METABOLIC THEORY OF PULMONARY ARTERIAL HYPERTENSION: CONNECTING MITOCHONDRIAL ROLES WITH DISEASE CONTROL

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ABSTRACT
Pulmonary arterial hypertension (PAH) is characterized by enhanced pulmonary vascular resistance, which causes right ventricular pressure overload and can lead to right-sided heart failure and death. A close link between PAH and cancer has been extensively suggested, with increasing evidence of a metabolic theory that underlies the pathogenesis of both diseases, mainly due to similarities in the processes responsible for triggering a hyperproliferative and apoptosis-resistant phenotype in both cardiopulmonary and malignant cells. Similar to cancer, abnormalities in mitochondrial biogenesis might lead to the following consequences: dysfunction of this organelle, which, in turn, causes the Warburg effect, a shift from mitochondrial respiration toward glycolysis, culminating in mitophagy in diseased pulmonary vessels and right ventricular cardiomyocytes. The role of these mitochondrial abnormalities offers new therapeutic avenues. Therefore, this study reviews the bases of mitochondrial derangements in PAH and explores the therapeutic implications of mitochondrial dysfunction and metabolic disturbances in cells from the pulmonary vasculature and right ventricular myocardium by addressing promising and challenging areas of investigation.
Keywords: Pulmonary arterial hypertension, right ventricular failure, mitochondria, oxidative stress, metabolic shift, apoptosis resistance.

RESUMEN
La hipertensión arterial pulmonar (HAP) se caracteriza por una mayor resistencia vascular pulmonar, que provoca una sobrecarga de presión del ventrículo derecho (VD) y puede provocar insuficiencia cardíaca del lado derecho y la muerte. Se ha sugerido ampliamente un vínculo estrecho entre la HAP y el cáncer, con evidencia creciente de una teoría metabólica que subyace a la patogénesis de ambas enfermedades, principalmente debido a las similitudes en los procesos responsables de desencadenar un fenotipo hiperproliferativo y resistente a la apoptosis tanto en células cardiopulmonares como malignas. De manera similar al cáncer, las anomalías en la biogénesis mitocondrial pueden tener las siguientes consecuencias: Disfunción de este orgánulo, que a su vez provoca el efecto Warburg, un cambio de la respiración mitocondrial hacia la glucólisis, que culmina en una mitofagia en los vasos pulmonares enfermos y en los cardiomiocitos del ventrículo derecho. El papel de estas anomalías mitocondriales ofrece nuevas vías terapéuticas. Por lo tanto, este estudio revisa las bases de los trastornos mitocondriales en la HAP y explora las implicaciones terapéuticas de la disfunción mitocondrial y los trastornos metabólicos en las células de la vasculatura pulmonar y el miocardio del VD abordando áreas de investigación prometedoras y desafiantes.
Palabras claves: Hipertensión arterial pulmonar, insuficiencia ventricular derecha, mitocondrias, estrés oxidativo, cambio metabólico, resistencia a la apoptosis.

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Introduction

Pulmonary hypertension (PH) is a complex group of diseases characterized by pulmonary vascular remodeling, vessel wall hypertrophy with deleterious obstruction, and severe loss of cross-sectional area of pulmonary vessels. These factors are responsible for a progressive increase in pulmonary arterial (PA) pressure and pulmonary vascular resistance (PVR), leading to impairment of the performance of the right ventricle (RV). In advanced stages, PH eventually results in irreversible failure of the right heart chamber and sudden cardiac death [1].

Pulmonary arterial hypertension (PAH) is a pre-capillary-type PH (Group 1 within the PH clinical classification system), hemodynamically defined by a mean PA pressure (mPAP) >20 mmHg, PA wedge pressure ≤15 mmHg, and PVR ≥3 Wood units [2]. Remodeling of pulmonary vessels in PAH is depicted by accumulation of pulmonary artery smooth muscle cells (PASMCs), endothelial cells (ECs), fibroblasts, myofibroblasts, and pericytes in the PA walls. In addition, this remodeling process results in a loss of pre-capillary arteries and exacerbates perivascular infiltration of inflammatory cells[1].

Exposure to several injuring factors (e.g., shear stress, local inflammation, genetic susceptibility, toxins, and reactive oxygen species [ROS]-induced cell damage) can cause pulmonary artery endothelial cells (PAECs) dysfunction during the development of PAH. Although the following events are not separated in time, for the sake of simplicity, they are explained here as a temporal sequence. In this context, PAECs first undergo apoptosis, leading to obliteration of the vessels due to structural degeneration. Excessive loss of PAECs promotes the development of an apoptosis-resistant and hyperproliferative phenotype (Figure 1) [3].

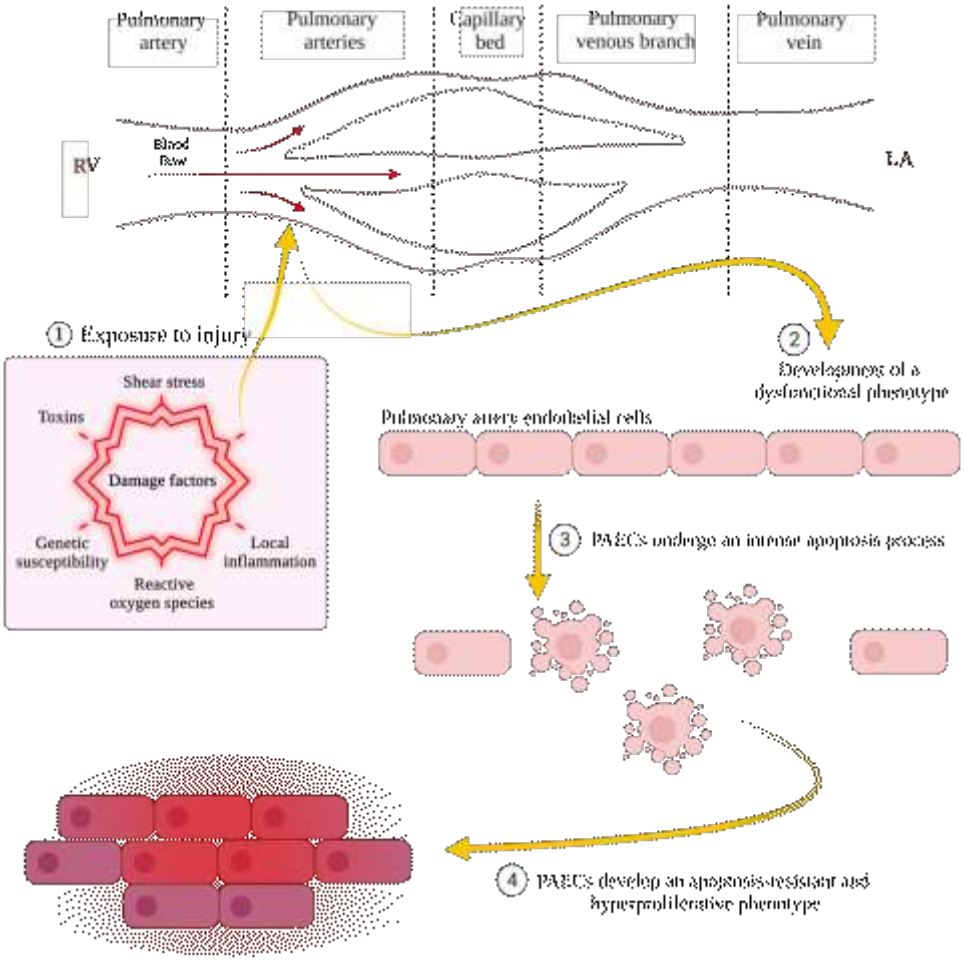

Figure 1. A schematic diagram showing the pathophysiologic mechanisms responsible for initiating the onset of pulmonary arterial hypertension in lung pre-capillary arterioles. The events are numbered sequentially: (1) pulmonary artery endothelial cells (PAECs) are exposed to injuring factors that trigger (2) a dysfunctional phenotype in which these cells (3) first undergo an intense apoptosis process and (4) subsequentially become resistant to apoptosis and develop a hyperproliferative phenotype. Such events lead to an increase in the number of dysfunctional PAECs at the intima cellular layer. RV, right ventricle; LA, left atrium.

Subsequently, an intense proliferation of PAECs induces the formation of plexogenic lesions, a histopathologic hallmark of PAH [4]. Loss of function of the endothelium also stimulates vessel constriction and the emergence of a highly proliferative/apoptosis-resistant state in PASMCs and fibroblasts that respond to the activation of surface tyrosine kinase receptors by potent mitogens and chemoattractants for vascular cells released from dysfunctional PAECs [4]. Consequently, these abnormal changes culminate in a gradual narrowing of the PA vessel lumen and an increase in PVR and mPAP, causing an insult to the RV myocardium (Figure 2) [5].

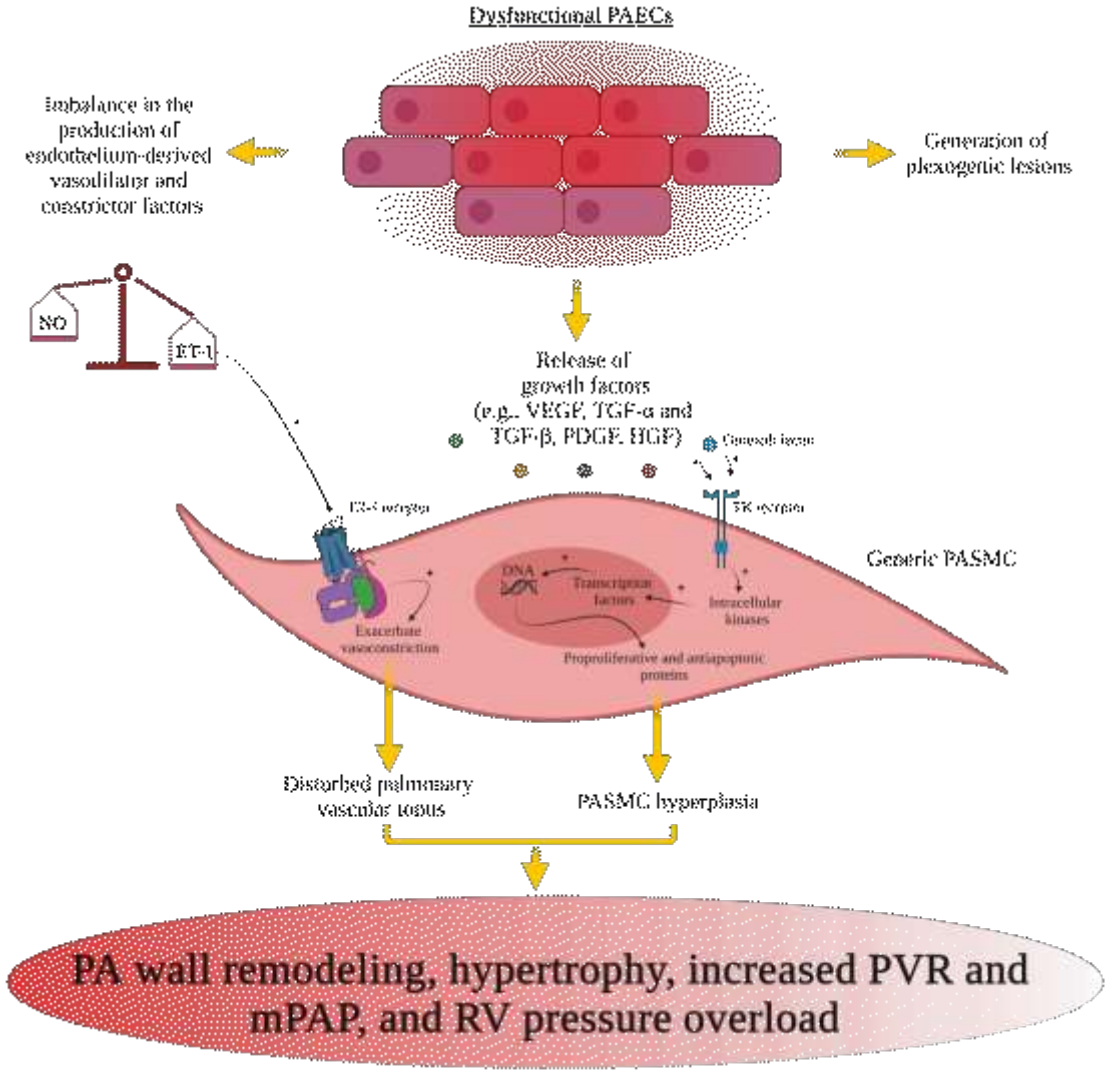

Figure 2. Disturbed crosstalk between pulmonary artery endothelial cells (PAECs) and pulmonary artery smooth muscle cells (PASMCs) during the remodeling process of pulmonary artery vessel walls. The hyperproliferation of PAECs induces generation of plexogenic lesions. In addition, dysfunctional endothelium releases growth factors that activate, tyrosine kinase (TK) receptors in PASMCs, leading to signaling downstream, which stimulates intracellular kinases. Subsequentially, these kinases activate transcriptor factors in the nucleus that, in turn, induce the synthesis of proproliferative and antiapoptotic proteins. This event culminates in PASMC hyperplasia. Furthermore, an imbalance in the production of endothelium-derived vasodilator, nitric oxide (NO), and vasoconstrictor (ET-1) factors promote a disturbance in the vasomotor tone of pulmonary artery vessels. Finally, all these phenomena lead to vessel wall hypertrophy of the pulmonary artery (PA), increase pulmonary vascular resistance (PVR) and mean pulmonary arterial pressure (mPAP), and right ventricle (RV) injury by pressure overload. HGF, hepatocyte growth factor; PDGF, platelet-derived growth factor; TGF-α and TGF-β, transforming growth factor alpha and beta; VEGF, vascular endothelial growth factor.

Initially, the RV responds to this increased pressure load within the pulmonary vascular system with maladaptive myocardial remodeling and hypertrophy, followed by progressive contractile dysfunction, persistent reduction of cardiac output, and global heart failure. Clinically, the severity and chronicity of PAH are demonstrated by the function and size of the RV, which are the most important determinants of longevity in diagnosed patients [6].

Available pharmacologic therapies for PAH are palliative and fail to improve long-term survival, perhaps because they specifically target only one of the multiple molecular and physiologic abnormalities in the disease, i.e., the disturbed pulmonary vascular tone. Some of these pathophysiologic mechanisms of PAH might help us to understand that, in addition to PA cells, favorable actions in the failing heart and other cells (e.g., immune cells) are required for better outcomes.

Nevertheless, in a meta-analysis study, Barnes et al. [7] have reported that sildenafil, tadalafil, and vardenafil are all efficacious in the clinical setting of group 1 PH by increasing the quality of life of patients, as depicted by a higher 6-minute walk distance and better hemodynamics parameters. In this regard, these phosphodiesterase-5 inhibitors might provide benefits when combined with novel treatment candidates for PAH by reversing most of disturbances observed in the cardiopulmonary system from such patients.

It has been suggested that the development of diseases might be linked to alterations in the bioenergetics of an organism, the so-called “metabolic theory of diseases”. This process is mostly described in cancer pathophysiology [8]. Nevertheless, this theory is currently being expanded to the pathophysiology of PAH [9, 10]. Mitochondria have many functions other than supplying energy to living organisms. This organelle is responsible for providing signals that can affect many cell functions [11]. Accordingly, the metabolic theory of PAH proposes that different biomolecular abnormalities observed during disease progression merge from one common affection, a metabolic shift of aerobic energy production to glycolysis (the so-called Warburg effect) in some pulmonary vascular cells (Figure 3) [11]. Interestingly, cells with suppressed mitochondrial function acquire a hyperproliferative and apoptosis-resistant phenotype, which is potentiated when dysfunctional mitochondria persist to develop alternative sources of energy [11] This is considered as a consequence of the metabolic shift that may promote suppression of mitochondrial activity and, in turn, can explain numerous features of PAH similar to those seen in cancer. Interestingly, cells with suppressed mitochondrial function acquire a hyperproliferative and apoptosis-resistant phenotype, which is potentiated when dysfunctional mitochondria persist to develop alternative sources of energy (Figure 3) [11].

In patients with PAH, there is evidence that mitochondrial dysfunction is also observed in RV cells, suggesting upregulation of glycolysis and metabolic disturbances through the cardiopulmonary system. As elegantly discussed by Paulin and Michelakis [11], the concept of PAH is changing significantly from a disease restricted to the pulmonary vasculature to a pathologic condition that affects mitochondria in lungs and extrapulmonary cells (e.g., cardiomyocytes). Thus, future therapies targeting mitochondria can address this multiplicity of pathogenic signaling in the cardiopulmonary system simultaneously, an advance to achieve the specific biology of PAH.

There are three well studied and published animal models of PH [12, 13]: chronic hypoxia [14], PH induced by the mitogenic alkaloid monocrotaline (MCT) [15], and an alternative animal model of PH that has been developed in rats by the administration of the vascular endothelial growth factor receptor antagonist Sugen 5416 in combination with 3 weeks of hypobaric hypoxia (Sugen 5416-hypoxia-induced PH model) [16]. The first two models have been used for decades and have undoubtedly contributed to a better understanding of the pulmonary hypertensive process and new drug development [12-15]. The Sugen 5416-hypoxia-induced PH model is considered preferable compared with chronic hypoxia alone and with the MCT model because it is characterized by severe and progressive development of neointimal and angioobliterative plexiform lesions in PAs, thus more closely resembling PAH in humans [16]. Therefore, a preferred model of the disease remains a matter

of concern. Nevertheless, the choice of pre-clinical model should be aligned to the main research question.

In this minireview, we focus on discussing seminal findings and some of the newest advances in our understanding of the metabolic theory of PAH, mainly in the cardiopulmonary system (e.g., PAECs, PASMCs, and RV cells) from animals with PH. Finally, some of our discussion is based on clinical studies of the lungs or hearts of patients with PAH.

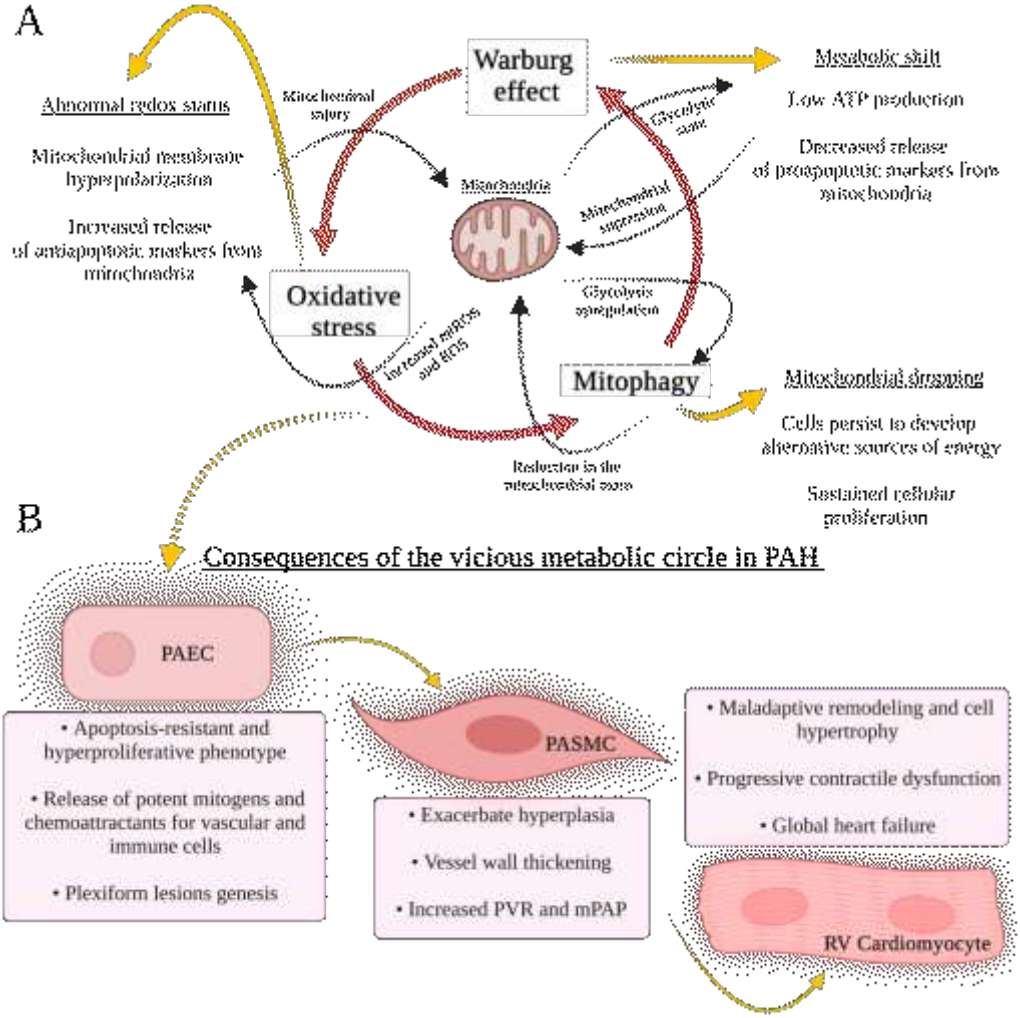

Figure 3. Overview of the metabolic theory of pulmonary arterial hypertension (PAH). (A) Vicious cycle between the Warburg effect, oxidative stress, and mitophagy. Note that PAH pathogenesis is depicted by different biomolecular abnormalities observed during disease progression, such as the metabolic shift of aerobic energy production to glycolysis (the Warburg effect), promoting suppression of mitochondrial function and induces a cellular hyperproliferative and apoptosis-resistant phenotype, which is potentiated when dysfunctional mitochondria persist to develop alternative sources of energy. The increase in cellular reactive oxygen species (ROS)/mitochondrial ROS (mtROS) content is a consequence of oxidative stress deregulation and also impairs mitochondrial function, sequentially leading to removal of these debilitated organelles by mitophagy. In addition, the Warburg effect, together with the synthesis of unbalanced free radical levels, activate downstream signaling targets that stimulate the hyperproduction of antiapoptotic and proproliferative markers. (B) Consequences of the metabolic theory of PAH in pulmonary artery endothelial cells (PAECs), pulmonary artery smooth muscle cells (PASMCs), and right ventricle (RV) cardiomyocytes. mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance.

Underpinning the metabolic theory of PAH in pulmonary vascular cells

Pulmonary vascular endothelial cells

ECs from distinct vascular compartments differ in response to stress, circulating molecules, and surrounding cells. Most PAECs depend on cellular respiration to produce the ATP necessary for their energetic demands. In contrast, ECs from the pulmonary microvasculature use glycolysis as the main

source of ATP. Accordingly, in PAECs, the Warburg effect is described as a maladaptive mechanism involved in the pathogenesis of PAH. The high sensitivity of PAECs to this increase in glycolytic capacity highlights these cells as the first components in the pulmonary vessel walls to be affected during the development of PAH [10].

Commonly, ROS synthesis and neutralization are mechanisms strictly regulated by mitochondria [10]. When the energy generation shift affects PAECs, they become less efficient in producing ATP, which might lead to an unexpected increase in cellular ROS content with impairment of oxidative stress regulation. Thus, an imbalance in oxidative stress in PAECs can be considered a hallmark of metabolic or mitochondrial disease. Consequently, the increased ROS levels activate downstream signaling targets such as the transcription factors that reduce apoptosis, increase cellular proliferation, gene expression, and angiogenesis, including hypoxia-inducible factor 1α (HIF-1α), SRY-Box transcription factor 18, STRA13 (a basic helix-loop-helix [bHLH] transcription factor), and nuclear factor kappa B [10, 17]. Deregulated oxidative stress impairs mitochondrial function and leads sequentially to the removal of these debilitated organelles through a phenomenon known as mitophagy [18]. Intense mitophagy in Warburg-effect-induced PAEC dysfunction contributes to reduced mitochondrial mass and ATP production, which culminates in potentialization of the glycolytic state. PTEN-induced kinase 1 (Pink1) and Parkin are potential markers of mitophagy and are discussed later in the text.

It is clear that for a cell to proliferate, the bulk of the glucose cannot be committed to carbon catabolism for ATP production. In addition, the resulting increase in the ATP/ADP ratio would severely impair flux through glycolytic intermediates, limiting the production of the acetyl-CoA and NADPH required for macromolecular synthesis. Intermediate cells using aerobic glycolysis also exhibit high ratios of ATP/ADP and NADH/NAD+ [19, 20]. Further, even minor perturbations in the ATP/ADP ratio can impair growth [8]. Accordingly, in PAH, it its postulated that glycolysis may decrease the release of proapoptotic biomolecules from mitochondria, thus supporting the apoptosis-resistant phenotype of PAECs [8, 21]. In addition, residual disturbed mitochondria in stressed PAECs release inhibitors of apoptosis, such as succinate dehydrogenase (ubiquinone) iron-sulfur subunit, mitochondrial (SDHB) and survivin [22]. All these pathobiological factors are involved in pulmonary vessel wall remodeling and comprise, in part, the basis of the metabolic theory of PAH (Figure 3).

Nitric oxide (NO) levels are lower in the lungs of patients with PAH than in healthy individuals, and the approved treatments for the disease rely on attempts to normalize NO signaling through indirect mechanisms of action such as antagonism of endotelhin-1 (ET-1) receptors in PAECs, which in turn results in an increase in endothelial NO synthase (eNOS) activity, subsequent normalization of NO bioavailability, and pulmonary vasorelaxation [23]. Interestingly, it has been suggested that decreased NO production and reduced mitochondrial function, coupled with an increase in the glycolytic state in PAECs, are consistent markers of PAH [24]. Accordingly, Sun et al. [25] created a hypothesis to investigate how these factors mechanistically underly the metabolic theory of PAH in PAECs. In a model of MCT-induced PH, they have shown that ET-1 induces eNOS uncoupling and translocation of this enzyme to the mitochondria, which results in perturbation of carnitine metabolism and reduced mitochondrial bioenergetics. Furthermore, they found that the balance of ATP synthesis under ET-1 treatment shifted from oxidative phosphorylation to glycolysis in cultured PAECs from rats. Additional investigations indicated that ET-1-induced mitochondrial redistribution and the disruption of mitochondrial bioenergetics occur via protein kinase C δ (PCKδ), which promotes the phosphorylation of eNOS enzyme and its translocation to the mitochondria [25]. Importantly, this experimental study also showed that the Warburg effect in PAECs induced an increase in ROS, which in turn activated HIF-1α [25].

Hypoxia has long been linked to the Warburg effect. It is also not known if long non-coding RNAs (lncRNAs) are involved in the contribution of hypoxia to the Warburg effect or if lincRNA-p21 is a hypoxia-responsive lncRNA and is essential for hypoxia-enhanced glycolysis. Hypoxia/HIF-1α-induced lincRNA-p21 is able to bind HIF-1α and Von Hippel-Lindau (VHL) and thus disrupts the VHL-HIF-1α interaction. This disassociation attenuates VHL-mediated HIF-1α ubiquitination and

causes HIF-1α accumulation. This indicates the existence of a positive feedback loop between HIF-1α and lincRNA-p21 that promotes glycolysis. Thus, HIF-1α is further involved in the switch from oxidative phosphorylation to glycolysis in pulmonary hypertensive PAECs [10]. In the context of PAH, HIF-1α is also responsible for a decrease in the mitochondrial content in cells from PAs, because it induces the transcription of molecules involved in the process of mitophagy [10].

Uncoupling protein-2 (UCP2), which is overexpressed in the mitochondrial membrane of rodent cardiomyocytes, prevents influx of calcium into the mitochondria and reduces the overproduction of ROS. Conversely, if mitochondrial calcium levels are reduced, mitochondrial function is impaired [10]. The role of UCP2 in ECs has been investigated in an intermittent hypoxia model of PH [26]. This study identified that UCP2 is involved in the mitophagy process that is initiated by a change in the mitochondrial membrane potential, leading to an accumulation of Pink1 in the outer mitochondrial membrane. This mechanism is responsible for the recruitment of parkin and subsequent ubiquitination of damaged mitochondria [10]. ROS-induced oxidative injury increases mitophagy and culminates in cell death. In addition, it was found that the loss of endothelial UCP2 increased the levels of Pink1 and Parkin, which led to increased mitophagy [26]. Thus, increased mitophagy and inadequate mitochondrial bioenergetics were significantly associated with reduced apoptosis in PAECs. These alterations were associated with the development of a PH phenotype in mice, as shown by increased RV systolic pressure and RV hypertrophy. Finally, the authors of this study also found that even in room air, the loss of endothelial UCP2 resulted in increased expression of Pink1 and Parkin, which resulted in the development of spontaneous PH, emphasizing the role of endothelial mitophagy and the UCP2 pathway as triggers of pulmonary vascular remodeling [10, 26].

Pulmonary vascular smooth muscle cells

Evidence from animal studies of persistent PH shows that smooth muscle cells (SMCs) play a role in the balance of cytosolic ROS and mitochondria-derived ROS (mtROS) in response to cyclic stretching, leading to an increase in the expression of growth factors that act in both ECs and SMCs. This culminates in a so-called “feed forward” mechanism of proliferation in these components of PA walls [10, 27], which may contribute to the major factor in the pathobiology of PAH: resistance to apoptosis. The caspase inhibitor survivin was first described in tumor cells. A mitochondrial pool of this anti-apoptotic molecule was found to be released within the cytosol when tumor cells received proapoptotic signals [28]. Survivin upregulation was demonstrated in patients with PAH and in rats with MCT-induced PH [29]. Furthermore, survivin expression in PASMCs was significantly correlated with disease severity, and its inhibition attenuated PH characteristics in this animal model [29].

The metabolic modulator dichloroacetate (DCA) is known for its ability to favor oxidative phosphorylation via the activation of pyruvate dehydrogenase. DCA also upregulates the potassium channels Kv 1.5 in the mitochondrial membrane, leading to its depolarization and subsequent caspase activation, which trigger apoptosis in PASMCs [30]. Administration of DCA in rats with PH induced by chronic hypoxia reversed the disease in these animals [30]. Thus, it has been demonstrated in two classic models of PH that when DCA regulates the disturbed PASMC bioenergetics by preventing the metabolic shift from cellular respiration to glycolysis, PASMC hyperplasia and PA vessel remodeling and hypertrophy are significantly mitigated mainly by the stimulation of apoptosis when caspase is released from functional mitochondria [30, 31]. The importance of a balanced mitochondrial membrane potential is clear, and hyperpolarization of this membrane is associated with the development of PH and PAH (Figure 3) [10]. It has been found that patients with PAH presents PASMCs with a hyperpolarized mitochondrial membrane compared with normal controls [32]. This was further recapitulated in rats with PH induced by MCT and in UCP2-knockout mice. Interestingly, PASMCs from UCP2-knockout mice developed a hyperproliferative and antiapoptotic phenotype [32].

A recent study investigated whether PASMCs present the same biological behavior as PAECs in the mitophagy process in the setting of PAH [33]. The proliferation and apoptosis of human PASMCs after hypoxia and normoxia treatments have been verified. Importantly, the authors found that hypoxia can induce Pink1/Parkin-mediated mitophagy and that this maladaptive mechanism led to

excessive proliferation of PASMCs, blocked apoptosis, and promoted exacerbated pulmonary vascular remodeling [33].
After the discussion of these findings, we may now understand that the metabolic theory of PAH is probably a vicious cycle between the Warburg effect, hyperpolarized mitochondria, exacerbated oxidative stress, and reduction in the number of mitochondria due to the process of mitophagy in both PAECs and PASMCs (Figure 3).

Can the metabolic theory of PAH be extended to RV cells?
In cardiomyocytes, mitochondria are the dominant source of energy, and mitochondrial abnormalities play a pivotal role in the progression from cardiac dysfunction to heart failure [34]. In the Sugen 5416-hypoxia model of PH, substantial mitochondrial hyperpolarization, increased ROS synthesis, structural and functional abnormalities of this organelle, and a metabolic shift from fatty acid oxidation to glycolysis in RV cells from PH rats that developed myocardial hypertrophy and failure were demonstrated [35, 36]. Similar metabolic disturbances were observed in PAECs and PASMCs from humans and animals with PH as addressed earlier. Another study demonstrated decreases in mitochondrial density in dysfunctional RV cells from female rats with 5416-hypoxia-induced PH, probably as a result of defects in the translational pathway in mitochondrial biogenesis [37]. In addition, mitochondrial quality measured through the respiratory control ratio (RCR) and ADP-stimulated oxidation capability tended to be depressed in cells from hypertrophied RV [37]. The authors discussed that a low RCR in Sugen 5416-hypoxia rats implies that RV mitochondria in these animals were damaged or prone to be damaged, because in PH-induced failing RV, failure is significantly associated with increased ROS production, which is known to cause injury to mitochondrial structure and function [37].
In MCT-induced pulmonary hypertensive rats, the mitochondrial oxygen consumption rate of RV cells was decreased, suggesting that impairment of the mitochondrial energy-producing ability is involved in the development of RV dysfunction and failure [38]. Oxidative stress followed by calcium overload, ATP depletion, and increased phosphate levels induce opening of mitochondrial permeability transition pores (MPTPs), which might result in eventual mitochondrial swelling, rupture, and cell death. It is well known that RV myocardial apoptosis plays a pivotal role in RV failure. Zungu-Edmondson et al. [39] revealed that apoptosis is a feature in the early stages of RV dysfunction, and that in the end stages of RV failure, apoptosis is significantly decreased. This can explain the high degree of RV wall remodeling and hypertrophy when the right heart chamber is affected by long-term pressure overload in PAH. The opening of MPTPs in mitochondria from RV cardiomyocytes leads to the release of a proapoptotic protein known as cytochrome C from the mitochondria to the cytosol. The released cytochrome C activates caspase-9, which activates caspase-3, leading to cell apoptosis, the main apoptotic pathway of MCT-induced RV failure [40]. Electron microscopy further showed prominent damage of RV mitochondria in MCT-induced PH [40], which is probably related to the process of mitophagy in RV cardiomyocytes.
Another study found that cardiomyocytes from the RV of MCT rats were enlarged, primarily due to an increase in myofibrillar protein. The ratio of mitochondria per myofilament area was lower in MCT-induced PH rats than in control rats. This not only implies impaired energy production in PH but also increased diffusion distance for metabolites within the MCT cardiomyocytes, adding an additional hindrance to the energy supply. Together, these changes may limit the energy supply in MCT rat hearts, particularly at high cardiac workloads [41].

Concluding remarks
The available PAH therapies were not specifically developed for this disease, but for other vascular conditions such as erectile dysfunction, which is satisfactorily treated with phosphodiesterase-5 inhibitors. Each vasodilator used to treat PAH addresses only one pathophysiologic feature presented in patients with this diagnosis. Hence, if we agree that the metabolic theory of PAH is proposed as a phenomenon with multiple unrelated abnormalities that have a common denominator – a vicious

cycle between the Warburg effect and exacerbated oxidative stress and mitophagy (Figure 3) – we can consider integration of signaling mechanisms involving the mitochondria that explain several characteristics of the PAH vascular phenotype (e.g., hyperproliferation and apoptosis resistance). These mitochondrial abnormalities are not restricted to the pulmonary vascular bed but are also observed in PAH cardiomyocytes, thus suggesting a global metabolic disturbance in the cardiopulmonary system. Accordingly, the metabolic theory of PAH puts mitochondrial structure and function at the center of our understanding of PAH biology and provides undoubted benefits for the development of innovative therapeutics targeting only damaged mitochondria in a selective manner with the reward of addressing the multiplicity of pathogenic mechanisms involved in the evolution of PAH and RV failure at the same time.

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