Control and si-Parkin reveal an intriguing process that Parkin may regulate remodeling phenotypes, which assesses for the correlation of mitophagy and proliferation in PAH PASMCs [66]. Regulated in Development and DNA Damage Responses 1 (REDD1), an important transcription factor regulating mitochondria homeostasis, impresses hemodynamic changes effectively in significant measure, by which Parkin prompts the increasing of mitochondrial membrane potential and mROS-release in

chronic hypoxia model of PH [67]. Simultaneously, certain OMM proteins, including VDAC and mitochondrial Rho GTPase (MIRO) could be ubiquitinated through activating Parkin, which subsequently initiate expression of multiple target genes to regulate pathological characteristics of PH [68, 69]. To some extent, mitophagy, via a compensatory increase of PINK1/Parkin-mediated mitophagy, may be a pathological manifestation from accumulation of dysfunctional mitochondria, but it may also select hyperpolarized mitochondria [70]. This offers a plausible explanation for seemingly paradoxical expression of mitochondrial dynamics and death factors in PH. Those suggest that, acting together, PINK1/Parkin-mediated mitophagy plays an important role on PH.

Receptor-dependent mitophagy in pulmonary hypertension

In setting of mitophagy, numerous experiments have investigated which receptors, located at the mitochondrial outer membrane, are involves in mitophagy including FUN14 domain-containing protein 1 (FUNDC1), BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) and its homolog Nix. In addition, mitochondrial E3 ubiquitin protein ligase 1 (Mul1), prohibitin 2 (PHB2), NLR family member X1 (NLRX1) and recombinant FK506 binding protein 8 (FKBP8) have been gradually found to mediate mitophagy [71–74]. And the effect of mitophagy is partly mediated by those receptors to accommodate upstream oxidation stimulation in an ubiquitinated independent manner [75]. However, in PH, the regulation of mitophagy is mainly concentrated in the former part (Fig. 3). The BH3 domains of BNIP3 and Nix, as two protein members of the BH3-only subfamily of the Bcl-2 family, could inhibit the anti-apoptotic function of Bcl-2 protein and transform it into pro-apoptotic proteins [76]. BNIP3 and Nix have the same LIR domains that help BNIP3 and Nix bind LC3 on the mitophagosome. And phosphorylation of serine residuing 17 and 24 on both sides of LIR promotes to bind to specific LC3B and GATE-16, resulting in the phosphorylation state of LIR of BNIP3 triggers mitophagy [77]. That is, the mitochondrial perturbations triggered by BNIP3 gene activation is mainly manifested as the opening of the mitochondrial permeability transition pore and the loss of mitochondrial membrane potential in the RV remodeling of MCT rat model [78]. In addition, studies have shown that NIX is involved in mitophagy under hypoxia conditions. HIF-lα could increase the level of NIX mRNA, making phosphorylated at Ser81, thus mediate linear particle mitophagy under hypoxia conditions [79, 80]. NIX, as a substrate of Parkin, is also involved in Parkin-dependent mitophagy that could collect NBR1 into mitochondria, while knockouting Parkin and NIX synergistic decreases mitophagy [80, 81]. So *Ning* et al. have demonstrated the expression of BNIP3 and NIX is upregulated by hypoxic stress in the injured pulmonary arterial endothelial cells [82]. Therefore, NIX may mainly regulate mitophagy under hypoxia conditions. For FUNDC1, its dephosphorylation regulates non-Parkin-dependent mitophagy by binding to LC3 under hypoxia conditions. Intriguing, casein kinase II (CK2) phosphorylates FUNDC1 at Tyrl8 via SRC and Serl3, thereby inhibiting its interaction with LC3 in the presence of sufficient oxygen [83]. Under hypoxia, FUNDC1 is dephosphorized by phosphoglycerate mutated enzyme 5 (PGAM5) at Serl3 and phosphorylated by ULK1 at Serl7 [83]. Recently, *Liu* et al. have revealed that FUNDC1 per se could mediate sensing hypoxic PH through dephosphorylating FUNDC1 at Tyr18 combined with LC3B-II [84]. As for ubiquitination of HIF-α and proliferation-promoting feature of ROS, multiple experiments have offered further evidence that the phosphorylation of FUNDC1 places a premium on PASMCs proliferation through ROS-HIF1α pathway, leading to thickening of the medial layer of the pulmonary blood vessels and right heart failure of PH.

Other factors-mediated mitophagy in pulmonary hypertension

Several studies have proposed that mitophagy has the intimate correlation with certain mitochondrial membrane proteins and/or circulation cures, which mentioned the above, thus convey malignant revascularization-promoting signaling to pulmonary vascular. However, these proteins or factors are largely dependent on the mitophagy receptors described above. Mitochondrial Uncoupling protein 2 (Ucp2), a family of anion transporters, is attributed the target molecule to mitochondrial dysfunction and ER stress (ERs) in PASMCs, such as mitochondrial calcium influx imbalance, mitochondrial hyperpolarization and inadequate mitochondrial clearance by mitophagy [14, 85, 86]. Mouse lung endothelial cells transfect with Ucp2 siRNA sensing chemical hypoxia, leading to excessive PINK1-induced mitophagy in PAECs [87]. At the meantime, the effects of Ucp2 silencing on mitochondria and apoptosis may be calcium and mitophagy mediated. Similar results are obtained in Ucp2 endothelial knockout mice, illustrating that Ucp2-PINK1 axis has an important potential target for future clinical therapeutic progress of PH. This also provides favorable evidence for the association of mitophagy with the surrounding environment to induce apoptosis of PAECs. Meanwhile, mitophagy induced by various factors is closely related to energy metabolism. Apoptosis-inducing factor (AIF) is anchored to the mitochondrial membrane space under normal physiological conditions, and performs its oxidoreductase and electron transport functions to maintain cell survival [88]. *Ma* et al. validated that mitochondrial

homeostasis is bust via the ubiquitinated AIF, giving rise to deranged PASMCs proliferation by PINK-associated mitophagy and mitochondrial complex I lesions in PH [89]. Also, Rats with mitochondrial Tu translation elongation factor (TUFM) silence or overexpression in model MCT of PH, which is implicated in protein translation elongation, oncogenesis, oxidative stress, and mitophagy [90, 91], suggest that TUFM mediates mitophagy through the verification of LC3II/I and BECN1 levels and impact the imbalance proliferation/apoptosis of PASMCs sensing hypoxia condition by AMPK/mTOR pathways controlled anabolism and catabolism [92]. Gradually, β-arrestins (ARRBs), as originally known as negative adaptors of G protein-coupled receptors (GPCRs), might be an optimal target to suppress the development of PH and the detailed molecular mechanism through inducing to upregulate BNIP3/Nix and perturbing Akt/mTOR signaling pathway treated with si-ARRBs [82]. Although the regulation of key factors on mitophagy and PASMCs proliferation was described in these articles, the relationship between mitophagy and proliferation is not clearly expounded, and it's still hotly debated.

Unfortunately, few drugs or derivatives have examined the involvement of underlying biology effect of mitophagy in PH and inhibit excessive mitophagy induced by various pathways. One of the endogenous derivatives of NO, named S-nitroso-L-cysteine (CSNO), inhibited excessive ERS and mitophagy induced by AngII and IL-6 in a concentration-dependent manner that attenuates PAP and improves RV hypertrophy in vivo [93]. Also, it has been proved experimentally in PH rat model using monocrotaline to trigger PINK1/Parkin-dependent mitophagy injects Qiliqiangxin (QLQX) to retain cytochrome c in the mitochondria, upregulates the expression of SOD2 and triggers metabolism shift, which means that symptomatic relief and metabolic reprogramming [94]. Broadly speaking, all the above conclusions suggest that mitophagy could further aggravate PH pathological features in both PAECs and PASMCs. In some sense, mitophagy induced by some stimulus provides "corresponding protection" for PASMCs to inhibit mitochondrial-dependent apoptosis in PH, whereas its subsequent outcomes differ from tumor cells manifestations [95, 96]. Despite these efforts to understand the contribution of mitophagy in PH, there are still potential problems that have not been thoroughly delineated. Increasing mitophagy and decreased apoptosis at PASMCs are contrary to the relationship in tumor cells, and what is the correlation between increased mitophagy and proliferation of PASMCs? Also, it's still unknown whether the temperate mitophagy could provide shelter for PH within a range, and the threshold for switching between these two states is unclear. Hence, further experiments are required to determine the interacting factors involved in mitophagy, providing a fresh perspective for the treatment of PH.

Mitochondrial dynamics in pulmonary hypertension

The complex and dynamic behavior of mitochondria in cells has been known for more than a century, but the function of mitochondrial homeostasis is poorly understood because of the limitation of scientific research. It was not until the late 1990s that the first molecule mediating mitochondrial fusion and fission was discovered, indicating that the molecular basis of mitochondrial homeostasis was gradually revealed. Mitochondria are highly dynamic organelles that constantly move and shuttle in tissues and cells, following their morphology also are changed to be balanced to support normal mitochondrial function and prevent disease. Mitochondrial fission, mitochondrial fusion and cristae remodeling events are collectively referred to as mitochondrial dynamics. In a narrow sense, mitochondrial dynamics refers to the process of mitochondrial fission and fusion. Mitochondrial fusion is the fusion of two mitochondria into one mitochondrion; and mitochondrial fission is when one mitochondrion splits into two smaller mitochondria. Mitochondrial fission and fusion are inseparable as a whole. Dysfunctional mitochondria are isolated by dynamic mitochondrial fission, and the fluctuation of mitochondrial fission is determined by the metabolic demand of cells. The connections between mitochondria are the home field of mitochondrial fusion through mtDNA, mitochondrial protein, metabolites and lipids. In normal cells, they maintain a dynamic equilibrium, which affects the morphological changes of the cellular mitochondrial system to adapt to different cellular functional states such as cell cycle, proliferation and apoptosis [97, 98]. Taking cues from those characteristics, data demonstrated that mitochondrial motility has a non-negligible effect on PH pathogenesis mediated mitochondrial morphology. Here, mitochondrial fission and mitochondria fusion are discussed synthetically the correlation with PH.

Mitochondrial fission in pulmonary hypertension

Mitochondrial fission is an intricate process involving a variety of proteins and molecules. Although some of the mechanisms have not yet been elucidated, the present study could be given us a rough outline (Fig. 4). At the molecular, mitochondrial fission mainly involves the both basic pathomechanism, one is the restriction of mitochondria by the endoplasmic reticulum (ER) and the other is the recruitment of dynamic-related protein 1 (Drp1). As for the former, the ER-associated Actin regulators INF2 and Spire1C, located at the interface between ER and mitochondria, cooperate to realize the polymerization process of Actin and bind the mitochondria into tubes at the site of mitochondrial fission [99–101]. In addition to Actin binding proteins, Cofilin, Cortactin, and actin-related protein 2/3 (Arp2/3) complexes may also be involved in this process [102]. The latter is the

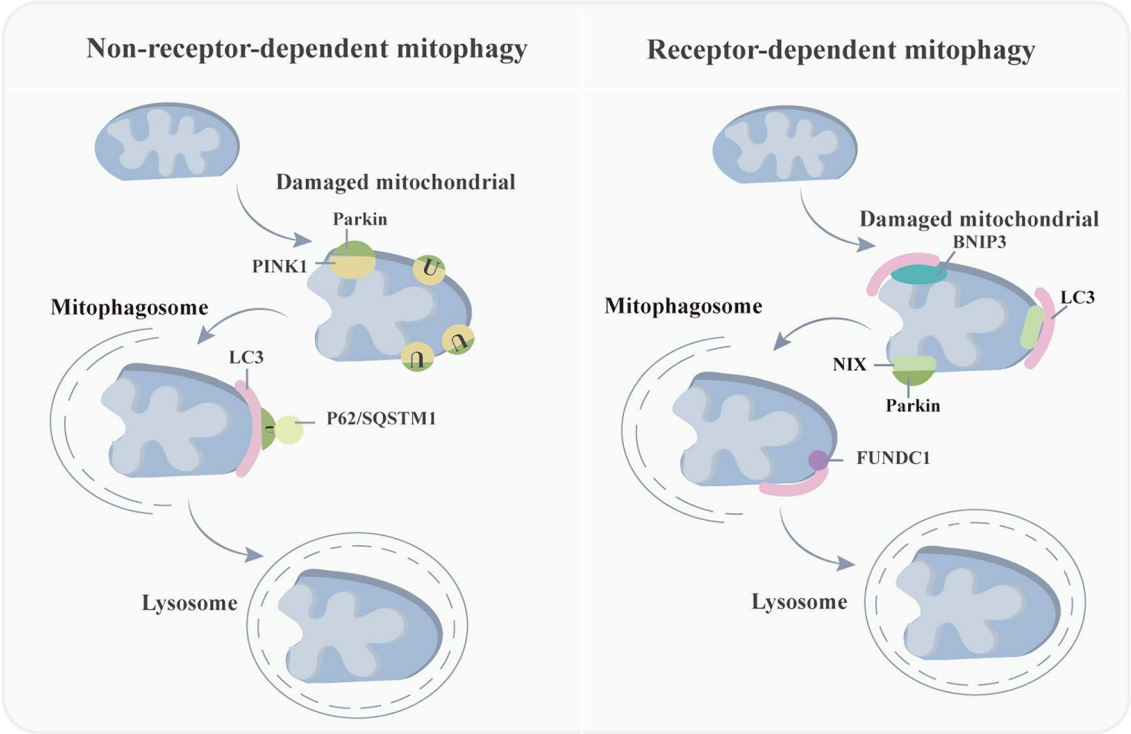

Fig. 4 Potential mechanism of mitochondrial dynamics; mitochondrial fission is regulated by dynamic-related protein 1 (Drp-1) and its receptors. Also, Drp-1 itself can also be phosphorylated at different sites and have different effects on the PASMCs proliferation and vascular remodel. For mitochondrial fission, it's mainly regulated by Mfn2 and OPA1. Once reversion of decreasing mitochondrial fusion, mitochondrial function would ameliorate mtDNA replisome depletion, calcium process and PH progress

main regulator of mitochondrial fission and the Drp1 receptors mainly include mitochondrial fission factor (Mff), mitochondrial dynamics protein of 49 kDa/51 kDa (Mids) and mitochondrial fission 1 protein (Fis1) on the mitochondrial surface [103, 104]. Under physiological conditions, Drp1 is free in the cytoplasm, and once stimulated by oxidative stress, the above mitochondrial fission receptors would attract Drp1 to bind with them that activating the progression of mitochondrial fission [105]. Therein, Fis1 alone cannot recruit Drp1 to the mitochondrial surface, but Fis1 can form as a whole with Drp1 or Mff to participate in the process of mitochondrial dynamics, whereas Mff and Mids could recruit Drp1 independently, and the loss of Mff has the most striking impact on the process of mitochondrial fission, suggesting that Mff plays a major role in the recruitment of Drp1 to mitochondria [106, 107].

Against this background, Drp1 would undergo conformational changes to modulate the direction of it through post-transcriptional phosphorylate modifications including Ser616 and Ser637, yet the coordinate ending is at opposite poles. In PASMCs, under hypoxia-inducible factor-1α (HIF-1α) activation, phosphorylation at Ser616 of Drp1 would monitor the cell cycle checkpoint to fuel PASMCs proliferation and perturb exercise capacity, right ventricular function and hemodynamics [108]. Mitochondrial division inhibitor-1 (Mdivi-1), as an inhibitor of Drp1, phosphorylation at Ser616 of Drp1 is relieved in lung tissues after injecting Mdivi-1 [109]. And in the context of chronic thromboembolic pulmonary hypertension (CTEPH), WNT family member 5B (WNT5B) induces mitochondrial fission mediated higher phosphorylation of Drp1 Ser616 comparing to the control group, contributing to vascular smooth muscle cell (VSMC) phenotype switching [110]. With insight into research, *Feng* et al. elucidate that HMGB1 is couple with the activating ERK1/2 signaling pathway to change the Drp1 expression and phosphorylation of Drp1 at Ser616, resulting in vascular remodeling progress of PAH [111]. The phosphorylation of Drp1 at Ser637 has the opposite effect of impairing Drp1 oligomerization and subsequently restrains mitochondrial fission [112, 113]. With the in-depth study, phosphorylated Drp1 Ser600 is deemed to be stimulus-dependent, regulating mitochondrial fission through concomitant binding with Mff and Arp3, ultimately making F-actin and Drp1 to accumulate on the mitochondria [114].

As with all such correlations, post-transcriptional modification of mitochondrial fission receptor proteins is bound up with Drp1 phosphorylation and per se. Therein, Fis1 with a native N-terminus could block access to the Drp1 binding

site, whereas Fis1 phosphorylating of this N-terminal arm binds tightly to Drp1 [115]. *Lian* et al. attempt to evaluate the role of Drp1-Fis1 direct interaction in MCT-induced pulmonary arterial hypertension (PAH), but they just verify that RV fibrosis, RV vascular rarefaction, and RV vascular rarefaction increases Drp1-mediated mitochondrial fission [116]. After that, they explore mitochondrial fission mediated Drp1-Fis1 using Mdivi-1 and a competing polypeptide P110 that regulates the Drp1-Fis1 interaction, but it just stops here [117]. And phosphorylation at Ser146 of Mff enhances its affinity for Drp1, in turn finally initiated mitochondrial fission, which causes damage to the structure and function of vascular endothelial mitochondria leading to endothelial apoptosis [118]. With activating the pro-fission mode of the Mid49/51, recruitment of Drp1 is enhanced, but there is also exaggerated inhibitory phosphorylation of Drp1 on Ser637 [119]. And once the presence of external stressors, Drp1-Mid51 binding is decreased underlying Drp1-dephosphorylation at Ser637, which is coordinated to mediate mitochondrial fission [120]. Following supra-coronary aortic banding (SAB) caused group 2 PH, mitochondrial fission and expression of MiD51 are increased, which associated with impaired RV function and RV fibrosis, but they don't find the phosphorylation of Drp1 at Ser616 and it may be degraded during the tissue harvesting process[121]. This is different from previous findings, but the concrete reasons for this have yet to be confirmed, suggesting that the subtle regulation between PH and mitochondrial fission needs further excavation.

The increasing mitochondrial fission under PH is known to induce other pathological alterations, such as the formation of a positive feedback loop of ROS/mROS, metabolic shift towards non-mitochondrial ATP generation, the afresh translocation of mitochondrial Ca^{2+} and the disturbance of mitochondrial membrane potential; those stress responses are applied jointly to mitochondria and pulmonary vasculature [122–124]. Underlying these responses are controlled by several microRNAs (miRNAs) to reinforce the down-regulation of fragmentation of the mitochondrial network and cause to cell cycle arrest in some lectures[125, 126]. Mff silencing by miR-340-5p significantly perturbs excessively ROS supplementation and ameliorates mitochondrial function to sustain proliferation-apoptosis balance of hypoxia-treated PAMSCs through the regulation on Sirt1/3 pathway [127]. Of note, autophagy, a procedure that maintains normal cell homeostasis and baseline function of the body, is reported to be coordinately activated by mitochondrial fission under hypoxia condition, which further led to BMPR2, lysosome degradation and DNA binding 1 down-regulation [111]. Moreover, PASMCs proliferation induced by hypoxia, as caused by the excessive production of ROS derived from mitochondria, promote the oxidation of lipids and production of toxic aldehydes [128]. Aldehyde dehydrogenases (ALDHs), as the detoxifier of aldehydes, regulate mitochondrial fission and PASMCs proliferation via 4-hydroxynonenal/HIF/Drp1 signal pathway to attenuates the development of HPH [129]. Nevertheless, the additional effect of ALDH2 on mitochondrial function is needed to be explored.

On the other hand, some pharmacologic pathways could block mitochondrial fission and restore the balance of mitochondrial motility (Table 2). Trimetazidine (TMZ), a partial inhibitor of lipid oxidation, renders mitochondrial fusion and further ameliorates mitochondrial function to antagonize the establishment of a proliferative phenotype, which is one of the critical events associated with PH onset and progression [123]. Ru360 is the specific mitochondrial Ca^{2+} uniporter inhibitor, reduced the DNA fragmentation, inhibited the caspase-3 activation, and prevents from apoptosis via Drp1-dependent pathway in PAECs leading to pulmonary angiogenesis [124]. Treprostinil, a commonly used prostacyclin analog in patients with PH [130, 131], has been shown to stimulate the phosphorylation of Drp1 via either the IP or EP2 prostanoid receptors, resulting in the inhibition of phosphorylate Drp1 and recover mitochondrial fusion and elongation in PASMCs [132, 133]. Drp1-Fis1 interaction could be regulated by P110 that also reduces mitochondrial fission and improves RV diastolic function ex vivo in both normal and PH rats [117], however, that's opposite what *Tian* et al. found as the fact that P110 can only be activated at high doses [116]. The glucagon-like peptide-1 (GLP-1)

Table 2 Drugs or compounds regulate mitochondrial fission improve PH pathological changes

Name	Target	Functions	References
TMZ	Decrease Drp1	Preclude the establishment of a proliferative phenotype	[123]
Ru360	Decrease Drp1	Prevent apoptosis in PAECs	[124]
Treprostinil	Phosphorylation of Drp1	Restore mitochondrial function	[132]
P110	Reduce mitochondrial fission	Improve RV diastolic function	[117]
Liraglutide	Influence mitochondrial fission–fusion imbalance	Inhibit PDGF-BB-induced PASMC proliferation, migration and improve disturbed mitochondrial function in the failing RV	[134]
Mdivi-1	Decrease Drp1	Relieve PVR and PFVP, and attenuate mitochondrial fragmentation-mediated ER stress	[109, 135]

receptor agonist, liraglutide, inhibits PDGF-BB-induced PASMC proliferation and phosphorylation of Drp1 at Ser616, making mitochondrial homeostasis tilted towards mitochondrial fusion, those suggest GLP-1 holds the promise as a drug through a mitochondrial dynamic-dependent mechanism against PH [134]. And Mdivi-1 treatment, as Drp-1 inhibitors, can be used as a control group for pharmacological treatment, which directly explains the feasibility of pharmacological treatment and relieves mitochondrial fission dysfunction. Also, Mdivi-1 treatment could relieve PVR and PFVP (Peak Flow Velocity of Pulmonary Artery) after the administration of Mdivi-1, improving hyperoxia-induced obstruction of pulmonary microvascular development [109]. Mdivi-1 treatment could attenuate mitochondrial fragmentation-mediated ER stress and improve PASMCs function as well [135].

Although Drp1 has been systematically studied, the mechanism by which mitochondrial fission is closely related to cell fate has not been described thoroughly. Recently, *Rajarshi* et al. conducted careful analysis of the ways of mitochondrial fission from different angles, and the role of mitochondrial fission on cell proliferation/apoptosis was analyzed in detail [136]. Using super-resolution microscopy, they found two special forms of mitochondrial fission, called peripheral division and midzone division. Peripheral division mainly occurs at the end of mitochondria, accompanied by changes in mitochondrial membrane potential, increase in ROS and damage to mtDNA, while midzone division mainly occurs in the middle of mitochondria, resulting in the increase of mitochondria and continuous proliferation of cells. Different ways of dividing mitochondria lead to different cell fates. Although this division pathway has been found, it is uncertain whether it exists in PH. If so, whether these two divisions exist simultaneously or independently to regulate cell fate that needs further investigation.

Mitochondrial fusion in pulmonary hypertension

The opposite of mitochondrial fission is mitochondrial fusion, which promotes the mixing of mitochondrial membranes, inter-membrane spaces, and mitochondrial matrix. Fusion between the inner mitochondrial membrane (IMM) and outer mitochondrial membranes (OMM) occurs in a coordinated and nearly simultaneous manner, meaning that fusion of mitochondrial inclusions initiates as soon as the outer membrane of the mitochondria touch (Fig. 4). In some degree, regulating mitochondrial fusion of proteins have been highly conserved during evolution that mediated by large guanosine triphosphatases (GTPase) [137]. Among them, mitochondrial fusion proteins Mfn1 and Mfn2 are transmembrane GTPases situated in the OMM that is dependent on transmembrane domains (TMs) and complete mitochondrial membrane binding through GTP dimerization [97, 138, 139]. Optic atrophy 1 (OPA1) is a dynein-related GTPase, which is related to the fusion of OMM and intermembrane space [140, 141]. OPA1 as a precursor requires complex process hydrolysis in mitochondria to produce the OPA1 long-anchored form. Under various stress conditions, including mitochondrial membrane potential decline and dysfunction, long-anchored form of OPA1 was significantly processed to short-anchored form of OPA1 [142]. Is it possible that knockdown of any of these GTPases in PH would lead to a substantial reduction in mitochondrial fusion?

The primary mechanism of mitochondrial fusion is to regulate mitochondria related apoptosis of HPH through those steps. First, mitochondria fusion is also necessary to maintain the stoichiometry of the protein components of mtDNA replisome, a following effect by mtDNA depletion that caused occurrence of disease [143]. Impaired mitochondrial DNA (mDNA) double-strand further reduces the relative activity of ETC, and thus causes the increasing of proton leak, which is given rise to overall mROS production [144]. The boom of mROS and mitochondrial damage form a positive feedback loop within compartments to signal downstream targets, some of which include signal transducers and transcription factors that regulate apoptosis, cellular proliferation, angiogenesis, and even gene expression [145]. Subsequently, the overexpression of Mfn2 could activate PASMCs apoptosis-induced factors, involving cytochrome C release from mitochondria to cytoplasm, activation of pro-caspase 9 or PARP, and the other caspase downstream cascade [146, 147]. Second, the descend of fusion proteins may influence the mitochondrial morphology and ER-mitochondrial interactions by largely reducing the mitochondria surface area, bringing about vascular injury and severe PH [148]. Epigallocatechin-3-gallate (EGCG), as the most abundant bioactive component of green tea, has been previously identified as an inhibitor of the vascular cells proliferation and interferes with mitochondrial morphology of several diseases [149–151]. In the model of hypoxia-induced PH rats and PASMCs, injecting EGCG dose-dependently attenuates adaptive hypertrophy and normalizes mitochondrial morphology and network through KLF-4/MFN-2/p-Erk signaling pathway [152]. Also, adiponectin, an important adipocyte-derived hormone involving lipid and glucose metabolism and insulin sensitivity, modulates mitochondrial function with the consequences ranging from upregulation of Mfn-2 to inhibition of PASMCs proliferation via Ras-Raf-Erk1/2 signaling pathway [153]. And, the deficiency of Mfn2 could impairs the calcium-replenishing process of store-operated calcium entry (SOCE), eventually has effect on mitochondrial homeostasis and activates ERS after intracellular Ca^{2+} store depletion [154]. Similarly, *Robert* et al. have reported that mitochondrial OPA1 provides protection for mitochondrial function and its communication with ER, and subsequently to attenuate mROS production during

hypertension [155]. Although OPA1 could be an important determinant in regulating vasculature, its upstream regulatory mechanism is not clearly defined, which would be interesting to characterize in future studies.

Recent studies reveal that miRNAs play an important role in the pathogenesis of pulmonary hypertension by regulating PASMC proliferation and vascular remodeling [156, 157]. It's reported by *Ma* et al. that miR-125a could protect pulmonary artery vessels and mitochondrial homeostasis through the direct target of Mfn1 on hypoxia-mediated PASMCs and animal models [158]. In addition, miR-17 expression is upregulated in PASMCs treated by hypoxia that accelerates the pathogenesis of PH [159]. Consistent with the findings of research by *Ma* et al., aberrantly expressed miR-17 alters the intrinsic apoptotic state of PASMCs by targeting Mfn2, thereby activating caspase-3 [156]. MiR-31 plays a similar role to the above mentioned miR-17 that targets the down-regulation of Mfn2 expression performing with neointimal lesions in rats [160]. Moreover, another study using sugen5416/hypoxia-induced PH demonstrates microRNA-140 directly targets Mfn1 and negatively regulates its expression [161]. This negative regulation is correlated with increased RV systolic pressure and hypertrophy that plays a role in the pathogenesis of PH-associated RV dysfunction.

The above data indicate that mitochondrial dynamics is a complex and progressive process involving either positive or negative feedback signals between various signaling pathways. However, more work remains to be done for mitochondrial dynamics to attain their full potential as a target for PH treatment. Physiologically, pulmonary vascular damage caused by elevated mitochondrial fission can be mitigated by reducing its abnormal division and increasing mitochondrial fusion. Therefore, the balance of mitochondrial fusion and fission is essential for homeostasis. Once the balance is destroyed, it brings varying degrees of damage to all layers of vessel wall in PH, especially depending on the various functions of mitochondria. Based on this information, intervening or activating mitochondrial dynamics is critical when designing protective pulmonary vasculature therapies for PH injury.

Mitochondrial unfolded protein response (UPR^{mt}) in pulmonary hypertension

Mitochondria are made up of more than 1000 proteins, of which only 13 are made up of respiratory chains, or ATP synthases, encoded by the mitochondrial genome [162]. All remaining mitochondrial proteins are encoded by nuclear genes, synthesized on cytoplasmic ribosomes, and then introduced into mitochondria across one or both mitochondrial membranes [163]. Mitochondrial protein homeostasis can only be maintained through proper folding and assembly of newly translated proteins, as well as efficient transportation and turnover of those proteins that fail to fold properly. Perturbations to mitochondrial proteostasis induced by a diverse number of stressors, which are contained oxidative stress, the shift of energy focus, and the expression of abnormal proteins encoded by mtDNA and nuclear genome, may activate the UPR^{mt} to mitigate the secretory load of misfolded proteins and temporarily restore mitochondrial functions [164, 165]. Among inordinate mitochondrial proteostasis, those components mainly include molecular chaperones and quality control proteases, both belonging to the inducer of UPR^{mt}. For example, hypoxia-induced PH by treatment with 4-phenylbutyric acid (4-PBA), a chemical chaperone, stimulates the all branches of UPR [166]. Hsp90 regulatory network, a ubiquitous and essential molecular chaperone, is inhibited by specific inhibitor 17-AAG suppressing PDGF-stimulated proliferation and migration of PASMCs, is involved in UPR-mediated therapeutic strategy against PH [167, 168]. Also, *Boucherat* et al. have confirmed that the main actor of regulating PASMC proliferation and vascular remodeling through mtDNA damage in PH is the mtHSP90 [169]. Taken together, chaperones are potentially therapeutic agents on the basis of UPR^{mt} of pathogenic mechanisms and histological features in PH. In addition, the description of HSP60 and HSP70 in PH was mainly concentrated in cells as the whole, and the homeostasis and mechanism of HSP60 and HSP70 in mitochondria are not explored, wishing you could fill in this blank later.

Mitochondria-to-nuclear communication in pulmonary hypertension

Evidence in the model organism of *C. elegans* implicates the mitochondrial inner membrane peptide transporter HAF-1 and the bZip transcription factor activating transcription factor associated with stress-1 (ATFS-1) in UPR^{mt} signaling. In addition to containing a nuclear localization sequence (NLS), the UPR^{mt} transcription factor ATFS-1 also has mitochondrial targeting sequence (MTS) of N-terminus, which is essential for trafficking objective proteins. The MTS is a positively charged, facilitating ATFS-1 passage into the mitochondria. Once entering mitochondria, MTS is cleaved and the other degrades by the Lon protease, presuming that mitochondrial import efficiency is a key negative regulator of UPR^{mt} activation [170]. Under stressful conditions, ATFS-1 reduces input to mitochondria causing that a fraction of the transcription factors are trapped in the cytosol under the action of NLS [170]. In a way, the presence of NLS and MTS in a single transcriptional activator allows the cell to monitor global mitochondrial input efficiency and determine the level of mitochondrial dysfunction at some degree. With the increase of mitochondrial dysfunction, the efficiency of mitochondrial input decreases, which facilitates the translocation of ATFS-1 to the nucleus and the activation

of UPR^{mt}. Thus, mitochondrial homeostasis is maintained through a stress-dependent allocation of transcriptional activators between the inactive state of the mitochondria and the active state of the nucleus.

As ATFS-1 is transported to the nucleus during oxidative stress, how do mitochondria make the recovery of protein transport to equilibrium? Primarily, the nature characteristic of ATFS-1 labeling mitochondria is determined by MTS, in which case the characteristic of MTS is weakened under stress, ATFS-1 would be transferred to the nucleus [171]. Subsequently, mitochondrial membrane potential is weakened, which activated UPR^{mt} [172]. It could be inferred from the above results that a relatively weak MTS will have a relatively strong MTS. According to bioinformatics analysis, HSP60 or SPG-7 has a stronger activity of MTS than ATFS-1, which would also make it transfer to dysfunction mitochondria to reestablish proteostasis and promote organelle recovery [173]. Another possibility is that certain heat shock proteins or proteases, such as mtHsp70, could fill in for protein disturbances in perturbative mitochondria, which also play a part in transporting substances and folding proteins. At long last, it remains to be discussed whether the departure of ATFS-1 from mitochondria would activate the isomerization of some mitochondrial proteases to change the efficiency of the input pathway. However, there are few descriptions of UPR^{mt} in PH, mainly focusing on the role played by UPR. For UPR, vascular remodeling has been shown to activate UPR and mediate macrophage recruitment in IPAH patients, MCT and hypoxic rat models, and UPR is a novel therapeutic target associated with atherosclerotic plaque formation [174, 175]. Does this mean that UPR^{mt} also plays an indispensable role in PH, but it has not been explored yet? This may provide a potential direction for exploring the role of UPR^{mt} in PH and the precision treatment in the future.

UPR^{mt} regulation and inter-cellular integrated stress response in pulmonary hypertension

In addition to the above ATFS-1 regulation of UPR^{mt}, there is just an importantly homologous factor named ATF5 that also regulates the UPR^{mt} and controls the transport efficiency of mitochondrial proteins. ATF5 has a bZIP transcription factor similar to ATFS-1 that means it could upregulate inter-mitochondrial proteases and chaperones after being subjected to stimulation [176]. Synchronously, the regulation of UPR^{mt} is also subject to two additional bZIP proteins at least, ATF4 and CHOP [176, 177]. The three transcription factors are related to a conserved adaptive response, named integrated stress response (ISR), which is controlled by kinases that respond to specific stressors and phosphorylate serine 51 of the translation initiation factor subunit eIF2α [178]. The ISR kinases are consist of PERK, HRI, PKR, and GCN2, but their responsive criterion are completely discrepant that, respectively, are unfolded protein accumulation in the ER, cytoplasmic double ribonucleic acid chains, heme depletion, and mitochondrial stress. In short, ISR activation during stress causes eIF2α phosphorylation, which promotes activation of the transcription factors ATF4, CHOP, and ATF5.

Chronic hypoxia may induce the generation of ROS in mitochondria, promote ERS, cytoplasmic disorder and result in the ISR in the PH and uteroplacental tissues in a way. 18β-Glycyrrhetinic acid (18β-GA) has been found efficacious for attenuating PH through the inhibition of PERK/eIF2α/NF-κB signaling pathway [179]. It has been demonstrated that mTOR could act as the upstream of eIF2α to regulate hypoxic vascular remodeling in PH rat model [180]. Besides, intermittent hypoxia-induced PH could alleviate the proliferation of PASMCs and reverse the mitochondrial damage by inhibiting ATF4 [181]. Although UPR^{mt} has not been described in detail in these researches, the main regulatory factors of UPR^{mt} play an important role, suggesting that UPR^{mt} plays a non-negligible role in the occurrence and development of PH.

Mitochondrial redox homeostasis in pulmonary hypertension

On account of redox homeostasis stress related treatment options in animal models have not been successful in clinical trials, it realizes that redox homeostasis is not just an imbalance between oxidants and antioxidants, but that ROS, a key signaling molecule, dominate the balance of oxidative stress, including hydroxyl radicals, superoxide, and H_2O_2. As a primary source of ROS, mROS produced by the mitochondrial electron transport chain Rieske iron-sulfur protein in complex III could enter the cytoplasm through the voltage-dependent anion channel (VDAC) through the mitochondrial outer membrane and participate in more intracellular transfer events, which is one of the main sources of cytoplasmic ROS [182]. Knockdown Rieske iron-sulfur protein could inhibit PASMCs hypoxic-induced mROS and Ca^{2+}, whereas overexpressing Rieske iron–sulfur protein reverses this circumstance [183]. In particular, review of research has found that oxidase AOX could simulate the function of electron transport chain complexes III and IV in a mouse model ubiquitously expressing *Ciona intestinalis* AOX, it could prevent mitochondrial membrane hyperpolarization, increased superoxide production, and consequent hypoxic signaling, ultimately inhibiting the development of hypoxic pulmonary vasoconstriction (HPV) [184]. In addition, subtype 2 of mitochondrial electron transport chain complex IV subunit 4 (Cox4i2) has also been found to be an important site for the production of mROS, which plays a crucial role in acute hypoxic perception [185].

mROS exert an essential role in PAH due to their involvement in metabolism, cell signaling, mitochondrial dynamics and mtDNA damage. Aberrant antioxidants and mROS production are present in the pathological scenarios of PAH upon the transformation to aerobic glycolysis [186]. It's found that mROS could amplify the stimulus signal of glycolysis by inhibiting HIF-1α hydroxylation, promoting PASMCs hyperproliferation [187]. Meanwhile, ROS/mROS mediate mitochondrial fission of PASMCs contributing to pulmonary vascular remodeling, which is targeting on the positive feedback of ROS/mROS-DRP1 for the treatment of PAH [122]. And in PAs and PASMCs of fawn hooded rat (FHR)-PH, down-regulated mROS activates HIF could inhibit oxygen-sensitive voltage-gated K^+ channel, leading to PAH. However, striking discrepancy with research results may mainly present due to the influence of species variation, different treatment conditions and the integrative correlation between PH and pathogenic factor. Intriguingly, NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 4 like 2 (NDUFA4L2), as part of the electron transport chain (ETC) complex I (complex I) subunit, could also be used as downstream targets of HIF-1α, destroying the redox homeostasis and producing more ROS [188]. It's the realization that synergy of mROS, HIF and ROS stimulate oxidation, inducing mitochondrial function damage, energy deficiency and accompanying pathological manifestation.

Under physiological conditions, Ca^{2+} accumulation in mitochondria stimulates oxidative metabolism by activating TCA circulating enzymes, which can cause PASMC contraction, proliferation and migration, leading to pulmonary vasoconstriction and vascular remodeling [189]. In the mechanism of PH induced by mROS, there is increasing evidence that mROS can increase intracellular Ca^{2+} concentration through different intermediate mechanisms, and ultimately promote PH pathological process. For example, mROS can directly or indirectly interact with L-type calcium channels located on the cell membrane to open them and eventually lead to Ca^{2+} inflow [190, 191]. In addition, TRPC, as a non-selective cation channel, plays an important role in the regulation of Ca^{2+} [192]. The mRNA and protein expression of TRPC6 in IPAH patient PASMCs is much higher than that in control patients. When the level of TRPC6 protein is inhibited by small interfering RNA, the proliferation effect of PASMCs is significantly reduced [193]. At the same time, TRPC6 can be activated by second messenger diacylglycerol (DAG), and DAG production can be regulated by ROS. Furthermore, DAG can also activate protein kinase C (PKCs), which motivate the activity of NADPH oxidase, and ultimately positively up-regulate ROS levels, resulting in HPV [194]. In both MCT-PH rat models and PAH-PASMCs, the mitochondrial calcium mono-transporter (MCU) complex is a core component of the mitochondrial Ca^{2+} uptake system, and restoration or inhibition of its function could alter the mitochondrial Ca^{2+} and PAH-related PASMC phenotype [125]. Elevated Ca^{2+} levels induced by MCU have been shown to be the primary cause of mitochondrial reactive oxygen species (mROS) production, resulting in disrupted cellular metabolic patterns [195]. Collectively, Mitochondrial Ca^{2+} uptake and mROS production are interdependent phenomena, which contribute to the "mutual crosstalk" of cellular function with mitochondrial Ca^{2+} concentration representing the key to deciphering mROS signals (Fig. 5).

Current challenges and concluding remarks

In most cases, mitochondrial dysfunction is a pathological feature that appears early and persistently in cells involved in the development of acute and chronic lung diseases. This is one of the reasons why mitochondria are currently considered important targets for the design and development of drugs for lung diseases. Mitochondria have now discovered a variety of quality control pathways to maintain normal basic function and response to stress, which target individual proteins as well as measure the entire mitochondrial network, including different scales of MQC and redox homeostasis. These studies open up new areas of research to understand how mitophagy, mitochondrial dynamics, metabolic transformation, mitochondrial biogenesis, mitochondrial redox modifications are induced during these physiological processes and whether the same molecules and mechanisms are at work. Meanwhile, the function of mitophagy shown in PASMCs is different from the conventional "apoptosis is proportional to mitophagy", and the relationship between mitophagy and mitochondrial dynamics is also different from other diseases. In addition, the current detection methods for mitochondria also have certain limitations. The most direct and effective method to evaluate mitochondria is tissue biopsy, which has certain tissue damage. We still lack a comprehensive understanding of the relative contributions and dynamics of these processes after mitochondrial damage. Over the past few years, the field has gained significant mechanistic understanding of mitochondrial quality control as well as the redox homeostasis pathway. Although we are only in the early stages of understanding how these pathways work together to produce the functional mitochondrial network, therapeutic techniques based on mitochondrial quality control and redox homeostasis pathway of PH are promising. It is necessary to give further exploration and development.

For MQC, a compensatory molecular mechanism for improving mitochondrial function, its defects are often accompanied by mitochondrial damage, abnormal proliferation of PASMCs and even death of PAECs in the development of PH. In-depth studies have revealed complex mitochondrial quality control and redox homeostasis perturbations of PH vasoconstriction-vascular remodeling circuits in PH. These findings suggest that the development of

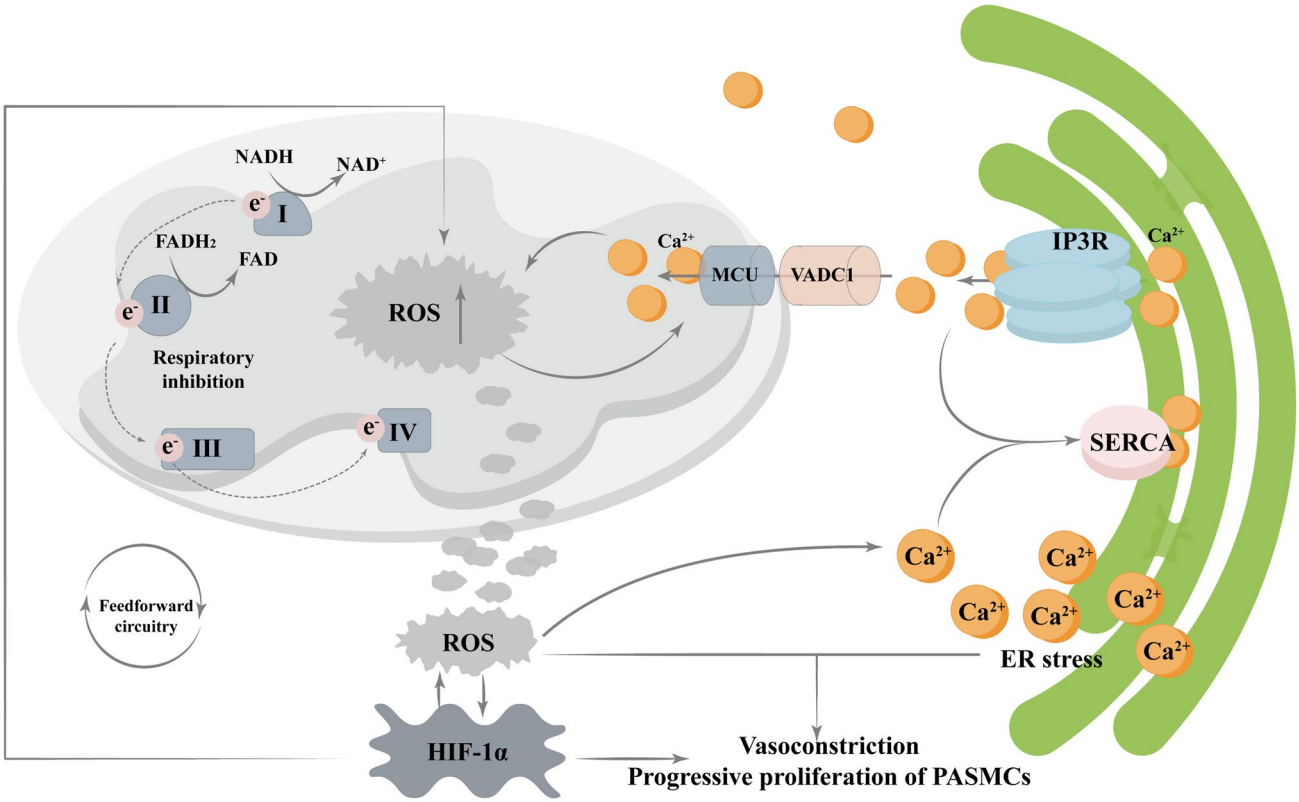

Fig. 5 In oxidative stress status, the mitochondrial respiratory chain acts as the central oxygen sensor of mitochondria to induce the explosive of mitochondrial ROS, which is also one of the main sources of intracytoplasmic ROS, thus activating HIF. At the same time, HIF could further amplify the intracellular oxidative stress signal by acting on ROS/mROS. Concurrently, the transfer between the ER and mitochondria is mediated by a multiprotein complex composed of IP3R in the ER or GRP75 and VDAC1 in OMM, and MUC in IMM. Mitochondrial Ca^{2+} uptake affects the production of mROS and affects pulmonary vascular remodeling by stimulating Krebs circulation. Loss of MCU in PAH reduces mitochondrial Ca^{2+} while increasing cytoplasmic Ca^{2+}, promoting ER stress and promoting pulmonary vasoconstriction. I, II, III, IV: complex I, II, III, IV; *ER* endoplasmic reticulum, *MCU* mitochondrial calcium uniporter, *VDAC1* voltage-dependent anion-selective channel protein 1, *IP3R* inosit1,4,5-trisphosphate receptor, *SERCA* sarco/endoplasmic reticulum calcium transporting ATPase

drugs and targets that promote mitochondrial biogenesis, maintain mitochondrial dynamics, balance UPRmt, and improve redox homeostasis may be an effective strategy to mitigate or treat PH. In this paper, deep studies reveal the complex reprogramming and perturbation of MQC and redox homeostasis mechanisms in PH, and explore their regulatory mechanisms in PASMCs and PAECs, and prove that MQC could protect pulmonary vascular walls and relieve duct stenosis. Although mitochondrial regulation of lung disease is a complex turnover process, we expand understanding of the characteristics of mitochondrial differences in specific pulmonary vascular diseases, which may help elucidate new pathological mechanisms and understand the clinical implications of various disease phenotypes. Therefore, we also hope to find more mechanisms to achieve targeted drugs that accurately control PH, and further realize the transformation basic research into clinical practice.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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