Mitochondrial metabolism, redox signaling, and fusion: a mitochondria-ROS-HIF-1α-Kv1.5 O2-sensing pathway at the intersection of pulmonary hypertension and cancer

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Archer SL, Gomberg-Maitland M, Maitland ML, Rich S, Garcia JG, Weir EK. Mitochondrial metabolism, redox signaling, and fusion: a mitochondria-ROS-HIF-1α-Kv1.5 O2-sensing pathway at the intersection of pulmonary hypertension and cancer. *Am J Physiol Heart Circ Physiol* 294: H570–H578, 2008. First published December 14, 2007; doi:10.1152/ajpheart.01324.2007.—Pulmonary arterial hypertension (PAH) is a lethal syndrome characterized by vascular obstruction and right ventricular failure. Although the fundamental cause remains elusive, many predisposing and disease-modifying abnormalities occur, including endothelial injury/dysfunction, bone morphogenetic protein receptor-2 gene mutations, decreased expression of the O2-sensitive K^+ channel (Kv1.5), transcription factor activation [hypoxia-inducible factor-1α (HIF-1α) and nuclear factor-activating T cells], de novo expression of survivin, and increased expression/activity of both serotonin transporters and platelet-derived growth factor receptors. Together, these abnormalities create a cancerlike, proliferative, apoptosis-resistant phenotype in pulmonary artery smooth muscle cells (PASMCs). A possible unifying mechanism for PAH comes from studies of fawn-hooded rats, which manifest spontaneous PAH and impaired O2 sensing. PASMC mitochondria normally produce reactive O2 species (ROS) in proportion to Po2. Superoxide dismutase 2 (SOD2) converts intramitochondrial superoxide to diffusible H_2O_2, which serves as a redox-signaling molecule, regulating pulmonary vascular tone and structure through effects on Kv1.5 and transcription factors. O2 sensing is mediated by this mitochondria-ROS-HIF-1α-Kv1.5 pathway. In PAH and cancer, mitochondrial metabolism and redox signaling are reversibly disordered, creating a pseudohypoxic redox state characterized by normoxic decreases in ROS, a shift from oxidative to glycolytic metabolism and HIF-1α activation. Three newly recognized mitochondrial abnormalities disrupt the mitochondria-ROS-HIF-1α-Kv1.5 pathway: *1*) mitochondrial pyruvate dehydrogenase kinase activation, *2*) SOD2 deficiency, and *3*) fragmentation and/or hyperpolarization of the mitochondrial reticulum. The pyruvate dehydrogenase kinase inhibitor, dichloroacetate, corrects the mitochondrial abnormalities in experimental models of PAH and human cancer, causing a regression of both diseases. Mitochondrial abnormalities that disturb the ROS-HIF-1α-Kv1.5 O2-sensing pathway contribute to the pathogenesis of PAH and cancer and constitute promising therapeutic targets.

hypoxia-inducible factor-1α; nuclear factor-activating T cells; voltage-gated potassium channels; fawn-hooded rats; mitochondrial fusion; pyruvate dehydrogenase kinase; lung cancer; reactive oxygen species; mitochondrial electron transport chain

PULMONARY ARTERIAL HYPERTENSION is a disease of the pulmonary vasculature, which occurs in a rare idiopathic form (sporadic-90%, familial-10%) and, more commonly, as a syndrome associated with connective tissue disease, congenital heart disease, anorexigen use (dexfenfluramine), portopulmonary disease, and human immunodeficiency virus (1). Predominantly affecting young women (female/male, 3/1), PAH has a 15% 1-yr mortality despite current therapy (91). The reported prevalence of idiopathic PAH (1/1,000,000) is likely an underestimation, due to lack of data on PAH syndromes in Africa and Asia, related to sickle cell disease and schistosomiasis, and to insensitivity of the history and physical examination, as suggested by the high prevalence of moderate pulmonary hypertension in active surveillance studies of high-risk cohorts with connective tissue diseases (71, 102).

Pathogenesis of PAH

PAH is a panvasculopathy. Abnormalities in each layer of the blood vessel contribute to this syndrome of obstructed, constricted small pulmonary arteries, right ventricular hy-

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pertrophy, and right ventricular failure. In the blood there is elevated plasma serotonin (40). In the endothelium there is a decreased ratio of vasodilators to constrictors (29, 88, 89). It is hypothesized that widespread endothelial apoptosis, early in PAH, culminates in the selection of apoptosis-resistant endothelial precursor cells that proliferate and ultimately form plexiform lesions later in the disease (80). In the media, pulmonary artery smooth muscle cell (PASMC) proliferation is enhanced, whereas apoptosis is depressed (54, 55, 57, 60). Many factors drive PASMC proliferation, including bone morphogenetic protein receptor-2 (BMPR-2) mutations (63) de novo expression of the anti-apoptotic protein survivin (54, 55), increased expression/activity of the serotonin transporter (SERT) (51), and increased expression/activity of platelet-derived growth factor receptor. Decreased expression of the voltage-gated channels Kv1.5 occurs in all forms of PAH and results in membrane depolarization and elevations of cytosolic K^+ and Ca^{2+} (75, 106). Although the Kv channel link to the voltage-gated Ca^{2+} channel is very important, over time the expression/function of L-type Ca^{2+} channels is downregulated in experimental PAH (unpublished observation). The persistent elevation of cytosolic Ca^{2+} in PAH may also reflect upregulation of Trp6 channels (105). Interestingly, early in the evolution of PAH in BMPR-2 dominant-negative mice, before vascular remodeling occurs (104), an elevation of cytosolic Ca^{2+} is driven by activation of voltage-gated L-type Ca^{2+} channels (in response to loss of Kv1.5). We speculate that the Kv-membrane potential L-type Ca^{2+} channel pathway is downregulated later in the disease due to reduced protein expression of both channel types. This may explain why only 10% of PAH patients have a long-term response to Ca^{2+} channel blocker therapy (1).

PAH is also characterized by inappropriate transcription factor activation, notably normoxic activation of hypoxia-inducible factor (HIF-1α) (20) and Ca^{2+}-calcineurin-dependent activation of nuclear factor-activating T cells (NFAT) (21). In the adventitia metalloprotease activation (31) causes architectural disruption, permitting cell migration and generating mitogenic peptides (tenascin) (31). Finally, infiltration of the lung with inflammatory cells (14, 22), endothelial-precursor cells (24), mesenchymal stem cells (35), and bone marrow-derived stem cells (74, 79, 108) occurs in PAH.

With the discovery of BMPR mutations in familial PAH, the cause of PAH appeared to be elucidated (33, 45). These mutations, which likely result in loss of function, favor PASMC proliferation (107). Consistent with this, a transgenic mouse with SMC-specific overexpression of a human dominant-negative BMPR-2 transgene develops PAH (101). However, BMPR-2 mutations occur in only 10% of PAH patients (66), and even in familial PAH, penetrance is low. Whereas modifier genes, such as SERT, may explain variable penetrance, BMPR-2 mutations only partially explain the cause of PAH (67). Moreover, BMPR-2 haploinsufficiency causes minimal (16) or no (50) PAH, although it enhances serotonin-mediated vasoconstriction (50). Finally, whereas BMPR-2 levels decline with the development of experimental PAH, adenoviral BMPR-2 gene therapy does not reduce PAH in the monocrotaline rat model (56). Although clearly associated with PAH, aberrant BMPR-2 function does not appear to be necessary or sufficient to cause PAH, suggesting that there could be another unifying cause for PAH.

Similarities Between Cancer and PAH

Otto Warburg, recipient of the 1931 Nobel Prize for his work on cellular respiration, proposed that a shift in glucose metabolism from oxidative phosphorylation to glycolysis (despite adequate O_2 supply) was central to the cause/maintenance of cancers (93). New data show that PAH and cancer share the Warburg phenotype (19–21), indicated by mitochondrial hyperpolarization (19, 20), depressed activity of pyruvate dehydrogenase complex and depressed H_2O_2 production (54). This supports the hypothesis of Voelkel et al. (92) that PAH is between inflammation and cancer (92). We propose that in PAH (20) and cancer (13, 19, 52), the rapid, reversible metabolic/redox shifts that initiate hypoxic pulmonary vasoconstriction (HPV) (i.e., decreased ROS generation, increased reduction of redox couples such as NADH and glutathione, and Kv1.5 inhibition) (10, 99) become entrenched and occur independent of P_{O_2} due to mitochondrial abnormalities that create a pseudohypoxic environment with glycolytic predominance and normoxic HIF-1α activation. This metabolic shift suppresses Kv1.5 expression, leading to membrane depolarization and an elevation of cytosolic K^+ and Ca^{2+}. In both PAH PASMC and cancer cell lines, this creates a proliferative, apoptosis-resistant phenotype.

Hypothesis

The intersection of O_2 sensing, PAH, and cancer suggest a unifying hypothesis, namely that PAH is a mitochondrial disorder resulting from reversible disruption of the mitochondria-ROS-HIF-1α-Kv1.5 O_2-sensing pathway (Fig. 1). This mitochondrial hypothesis builds on several prior theories: the Redox Hypothesis for HPV (10, 99), the Mitochondrial Metabolic Hypothesis of PAH (39, 55, 60), and the Warburg Hypothesis of carcinogenesis (19, 93) (Fig. 2).

Impaired Mitochondrial Fusion in PAH

The mitochondrial reticulum permeates the PASMC cytosol. With its close proximity to the plasma and nuclear membranes, it is well positioned to coordinate redox signaling. Mitochondria not only move within the cytosol (15, 17, 18, 34, 81) but also rapidly join and break apart (fusion and fission) processes that are regulated by soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)-like proteins, including mitofusin-1 and -2 (17, 81). Fusion is an important mechanism for redistribution of mitochondrial proteins/genes, protecting cells from the consequences of mitochondrial DNA mutations (82). Mitofusins-1 and -2 are expressed in the lung (82). Their hydrophobic heptad repeats mediate tethering through a GTPase-dependent mechanism (82). Mitophospholipase D enhances fusion by generating the fusogenic lipid, phosphatidic acid (43).

Mitofusin-2 not only controls mitochondrial form and function (20, 28, 36, 43, 65, 81–83) but also regulates SMC proliferation (27, 28). Indeed, mitofusin-2 was originally named hyperplasia suppressor gene because it prevents SMC hyperplasia in injured arteries by causing cell-cycle arrest through inhibition of ERK/MAPK signaling (28).

Fig. 1. Disruption of a mitochondrial O_2-sensing pathway in cancer and pulmonary arterial hypertension (PAH). Several mitochondrial disorders [pathological activation of pyruvate dehydrogenase kinase (PDK) reduced SOD2 activity/expression, impaired mitochondrial fusion] limit the production of H_2O_2 and activate a downstream pathway that promotes excess cell proliferation and impairs apoptosis. Key abnormalities include normoxic activation of hypoxia-inducible factor-1α (HIF-1α) and decreased expression of the O_2-sensitive Kv channel, Kv1.5. These abnormalities are shared, at least in part, by cancer, and each is a potential therapeutic target. Note the similarities to the pathway for O_2 sensing that initiates hypoxic pulmonary vasoconstriction. ETC, electron transport chain; ROS, reactive O_2 species; PASMCs, pulmonary artery smooth muscle cells; NFAT, nuclear factor-activating T cells, PDH, pyruvate dehydrogenase.
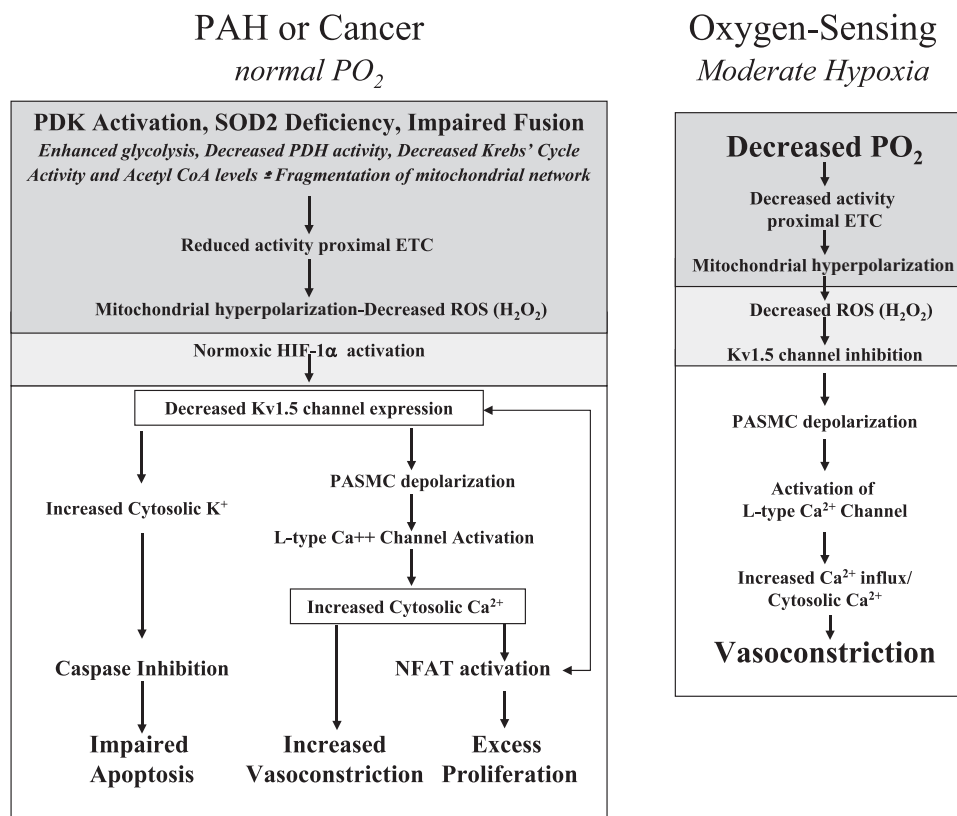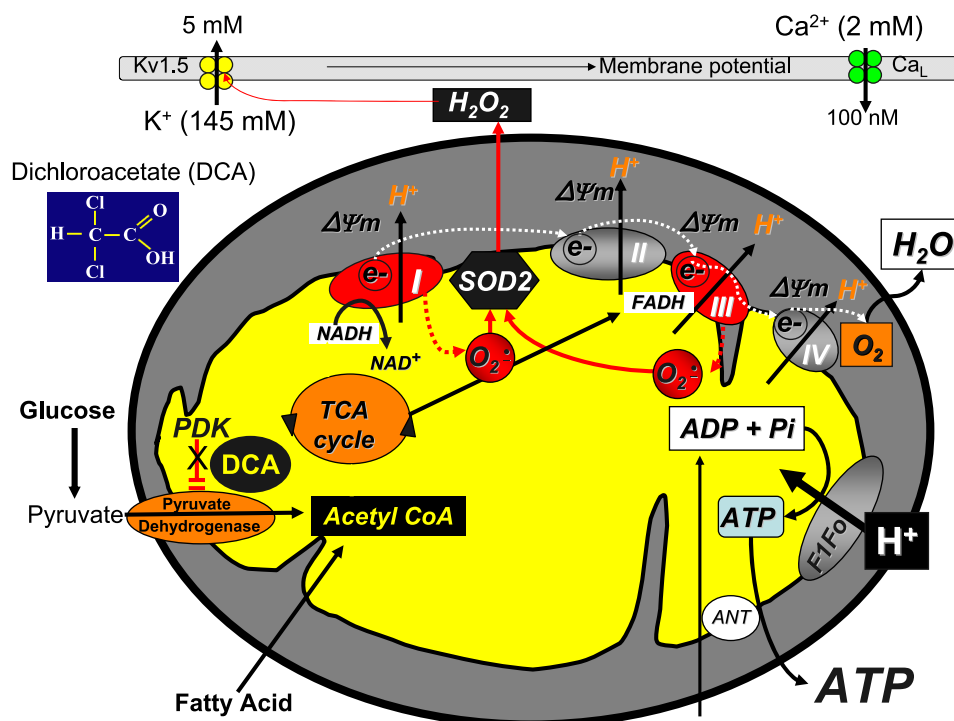
Impaired mitochondrial fusion also alters mitochondrial membrane potential ($\Delta\Psi m$) and respiration (27). Preliminary data presented here suggest that decreased mitofusin-2 contributes to disruption of mitochondrial fusion seen in PAH (20) (Fig. 3).

Mitochondrial ROS as Redox Signaling Molecules in O_2 Sensing

Tissues in the homeostatic O_2 sensing system (e.g., SMCs in the resistance pulmonary arteries, ductus arteriosus and feto-

Fig. 2. Changes in mitochondrial function in cancer and PAH. Schematic showing ROS generation from mitochondrial ETC complexes I and III. The superoxide is converted to H_2O_2 by SOD2. Dichloroacetate (DCA) can restore ROS production and mitochondrial membrane potential ($\Delta\Psi m$) by inhibiting PDK and thereby activating PDH with an attendant increase in intramitochondrial acetyl-CoA. This drives Krebs' cycle and increases availability of electron donors (NADH and FADH) for complex I and III within the mitochondria. Dichloroacetate effectively regresses experimental PAH and human cancers by exploiting a shared abnormality (PDK activation). TCA, tricarboxylic acid cycle; F1Fo, ATP synthase; ANT = ADP/ATP antiporter.
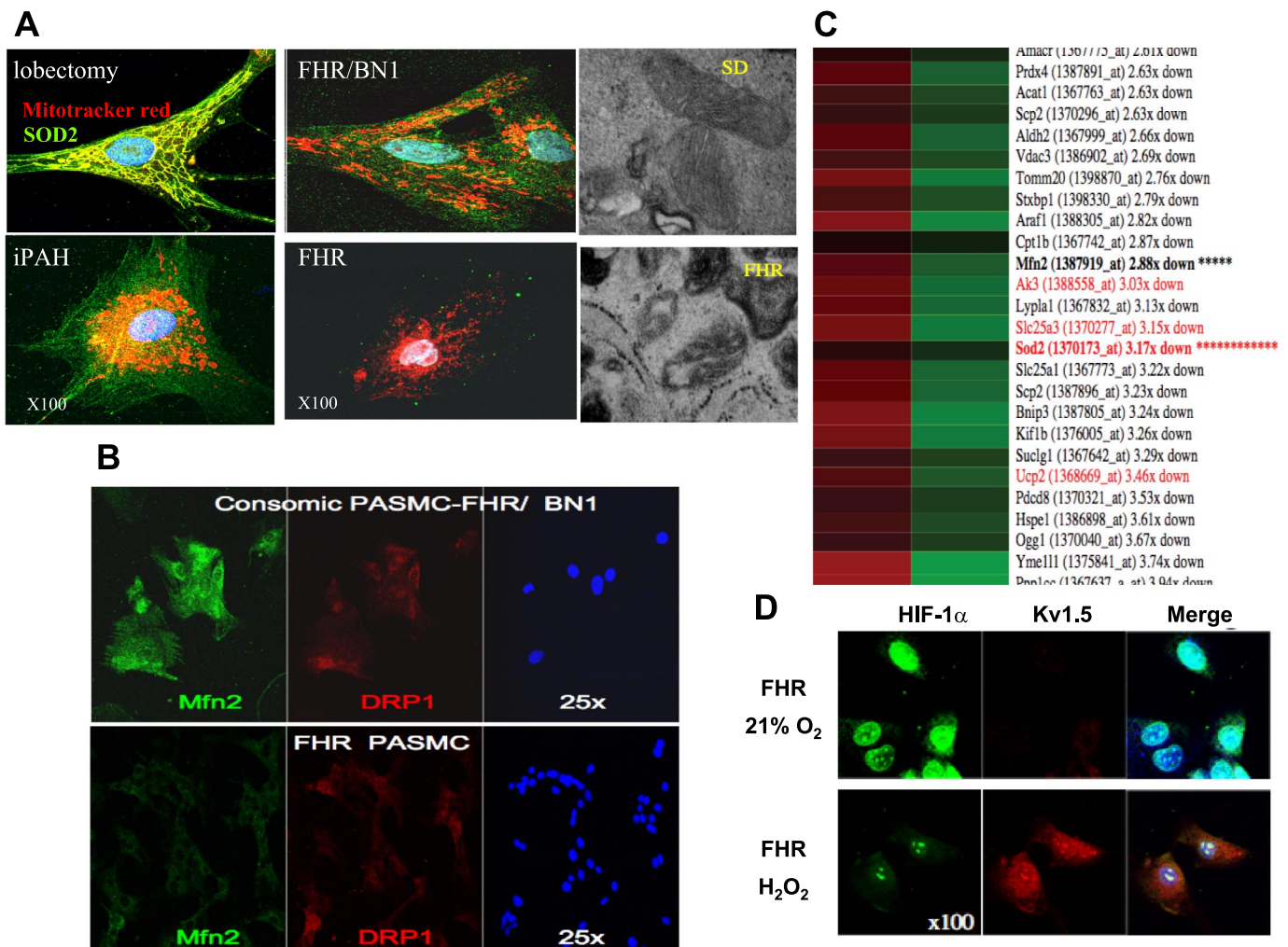
Fig. 3. Disruption in mitochondrial fusion in PAH: *A*: confocal microscopy reveals impaired mitochondrial fusion and SOD2 downregulation in human PAH PASMCs. Electron microscopy shows that fawn-hooded rat (FHR) PASMCs have small dysmorphic mitochondria at 12 wk, before development of PAH reproduced from Ref. 20. *B*: confocal microscopy reveals a deficiency of mitofusin 2 (green) in FHR PASMCs. There is no difference in dynamin-related protein 1 (DRP1) between FHR and consomic PASMCs in this representative image, suggesting the abnormality in FHR is impaired fusion rather than enhanced fission. Note increased 4,6-diamidino-2-phenylindole-stained nuclei (blue) in FHR, reflecting the accelerated smooth muscle cell proliferation in FHR. *C*: portion of a DNA microarray showing changes in mitochondria-related genes in FHR pulmonary artery. Probe sets with hybridization changes ≥2.0× between FHR at 20 and 40 wk, and no concordant changes in age-matched control rats are shown. Note depression of SOD2 and mitofusin-2 (mfn2). Chromosome 1 genes are highlighted in red. Values shown as a heat map (Java TreeView). *D*: 48-h incubation in H_2O_2 reverses nuclear translocation of HIF-1α and restores Kv1.5 (red) in FHR PASMCs, consistent with the hypothesis that a loss of mitochondrial ROS production causes the FHR's abnormalities, reproduced from Ref. 20. iPAH, idiopathic PAH; BN1, consomic rat.

placental arteries, and the carotid and neuroepithelial bodies) use a fairly well-conserved O_2 sensor-effector unit to optimize O_2 uptake/delivery (99). Cytochrome-based redox sensors monitor functions that, while tied to oxidative metabolism, are upstream from ATP production, such as the activity of the electron transport chain. They then generate redox signaling molecules (ROS and redox couples) that regulate the activity of O_2-sensitive K^+ channels. Teleologically, there is little value in ATP-sensing, because changes in high-energy phosphates occur only late with anoxia or severe ischemia (7).

The initial clue that mitochondria might serve as vascular O_2 sensors came from the parallels in the cardiovascular responses to authentic hypoxia and inhibitors of the proximal electronic transport chain (ETC) (rotenone-complex I; antimycin-complex III) (78). These particular ETC inhibitors are unique in mimicking hypoxia, causing the opposing effects on pulmo-

nary versus systemic arteries (constriction vs. dilatation) and activating the carotid body. The other class of agents that mimic hypoxia are reducing/oxidizing agents, which emulate hypoxia and normoxia, respectively (76).

A Mitochondrial O_2 Sensor in HPV

In aerobic metabolism, electrons are passed down a redox-potential gradient in the ETC from donors (mitochondrial NADH and FADH) to molecular O_2. At complex IV, cytochrome oxidase transfers the reducing equivalents to O_2, creating water. This electron flux powers H^+ ion extrusion, creating the proton-motive force responsible for the mitochondria's negative membrane potential ($-\Delta\Psi m$), the potential that powers ATP-synthase (26) (Fig. 2). Although the ETC strives to keep the series of single electron transfers localized, there

are illicit side reactions between semiquinones and molecular O_2, resulting in a creation of superoxide anion (2, 3, 6, 59). The mitochondrial ETC is the major source of H_2O_2 in the cell, most of which comes from the mitochondrial superoxide dismutase (SOD2), which rapidly converts superoxide anion produced at complexes I and III (3) to H_2O_2 (26). ROS account for ~3% of net electron flux. Hypoxic inhibition of normoxic ROS production is unique to pulmonary arteries (3, 5, 6, 9, 10, 20, 25, 61, 62, 68, 69, 75) and occurs within seconds of moderate hypoxia, before onset of HPV. In some cases, the ROS appear to originate from mitochondria (3); in other cases, from an NAD(P)H oxidoreductase (61, 62, 69). It is likely that both enzyme cascades produce ROS; however, HPV persists in the absence of the gp91^{phox} containing NADPH oxidase (8). In most systemic arteries, ROS production is much lower than in the pulmonary arteries and is not inhibited by moderate hypoxia (38, 59). It is this unique ability to rapidly alter production of a diffusible ROS that allows PASMC mitochondria to control Kv channel function (3, 6).

H_2O_2, by virtue of its relatively nontoxic nature and moderate diffusion radius, serves as a signaling molecule communicating the P_{O_2} (sensed in the mitochondria) to the plasma membrane (Kv channels) and transcription factors (10, 99). This mitochondrial-based O_2 sensor is central to the mechanism of HPV (3, 10, 59, 95). Indeed, when pulmonary arteries lose this dynamic mitochondrial ROS generation, as occurs upon exposure to chronic hypoxia, HPV is depressed (53, 72, 75, 85). By regulating the gating of channels, such as Kv1.5, mitochondrial H_2O_2 determines PASMC membrane potential (11, 72, 76). During normoxia, mitochondria-derived H_2O_2 opens O_2-sensitive Kv channel in PASMCs; conversely, in hypoxia ROS withdrawal inhibits these channels, depolarizing PASMC membrane potential, increasing Ca^{2+} influx and initiating HPV (59). Certain Kv channels are O_2 sensitive (e.g., Kv1.5, Kv2.1, Kv3.1b, and Kv9.3), due in part to key sulfhydryl-containing amino acids (64). Although there is controversy regarding the vector of the effect of hypoxia on ROS (down vs. up; Refs. 49, 95, and 97; see recent debate; Refs. 94 and 98), both camps confirm a central role of the PASMC mitochondria as the source of signaling ROS (95–97).

Mitochondrial and Ion Channel Diversity

There is both ionic and mitochondrial diversity among arterial beds, which explains the localization of HPV (and perhaps PAH) to small pulmonary arteries (4, 11, 59). The mitochondria in resistance PASMCs are relatively unique in making a relatively large amount of ROS during normoxia and even more importantly this ROS production is rapidly inhibited by moderate hypoxia (20, 59). Likewise, these small arteries are enriched in O_2-sensitive Kv channels (11). The renal artery, for example, lacks the hypoxia-inhibited mitochondrial ROS signal and dilates in response to hypoxia. PASMCs are also enriched in SOD2 (relative to renal arteries) (59), which serves both to create this redox signaling molecule and to neutralize more toxic superoxide anion, thereby protecting mitochondrial DNA. SOD2 activity is dynamically regulated within optimal ranges—the lower limit being sufficient to remove mitochondrial superoxide production, whereas the upper limit is kept low enough to avoid excess H_2O_2 production.

The Fawn-Hooded Rat

The common experimental models for creating PAH by exposing animals to monocrotaline (58), chronic hypoxia (73) [sometime augmented by the vascular endothelial growth factor (VEGF) receptor antagonist, SU5416 (80, 90)], do not fully mimic human PAH. Except for the latter model, the PAH models lack neointimal thickening, and none of the models displays plexiform lesions. Moreover, most models evolve rapidly (in 2 wk) in response to a single extrinsic toxic stimulus (monocrotaline, hypoxia, etc). The fawn-hooded rat (FHR), a mutant strain named for its brown mantle of fur, is unique in spontaneously developing PAH (42). FHR PAH is heritable (84) with high penetrance (42). FHR typically die of slowly evolving PAH at ~1 yr of age; notably PAH is absent until age 20 wk (20). FHR share additional similarities with human PAH, including enhanced vasoconstriction to serotonin, a platelet storage-pool deficiency (12), and exaggerated rates of PASMC proliferation. FHR are hypoxia sensitive, being prone to develop pulmonary hypertension and alveolar simplification (46, 47) when exposed to mild hypoxia, at levels that do not affect normal rodents (84).

We recently found that the FHR's PASMC mitochondria are dysmorphic, and the mitochondrial reticulum is fragmented before the onset of PAH (Fig. 3). The observed hyperpolarization of $\Delta\Psi$m and reduction in ROS production are mirrored in PASMCs from idiopathic PAH patients (20). In PAH, mitochondrial abnormalities that shift metabolism away from oxidative phosphorylation toward glycolysis (notably PDK activation) lead to a normoxic impairment of electron flux and reduced mitochondrial ROS production. This pseudohypoxic signal is associated with normoxic activation (nuclear translocation) of HIF-1α. HIF-1α activation appears to decrease expression of Kv1.5, and these abnormalities are reversed by either low-doses of exogenous H_2O_2 or a HIF-1α dominant-negative construct (20). The absence of PAH or mitochondrial dysfunction in consomic rats (FHR-BN1), which differ from FHR only in having a chromosome 1 introgressed from Brown Norway rats, indicates the initiating genes likely reside on chromosome 1. Using DNA microarrays, we identified a series of candidate genes that has biological plausibility to explain the mitochondria-ROS-HIF-Kv abnormalities, including SOD2 and HIF-3α, a HIF-1α repressor (20) (Fig. 3).

Decreased Kv expression is an emerging hallmark of the PAH PASMCs occurring in human PAH (20, 106) and all known experimental models (20, 55, 60, 75) [including those due to BMPR2 dysfunction (104) or excess SERT activity (37)]. Interestingly, Kv1.5 is inhibited by the anorexigens (70, 100) and by serotonin (30), and restoring Kv1.5 expression reduces experimental PAH (72). Decreased expression and function of PASMC Kv channels have two consequences that favor cell accumulation, leading to the proliferative obstructive vasculopathy. First, the depolarization resulting from the loss of Kv channels leads to Ca^{2+} overload that activates transcription factors that stimulate proliferation (notably NFAT) (21). Second, the loss of Kv channels leads to an accumulation of intracellular K^+, which inhibits caspase, impairing apoptosis, rendering the artery unable to eliminate abnormal cells (32, 44, 55, 77). This abnormal mitochondrial-ROS-HIF-1α-Kv pathway is recapitulated in human cancers. Supporting the notion that PAH and cancer share similar mechanisms, mitochondrial

therapy (inhibition of PDK) or Kv1.5 gene therapy partially regresses both PAH and cancer (19, 20, 72).

SOD2 and PAH?

SOD2 is a candidate tumor-suppressor gene, which supports the notion that SOD2 deficiency promotes cell proliferation (23, 48). Normally, SOD2 expression is induced or repressed to match ROS production (more ROS = more SOD2). This avoids damage to the ETC and mitochondrial DNA (26). Low SOD2 activity/expression in FHR occurs by mechanisms that are quite distinct from the deletion of alleles that creates $SOD2^{+/-}$ mice, mice that have an oxidative stress phenotype (103). In FHR, the low ROS levels result both from decreased SOD2 expression and from inhibition of electron entry to the ETC, due to excessive PDK activity. PDK inhibits pyruvate dehydrogenase activity, which limits Krebs' cycle activity (Fig. 2). This decreases delivery of reducing equivalents (NADH and FADH) to the ETC with a resulting reduction in ROS. In contrast, oxidative damage in SOD2 knockout mice likely occurs because the delivery of electrons to the ETC is unimpaired and yet they lack SOD2 and so have impaired capacity to dismutate a normal rate of superoxide radicals. The possibility that an inherited deficiency of SOD2 expression in PAH is mechanistically important is suggested by the localization of the SOD2 gene on FHR chromosome 1, early downregulation of SOD2 in FHR (before onset of PAH), and the discovery of a parallel SOD deficiency in human idiopathic PAH (20). It is unknown whether decreased SOD2 generation reflects epigenetic gene silencing or a response to the loss of ROS, which normally induce SOD2 transcription.

Therapeutic Implications

Dichloroacetate is a prototypical inhibitor of mitochondrial PDK. This agent has been safely used in children with inherited mitochondrial disorders and lactic acidosis (86, 87). Dichloroacetate restores oxidative metabolism in FHR PASMCs, shifting them away from the proliferative/apoptosis-resistant glycolytic state, while having no effects on normal cells (19, 20, 41, 86). These metabolic changes reverse the hypoxic phenotype of FHR, restoring the relatively depolarized $\Delta\Psi m$ of PASMCs and increasing ROS production to normoxic levels. This reverses HIF-1α activation and restores Kv1.5 expression, thereby lowering cytosolic Ca^{2+} and reducing the severity and mortality of FHR/PAH (20). Dichloroacetate also causes regression of PAH induced by chronic hypoxia or monocrotaline (20, 55, 60). The same doses of dichloroacetate decrease tumor growth, in an athymic rat model of transplanted human lung cancer cells, by an identical mechanism (19). Given the preexisting safety data based on the use of dichloroacetate in humans and its dramatic effects in preclinical models, it is reasonable to proceed with the investigation of this agent in human subjects afflicted with PAH and cancer. We do not advocate the off-label use of the drug. More preclinical studies and, eventually, more carefully performed clinical trials are required to assess the potential therapeutic agents that seek to normalize the mitochondria-ROS-HIF-1α-Kv1.5 in PAH (e.g., PDK inhibitors, HIF-1α inhibitors, and Kv channel augmentation).

Conclusions

The mitochondria are important O_2 sensors, and a disruption of the mitochondria ROS-HIF-Kv pathway contributes to both PAH and cancer. It is likely that this pathway can be therapeutically targeted to regress PAH and cancer.

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