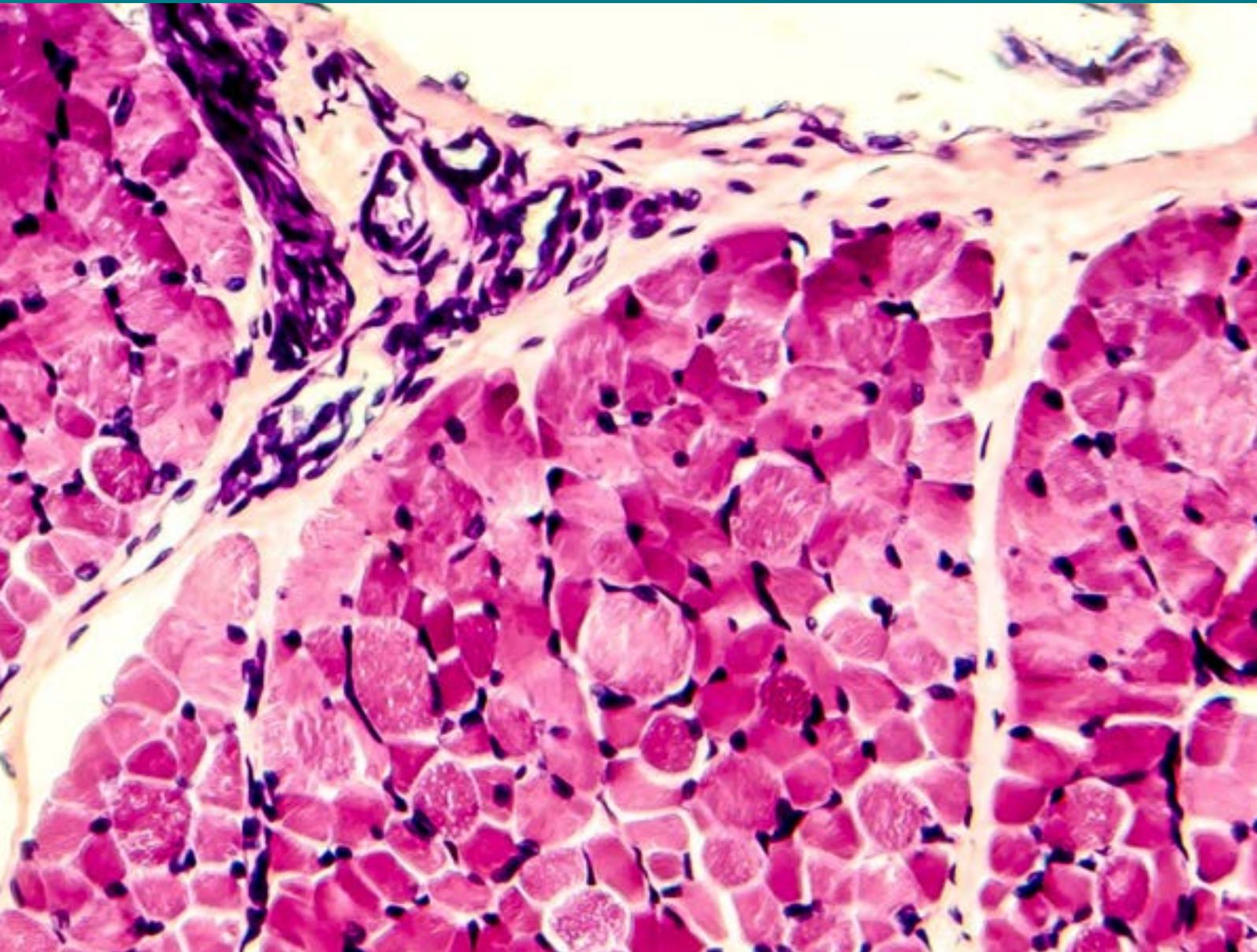


Physiological Mini Reviews

15
Volume



Vol. 15, January - February, 2022
ISSN 1669-5410 (Online)
pmr.safsiol.org.ar

Physiological
Mini
Reviews



Physiological Mini Reviews is the official journal of the Asociacion Latinoamericana de Ciencias Fisiológicas, (ALACF), which is constituted by the following Societies:

Sociedad Argentina de Fisiología (SAFIS)

Sociedad Brasileira de Fisiología (SBFis)

Asociación Colombiana de Fisiología (COLFISIS)

Sociedad Cubana de Ciencias Fisiológicas (SOCCF)

Sociedad Chilena de Ciencias Fisiológicas (SCHCF)

Sociedad de Fisiología de Haití (SHF)

Sociedad Mexicana de Ciencias Fisiológicas (SMCF)

Sociedad Peruana de Ciencias Fisiológicas (SCPCF)

Sección de Fisiología de la Sociedad Uruguaya de Biociencias (SUB)

SPONSORS

DEPARTAMENTO DE POSTGRADO
FACULTAD DE CIENCIAS MÉDICAS UNLP



maestría

EN INVESTIGACIÓN BIOMÉDICA

Acreditada y Categorizada CONEAU "C" Res. FC 2018-42
Resolución Ministerial de Reconocimiento oficial y
validez nacional del título: Res.1596/16

INSCRIPCIONES
ABIERTAS

INFORMES: maestriaibunlp@gmail.com

FACULTAD DE CIENCIAS MÉDICAS |  UNIVERSIDAD NACIONAL DE LA PLATA |  CONICET



LENF-MEDICINA DEL SUEÑO

www.institutomedicoplatense.com.ar

**Laboratorio de Electrofisiología y Medicina del Sueño.
Instituto Médico Platense. La Plata, Argentina
lenf.imp@gmail.com**

SPONSORS

We are very grateful to our sponsors



intemun s.a

DIVISION INSUMOS

Ventas de Insumos Médicos Hospitalarios
La Plata - Buenos Aires - Argentina
Tel: 0221 471 8951 011-75120306 0221-586 9111
ventas@intemun.com.ar administracion@intemun.com.ar

Distribuidor oficial : *Baño Fácil*



Physiological Mini-Reviews

[ISSN 1669-5410 (Online)]

Edited by the **Argentinean Physiological Society and the Latin American Association of Physiological Sciences**

Journal address: Centro de Investigaciones Cardiovasculares y Cátedra de Fisiología y Física Biológica.
Facultad de Ciencias Médicas; Universidad Nacional de La Plata;
La Plata, Buenos Aires, Argentina. Tel.-Fax: +54-211-4834833
<http://pmr.safisiol.org.ar>

Physiological Mini-Reviews is a scientific journal, publishing brief reviews on "hot" topics in Physiology. The scope is quite broad, going from "Molecular Physiology" to "Integrated Physiological Systems". As indicated by our title it is not our intention to publish exhaustive and complete reviews. We ask to the authors concise and updated descriptions of the "state of the art" in a specific topic. Innovative and thought-provoking ideas are welcome.

Founding Editor: Mario Parisi, Buenos Aires, Argentina

Editor in Chief: Alicia Mattiazzi, La Plata, Argentina

Associate Editors

Alejandro Aiello, La Plata, Bs. As., Argentina
Walter Boron, Cleveland, OH, United States
Maria Jose Campagnole-Santos, Belo Horizonte, MG, Brazil
Julio Copello, Springfield, IL, United States
Adolfo de Bold, Ottawa, ON, Canada
Ana Franchi, Ciudad Autónoma de Buenos Aires, Argentina
Cecilia Hidalgo, Santiago, Chile
Daniel Ortuño-Sahagun, Guadalajara, Jal, México
Eduardo Rios, Chicago, IL, United States
Luis Sobrevia, Santiago, Chile

Administrative Council

Presidents or delegates of Latin American Physiological Societies or Biological Societies

Ma. del Carmen Cortés Sánchez, Puebla, Pue, México
Paola Contreras, Montevideo, Uruguay
Jean-Claude Dorsainvil, Puerto Príncipe, Haití
Mayppee González Jardinez, La Habana, Cuba
Henry León, Chia, Cund., Colombia
Azael Paz Aliaga, Lima, Perú
Zully Pedroso, Santiago, Chile
Patricia Rocco, Río de Janeiro, RJ, Brazil
Martín Vila-Petroff, La Plata, Argentina

Editorial Board:

Vagner Roberto Antunes, Sao Paulo, Brazil
Cristina Arranz, Ciudad Autónoma de Buenos Aires, Argentina
Claudia Capurro, Ciudad Autónoma de Buenos Aires, Argentina
Daniel Cardinali, Ciudad Autónoma de Buenos Aires, Argentina
Marcelino Cerejido, México City, México
Alberto Crottogini, Ciudad Autónoma de Buenos Aires, Argentina
Osvaldo Delbono, Winston-Salem, NC, United States
Irene Ennis, La Plata, Bs. As., Argentina
Ariel Escobar, Merced, CA, United States
Ludmila Firaletova, St. Petersburg, Russia
Benjamín Florán Garduño, Ciudad de México, México
Ana María Gomez, Chatenay-Malabry, France
Guillermo González Burgos Pittsburg, PA, United States
Carlos González, Lubbock, TX, United States
Hilda Leonor González Olaya, Bucaramanga, SAN, Colombia

Sergio Gradilone, Rochester, MN, United States
Joost Hoenderop, Nijmegen, The Netherlands
Bredford Kerr Fuentes, Santiago, Chile.
Cecilia Larocca, Rosario, Santa Fe, Argentina
Elena Lascano, Ciudad Autónoma de Buenos Aires, Argentina
Reinaldo Marín, Caracas, Venezuela
Raúl Marinelli, Rosario, Santa Fé, Argentina
Susana Mosca, La Plata, Bs. As., Argentina
Cecilia Mundiña-Weilemann, La Plata, Bs. As., Argentina
Gustavo Pérez, La Plata, Bs. As., Argentina
Darío Protti, Sidney, NSW, Australia
Margarita Salas, La Plata, Bs. As., Argentina
Daniel Schulz, Gif sur Yvette, France
Gary Sieck, Rochester, MN, United States

Education Editorial Board

Robert G. Carroll, Greenville, NC, United States
Matilde Said, La Plata, Bs. As., Argentina
Roxana Troiano, Ciudad Autónoma de Buenos Aires, Argentina
Claudia Caldiz, La Plata, Bs. As., Argentina

Publishing Editorial Board

Carolina Caniffi, Ciudad Autónoma de Buenos Aires, Argentina
Verónica de Giusti, La Plata, Bs. As., Argentina
Luis Gonano, La Plata, Bs. As., Argentina
Alejandro Orłowsky, La Plata, Bs. As., Argentina

Zully Pedroso, Santiago, Chile
Matilde Said, La Plata, Bs. As., Argentina
Carlos Valverde, La Plata, Bs. As., Argentina
Alejandra Yeves, La Plata, Bs. As., Argentina

Editorial Assistant: María Ines Vera

Preparation and Submission of manuscripts:

"Physiological Mini-Reviews" will have a maximum of 3000 words, 50 references and 3 figures. Material will be addressed to scientific people in general but not restricted to specialist of the field. For citations in the text please refer to Instructions in our webpage. Final format will be given at the Editorial Office. Most contributions will be invited ones, but spontaneous presentations are welcome. Send your manuscript in Word format (.doc or .docx) to: pmr.alacf@gmail.com

Advertising: For details, rates and specifications contact the Associate Editor at the Journal address e-mail: pmr.alacf@gmail.com

The "Sociedad Argentina de Fisiología" is a registered non-profit organization in Argentina. (Resol. IGJ 763-04)

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

Allan Kardec Nogueira de Alencar^{1,2,3}, Fernanda Ferreira Cruz¹, Patricia Rieken Macedo Rocco¹, Pedro Leme Silva¹

¹ Laboratório de Investigação Pulmonar, Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Av. Carlos Chagas Filho, 21941-902, Rio de Janeiro, RJ, Brazil

² Faculdade de Medicina de Petrópolis/UNIFASE, School Clinic, Av. Barão do Rio Branco, 25680-120, Petrópolis, RJ, Brazil

³ Laboratório de Farmacologia, Departamento de Ciências Fisiológicas, Instituto Biomédico, Universidade Federal do Estado do Rio de Janeiro, Rua Frei Caneca, 20211-010, Rio de Janeiro, RJ, Brazil

Correspondence to: pedroleme@biof.ufrj.br

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.

Received: November 11, 2021. Accepted for publication: November 18, 2021

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].

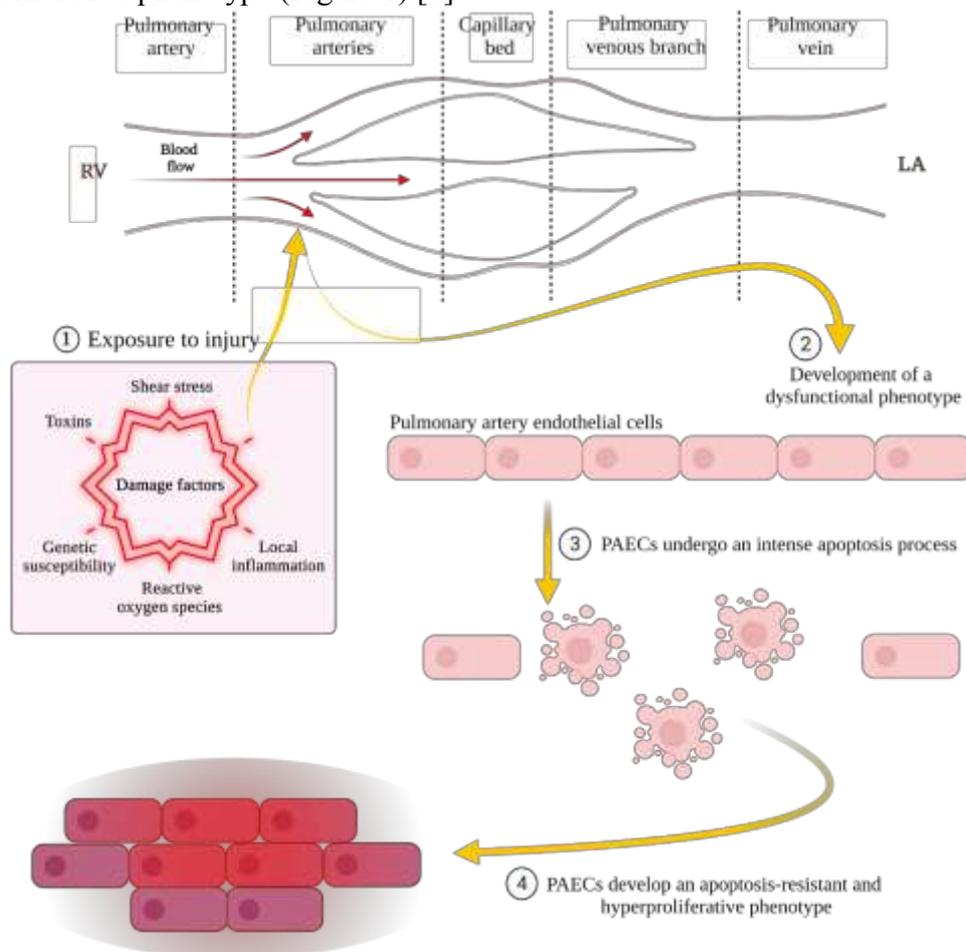


Figure 1. A schematic diagram showing the pathophysiologic mechanisms responsible for initiating the onset of pulmonary arterial hypertension in lung pre-capillary arterioles. The events are numbered sequentially: (1) pulmonary artery endothelial cells (PAECs) are exposed to injuring factors that trigger (2) a dysfunctional phenotype in which these cells (3) first undergo an intense apoptosis process and (4) subsequently 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 PSMCs 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].

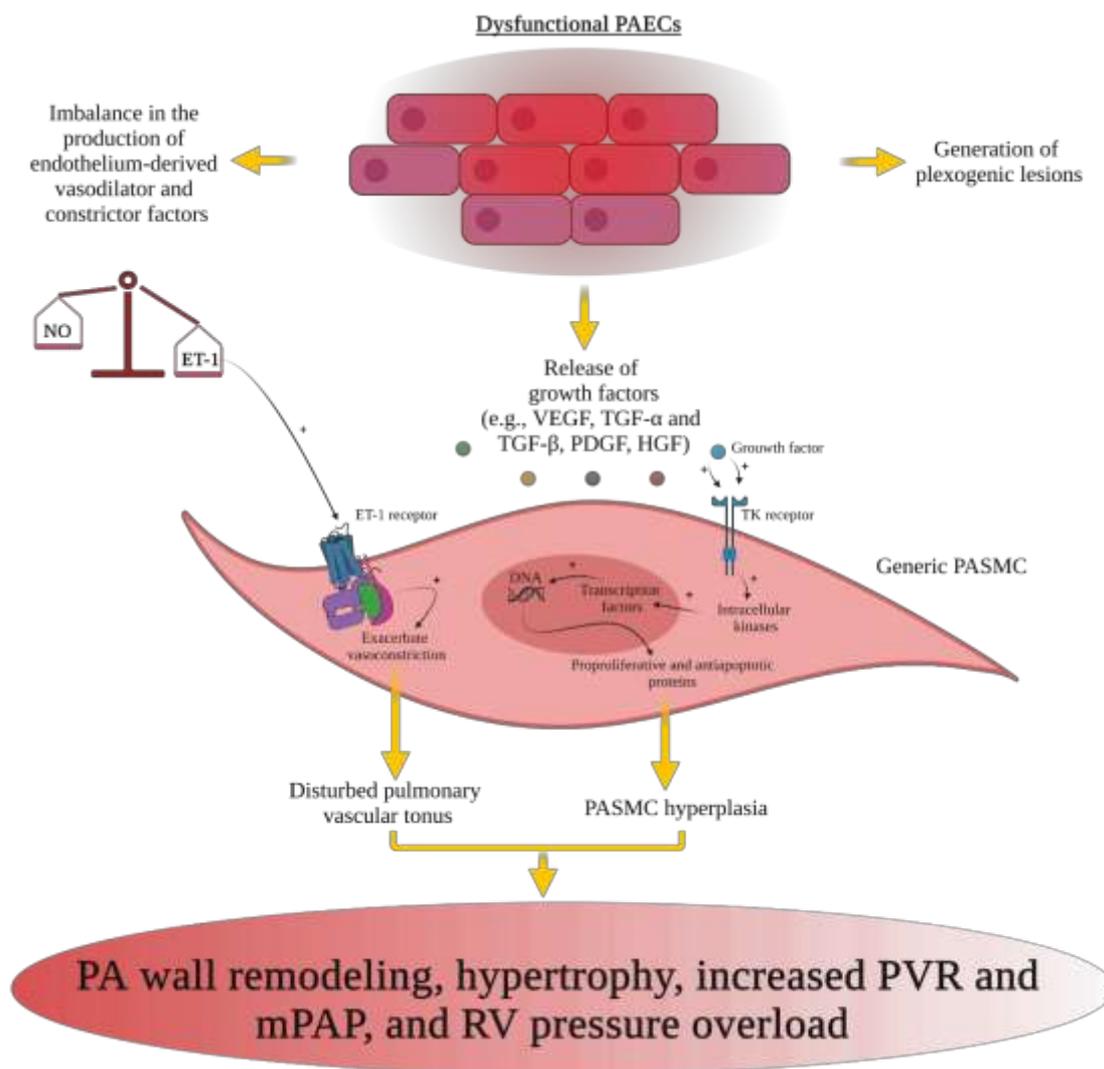


Figure 2. Disturbed crosstalk between pulmonary artery endothelial cells (PAECs) and pulmonary artery smooth muscle cells (PAMCs) during the remodeling process of pulmonary artery vessel walls. The hyperproliferation of PAECs induces generation of plexogenic lesions. In addition, dysfunctional endothelium releases growth factors that activate, tyrosine kinase (TK) receptors in PAMCs, leading to signaling downstream, which stimulates intracellular kinases. Subsequently, these kinases activate transcription factors in the nucleus that, in turn, induce the synthesis of proliferative and antiapoptotic proteins. This event culminates in PAMC 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.

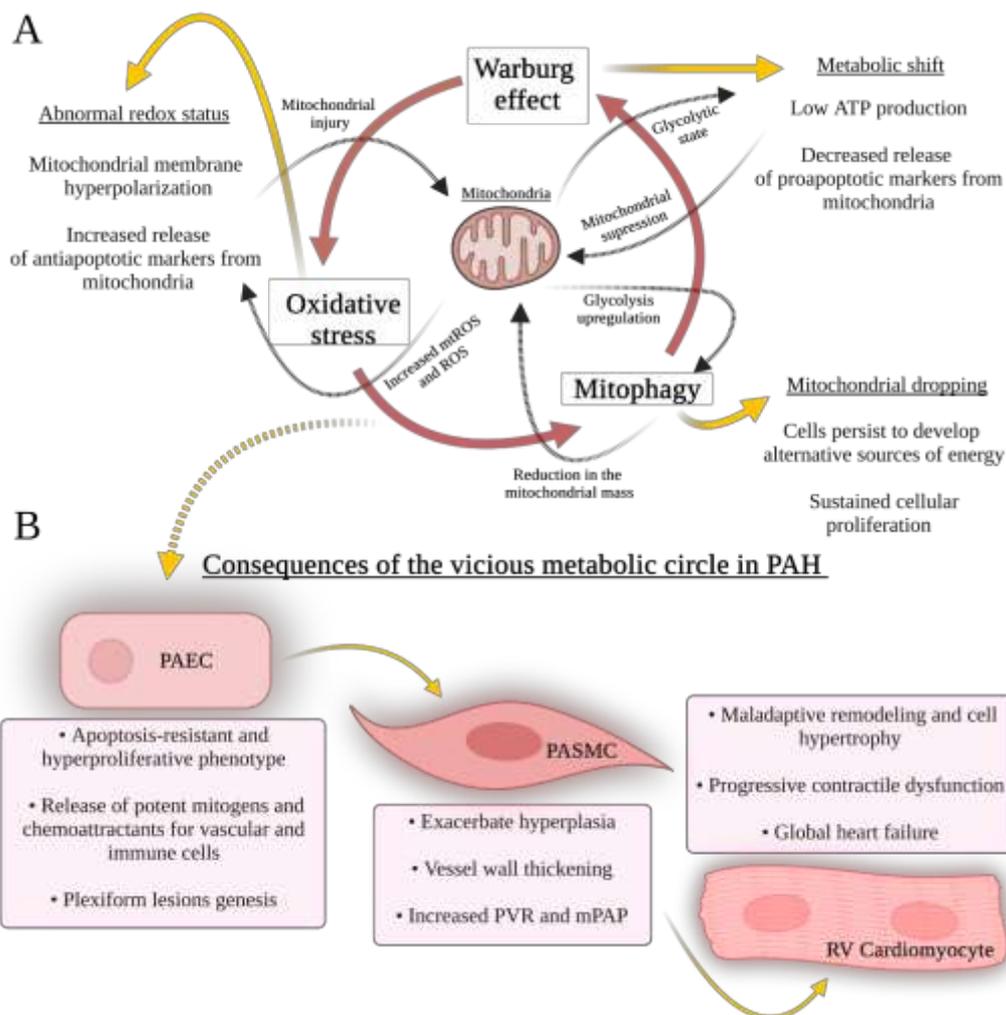


Figure 3. Overview of the metabolic theory of pulmonary arterial hypertension (PAH). (A) Vicious cycle between the Warburg effect, oxidative stress, and mitophagy. Note that PAH pathogenesis is depicted by different biomolecular abnormalities observed during disease progression, such as the metabolic 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 proliferative 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 1 α (HIF-1 α), 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 is 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 endothelin-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 (PCK δ), 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-1 α [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-1 α -induced lincRNA-p21 is able to bind HIF-1 α and Von Hippel-Lindau (VHL) and thus disrupts the VHL-HIF-1 α interaction. This disassociation attenuates VHL-mediated HIF-1 α ubiquitination and

causes HIF-1 α accumulation. This indicates the existence of a positive feedback loop between HIF-1 α and lincRNA-p21 that promotes glycolysis. Thus, HIF-1 α is further involved in the switch from oxidative phosphorylation to glycolysis in pulmonary hypertensive PAECs [10]. In the context of PAH, HIF-1 α 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 PASC bioenergetics by preventing the metabolic shift from cellular respiration to glycolysis, PASC 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.

References

- [1] **Humbert M, Guignabert C, Bonnet S, Dorfmüller P, Klinger JR, Nicolls MR, Olschewski AJ, Pullamsetti SS, Schermuly RT, Stenmark KR, et al.** Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur Respir J.* 2019; 53(1): 1801887.
- [2] **Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R.** Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J.* 2019; 53(1): 1801913.
- [3] **Voelkel NF, Cool C, Taraceviene-Stewart L, Geraci MW, Yeager M, Bull T, Kasper M, Tuder RM.** Janus face of vascular endothelial growth factor: the obligatory survival factor for lung vascular endothelium controls precapillary artery remodeling in severe pulmonary hypertension. *Crit Care Med.* 2002; 30(5 Suppl): S251-256.
- [4] **Schermuly RT, Ghofrani HA, Wilkins MR, Grimminger F.** Mechanisms of disease: pulmonary arterial hypertension. *Nat Rev Cardiol.* 2011; 8(8): 443-455.
- [5] **Bourgeois A, Omura J, Habbout K, Bonnet S, Boucherat O.** Pulmonary arterial hypertension: new pathophysiological insights and emerging therapeutic targets. *Int J Biochem Cell Biol.* 2018; 104: 9-13.
- [6] **Voelkel NF, Quaife RA, Leinwand LA, Barst RJ, McGoon MD, Meldrum DR, Dupuis J, Long CS, Rubin LJ, Smart FW, et al.** Right ventricular function and failure: report of a National Heart, Lung, and Blood Institute working group on cellular and molecular mechanisms of right heart failure. *Circulation.* 2006; 114(17): 1883-1891.
- [7] **Barnes H, Brown Z, Burns A, Williams T.** Phosphodiesterase 5 inhibitors for pulmonary hypertension. *Cochrane Database Syst Rev.* 2019; 1: CD012621.
- [8] **Vander Heiden MG, Cantley LC, Thompson CB.** Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science.* 2009; 324(5930): 1029-1033.
- [9] **Archer SL.** Acquired mitochondrial abnormalities, including epigenetic inhibition of superoxide dismutase 2, in pulmonary hypertension and cancer: therapeutic implications. *Adv Exp Med Biol.* 2016; 903: 29-53.
- [10] **Marshall JD, Bazan I, Zhang Y, Fares WH, Lee PJ.** Mitochondrial dysfunction and pulmonary hypertension: cause, effect, or both. *Am J Physiol Lung Cell Mol Physiol.* 2018; 314(5): L782-796.
- [11] **Paulin R, Michelakis ED.** The metabolic theory of pulmonary arterial hypertension. *Circ Res.* 2014; 115(1): 148-164.
- [12] **Stenmark KR, Meyrick B, Galie N, Mooi WJ, McMurtry IF.** Animal models of pulmonary arterial hypertension: the hope for etiological discovery and pharmacological cure. *Am J Physiol Lung Cell Mol Physiol.* 2009; 297(6): L1013-1032.
- [13] **Sztuka K, Jasinska-Stroschein M.** Animal models of pulmonary arterial hypertension: a systematic review and meta-analysis of data from 6126 animals. *Pharmacol Res.* 2017; 125(Pt B): 201-214.

- [14] **Stenmark KR, Fagan KA, Frid MG.** Hypoxia-induced pulmonary vascular remodeling: cellular and molecular mechanisms. *Circ Res.* 2006; 99(7): 675-691.
- [15] **Hill NS, Gillespie MN, McMurtry IF.** Fifty years of monocrotaline-induced pulmonary hypertension: what has it meant to the field? *Chest.* 2017; 152(6): 1106-1108.
- [16] **Taraseviciene-Stewart L, Kasahara Y, Alger L, Hirth P, Mc Mahon G, Waltenberger J, Voelkel NF, Tuder RM.** Inhibition of the VEGF receptor 2 combined with chronic hypoxia causes cell death-dependent pulmonary endothelial cell proliferation and severe pulmonary hypertension. *FASEB J.* 2001; 15(2): 427-438.
- [17] **Saygin D, Tabib T, Bittar HET, Valenzi E, Sembrat J, Chan SY, Rojas M, Lafyatis R.** Transcriptional profiling of lung cell populations in idiopathic pulmonary arterial hypertension. *Pulm Circ.* 2020; 10(1): 1-15.
- [18] **Aggarwal S, Mannam P, Zhang J.** Differential regulation of autophagy and mitophagy in pulmonary diseases. *Am J Physiol Lung Cell Mol Physiol.* 2016; 311(2): L433-452.
- [19] **DeBerardinis RJ, Lum JJ, Hatzivassiliou G, Thompson CB.** The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. *Cell Metab.* 2008; 7(1): 11-20.
- [20] **Christofk HR, Vander Heiden MG, Harris MH, Ramanathan A, Gerszten RE, Wei R, Fleming MD, Schreiber SL, Cantley LC.** The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. *Nature.* 2008; 452(7184): 230-233.
- [21] **Dromparis P, Sutendra G, Michelakis ED.** The role of mitochondria in pulmonary vascular remodeling. *J Mol Med (Berl).* 2010; 88(10): 1003-1010.
- [22] **Boucherat O, Peterlini T, Bourgeois A, Nadeau V, Breuils-Bonnet S, Boilet-Molez S, Potus F, Meloche J, Chabot S, Lambert C, et al.** Mitochondrial HSP90 accumulation promotes vascular remodeling in pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2018; 198(1): 90-103.
- [23] **Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, et al.** 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2016; 37(1): 67-119.
- [24] **Xu W, Koeck T, Lara AR, Neumann D, DiFilippo FP, Koo M, Janocha AJ, Masri FA, Arroliga AC, Jennings C, et al.** Alterations of cellular bioenergetics in pulmonary artery endothelial cells. *Proc Natl Acad Sci U S A.* 2007; 104(4): 1342-1347.
- [25] **Sun X, Kumar S, Sharma S, Aggarwal S, Lu Q, Gross C, Rafikova O, Lee SG, Dasarathy S, Hou Y, et al.** Endothelin-1 induces a glycolytic switch in pulmonary arterial endothelial cells via the mitochondrial translocation of endothelial nitric oxide synthase. *Am J Respir Cell Mol Biol.* 2014; 50(6): 1084-1095.
- [26] **Haslip M, Dostanic I, Huang Y, Zhang Y, Russell KS, Jurczak MJ, Mannam P, Giordano F, Erzurum SC, Lee PJ.** Endothelial uncoupling protein 2 regulates mitophagy and pulmonary hypertension during intermittent hypoxia. *Arterioscler Thromb Vasc Biol.* 2015; 35(5): 1166-1178.
- [27] **Wedgwood S, Lakshminrusimha S, Schumacker PT, Steinhorn RH.** Cyclic stretch stimulates mitochondrial reactive oxygen species and Nox4 signaling in pulmonary artery smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol.* 2015; 309(2): L196-203.
- [28] **Dohi T, Beltrami E, Wall NR, Plescia J, Altieri DC.** Mitochondrial survivin inhibits apoptosis and promotes tumorigenesis. *J Clin Invest.* 2004; 114(8): 1117-1127.
- [29] **McMurtry MS, Archer SL, Altieri DC, Bonnet S, Haromy A, Harry G, Bonnet S, Puttagunta L, Michelakis ED.** Gene therapy targeting survivin selectively induces

- pulmonary vascular apoptosis and reverses pulmonary arterial hypertension. *J Clin Invest.* 2005; 115(6): 1479-1491.
- [30] **McMurtry MS, Bonnet S, Wu X, Dyck JR, Haromy A, Hashimoto K, Michelakis ED.** Dichloroacetate prevents and reverses pulmonary hypertension by inducing pulmonary artery smooth muscle cell apoptosis. *Circ Res.* 2004; 95(8): 830-840.
- [31] **Michelakis ED, McMurtry MS, Wu XC, Dyck JR, Moudgil R, Hopkins TA, Lopaschuk GD, Puttagunta L, Waite R, Archer SL.** Dichloroacetate, a metabolic modulator, prevents and reverses chronic hypoxic pulmonary hypertension in rats: role of increased expression and activity of voltage-gated potassium channels. *Circulation.* 2002; 105(2): 244-250.
- [32] **Pak O, Sommer N, Hoeres T, Bakr A, Waisbrod S, Sydykov A, Haag D, Esfandiary A, Kojonazarov B, Veit F et al.** Mitochondrial hyperpolarization in pulmonary vascular remodeling. Mitochondrial uncoupling protein deficiency as disease model. *Am J Respir Cell Mol Biol.* 2013; 49(3): 358-367.
- [33] **Linqing L, Yuhan Q, Erfei L, Yong Q, Dong W, Chengchun T, Gaoliang Y, Bo L.** Hypoxia-induced PINK1/Parkin-mediated mitophagy promotes pulmonary vascular remodeling. *Biochem Biophys Res Commun.* 2021; 534: 568-575.
- [34] **Bayeva M, Gheorghiade M, Ardehali H.** Mitochondria as a therapeutic target in heart failure. *J Am Coll Cardiol.* 2013; 61(6): 599-610.
- [35] **Piao L, Marsboom G, Archer SL.** Mitochondrial metabolic adaptation in right ventricular hypertrophy and failure. *J Mol Med (Berl).* 2010; 88(10): 1011-1020.
- [36] **Gomez-Arroyo J, Mizuno S, Szczepanek K, Van Tassell B, Natarajan R, dos Remedios CG, Drake JI, Farkas L, Kraskauskas D, Wijesinghe DS, et al.** Metabolic gene remodeling and mitochondrial dysfunction in failing right ventricular hypertrophy secondary to pulmonary arterial hypertension. *Circ Heart Fail.* 2013; 6(1): 136-144.
- [37] **Liu A, Philip J, Vinnakota KC, Van den Bergh F, Tabima DM, Hacker T, Beard DA, Chesler NC.** Estrogen maintains mitochondrial content and function in the right ventricle of rats with pulmonary hypertension. *Physiol Rep.* 2017; 5(6): e13157.
- [38] **Daicho T, Yagi T, Abe Y, Ohara M, Marunouchi T, Takeo S, Tanonaka K.** Possible involvement of mitochondrial energy-producing ability in the development of right ventricular failure in monocrotaline-induced pulmonary hypertensive rats. *J Pharmacol Sci.* 2009; 111(1): 33-43.
- [39] **Zungu-Edmondson M, Shults NV, Wong CM, Suzuki YJ.** Modulators of right ventricular apoptosis and contractility in a rat model of pulmonary hypertension. *Cardiovasc Res.* 2016; 110(1): 30-39.
- [40] **Lee DS, Jung YW.** Protective effect of right ventricular mitochondrial damage by cyclosporine A in monocrotaline-induced pulmonary hypertension. *Korean Circ J.* 2018; 48(12): 1135-1144.
- [41] **Power AS, Norman R, Jones TLM, Hickey AJ, Ward ML.** Mitochondrial function remains impaired in the hypertrophied right ventricle of pulmonary hypertensive rats following short duration metoprolol treatment. *PLoS One.* 2019; 14(4): e0214740.

ABOUT AUTHORS



Dr Allan K N Alencar, PhD. Adjunct Professor of Pharmacology and Molecular Biology at Faculty of Medicine of Petrópolis - *School Clinic*, Petrópolis, Rio de Janeiro, Brazil. PhD in Pharmacology and Medicinal Chemistry by the Federal University of Rio de Janeiro, (UFRJ), Rio de Janeiro, Brazil. Awarded as the best Researcher of Brazil (2015) by the Brazilian Association of Biotechnology (*Biotech Space*). Received the first Research Innovation Award promoted by the Fleury Group (2015), Brazil. His doctoral thesis has been awarded as the best by the Postgraduate Program in Pharmacology and Medicinal Chemistry, UFRJ, Rio de Janeiro, Brazil (2016). Developed part of his PhD Thesis at the Department of Anesthesiology, Laboratory of Cardiac Aging, Baptist Hospital, Wake Forest University, North Carolina, USA. Post-doctoral degree (FAPERJ NOTA 10) from 2016-2019, at the Cardiovascular Pharmacology Laboratory, ICB, UFRJ. His basic research focus on development of novel drug candidates and discovery of new targets for the treatment of pulmonary arterial hypertension and right ventricular dysfunction/failure, type 2 diabetes, metabolic disturbances and diabetic cardiomyopathy, myocardial and vessel wall remodeling, inflammation and oxidative stress.



Fernanda Cruz, MD, PhD. Adjunct Professor at the Carlos Chagas Filho Biophysics Institute (IBCCF), Federal University of Rio de Janeiro (UFRJ). CNPq Researcher 2, Young Scientist of Our State (FAPERJ). Head of the Regenerative Medicine Program, IBCCF, UFRJ. Treasurer of the Brazilian Society of Physiology (SBFis) Management 2021-2022. Permanent advisor of the postgraduate course in Biological Sciences - Physiology (concept 7) IBCCF, UFRJ. Collaborating advisor at the Postgraduate Course in Clinical Medicine, Faculty of Medicine, UFRJ. Physician (cum laude) graduated from the Faculty of Medicine of UFRJ (2011/02). PhD in Biological Sciences (Physiology), IBCCF, UFRJ (2013). Postdoctoral fellow in regenerative medicine and bioengineering, from 2013 to 2014, at the University of Vermont School of Medicine (United States). Post-doctoral degree (Joven Talentos Scholarship - CNPq) from 2014-2017, at the Pulmonary Research Laboratory, IBCCF, UFRJ. Post Doctorate (Scholarship Grade Ten - FAPERJ) 2017-2018, IBCCF, UFRJ. Laureate with the L'oréal-Unesco-ABC Award for Women in Science 2018, and by the American Thoracic Society in 2019, 2018, 2016, 2014 and 2010. She was elected an affiliate member of the Young Medical Leadership Program of the National Academy of Medicine (2015-2020) and member of the 2019 Young Physician Leaders of the Interacademies Partnership for Health. Linked to research projects related to pulmonary physiology and pathophysiology, immunology, regenerative medicine, bioengineering and intensive care medicine. Experience in designing and planning experimental and clinical studies.



Patricia Rocco, MD, PhD, Full Professor at the Federal University of Rio de Janeiro, where she heads the Laboratory of Pulmonary Investigation. Elected Member of the National Academy of Medicine in Brazil and Brazilian Academy of Science. Prof. Rocco has authored and co-authored more than 400 peer-reviewed publications and 125 book chapters. Her publications have been frequently highlighted in editorials published in *Critical Care Medicine*, *Critical Care* and *Anesthesiology*. She is the President of the Brazilian Society of Physiology (2021-2022). Her research activities focus mainly on the development of new therapies for lung diseases.



Pedro Leme Silva, PhD. Pedro is currently Adjunct Professor III at the Pulmonary Research Laboratory of the Biophysics Institute Carlos Chagas Filho, General Coordinator of Graduation at IBCCF, Young Scientist of Our State (FAPERJ) since November 2015 and Research Productivity Scholar 2 - CA BF since 2016. First Laureate as a Young Researcher at the Latin American Sepsis Institute - Instituto Merieux. Former head of the Thematic Regenerative Medicine Program (2017 to 2019), through which I organized monthly meetings to discuss innovative methods with biotechnology companies (Thermo Fisher Scientific, Eppendorf and Promega) in an attempt to bring universities and companies closer together. Contributed for 16 months with experiments and analyzes for the company Startup Biozeus in the search for innovative drugs for the treatment of pulmonary arterial hypertension. Pedro works on projects related to: 1) ventilatory strategies in pulmonary diseases; 2) pharmacological treatment in models of pulmonary arterial hypertension induced by monocrotaline; 3) pulmonary biological markers; 4) Physiological Interactions between the Respiratory System and Cardiovascular System and Nervous System.