Novel Role for the Regulation of Mitochondrial Fission by Hypoxia Inducible Factor-1α in the Control of Smooth Muscle Remodeling and Progression of Pulmonary Hypertension

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In this issue of Circulation Research, Marsboom et al describe a novel involvement of a mitochondrial fission regulatory pathway that is likely to be of great importance in pulmonary arterial hypertension (PAH)-associated smooth muscle remodeling. Data in the study provide evidence that this process appears to be controlled by activation of hypoxia inducible factor-1α (HIF-1α). As illustrated in the model in Figure, the stabilization or activation of HIF-1α in PAH is shown to promote mitochondrial fission by cyclin B1/CDK1-dependent phosphorylation of dynamin-related protein-1 (DRP1) at serine-616. The CDK1-cyclin B-dependent regulation of tubular mitochondria fragmentation by DRP1 was identified in previous studies as a regulator of the even distribution of mitochondria during mitosis in HeLa cells. Data in the study of Marsboom et al document how this process appears to be essential for the in vitro proliferation of pulmonary arterial smooth muscle cells from human hypertensive patients. In addition, evidence is provided for these mechanisms appearing to be a prominent contributing factor to pulmonary arterial remodeling in several different models of PAH.

As described in the article of Marsboom et al, PAH is disorder in which small pulmonary arteries are obstructed, constricted, and inflamed in a manner that increases pulmonary vascular resistance, and this promotes right ventricular hypertrophy and eventually failure. Previous work from Archer et al identified many components of processes that evolved into the current new mechanism. For example, their studies provided evidence that an activation of HIF-1α under aerobic conditions in PAH was associated with a shifting from aerobic mitochondrial energy metabolism to a cancer cell-type emphasis on using aerobic glycolysis and mitochondrial fragmentation. Interestingly, promoting aerobic mitochondrial energy metabolism with the pyruvate dehydrogenase kinase inhibitor dichloroacetate has substantial protective effects against PAH associated with restoring a hypoxic sensing mechanism associated with mitochondrial-derived peroxide regulating voltage-gated potassium (Kv1.5) channels and decreasing HIF-1α activation. Dichloroacetate also prevents and reverses pulmonary hypertension by inducing pulmonary artery smooth muscle cell apoptosis. These previous observations suggest shifting to aerobic glycolysis–associated energy metabolism is potentially an important factor in promoting the remodeling-associated pulmonary arterial smooth muscle proliferation.

The article of Marsboom et al provides an extensive amount of impressive data to support the novel concepts in this article. Properties of this regulatory system were studied in lung tissue and pulmonary arterial smooth muscle cells from humans with PAH for comparison with pulmonary arterial smooth muscle cells from nonhypertensive controls. In addition, rat monocrotaline and chronic hypoxia models were studied, and a new model of pulmonary hypertension was developed based on cobalt chloride inducing HIF-1α in rats and pulmonary arterial smooth muscle cells. Human pulmonary arterial smooth muscle cells studies indicated that HIF-1α promoted a cyclin B1/CDK1-dependent phosphorylation of DRP1 at serine-616 in the mechanism of mitochondrial fission regulation using inhibitors of HIF-1α (chetomin) and DRP1 (Mdiv-1 and RO-3306). The PAH pulmonary arterial smooth muscle cells had elevated levels of HIF-1α under aerobic conditions, and studies with Mdiv-1 and siRNA for DRP1 resulted in evidence that cell-cycle arrest occurred in the G2/M phase. The impact of PAH conditions influencing mitochondrial fusion in pulmonary arterial smooth muscle cells was visualized in a movie showing the time-dependent spreading of a mitochondrial matrix fluorescent protein (Online Supplement). These cells also have properties suggesting there was a shift toward the use of aerobic glycolysis for energy metabolism in PAH. Activating HIF with CoCl2 or desferrioxamine or both promoted DRP1 serine-616 phosphorylation and rapid mitochondrial fragmentation in a manner attenuated by HIF-1α siRNA and Mdiv-1. Treatment of pulmonary arterial smooth muscle cells with CoCl2 was also shown to cause a shift in ion channel regulation associated with a reduction in Kv channels, depolarization, and increased intracellular calcium that are similar to changes seen in PAH. The mitochondrial fragmentation mechanism appears to be an active process in the remodeling observed in lung tissue from idiopathic PAH patients based on detection by imaging of elevated levels of HIF-1α, increased nuclear localization of cyclin B1, and increased
serine-616 phosphorylation of DRP1 in pulmonary blood vessels with an external diameter <150 μm that have undergone pulmonary arterial smooth muscle cells proliferation or “muscularization.” A chronic treatment of rats with CoCl2 for 4 weeks was observed to cause PAH associated with a reduction in mitochondrial size. The DRP1 inhibitor Mdivi-1 prevented the development of PAH in both this CoCl2 model and in a chronic hypoxia (4 weeks of 10% oxygen) rat model of PAH. Mdivi-1 also seemed to reverse indicators of hypertension when the therapy was started after 3 weeks in the rat monocrotaline model of PAH. Thus, data are provided showing the importance of the HIF-1α mitochondrial fission regulatory pathway across multiple animal and human models of PAH.

Recent studies provide evidence that mitochondrial dynamics associated with proteins promoting fission and fusion are regulated by signaling mechanisms associated with adaptive physiological and pathophysiological processes. In the current study, the expression of mRNA for mitochondrial fusion protein mitofusin-2 (MFN2) was decreased, whereas mitochondrial fusion proteins mitofusin-1 (MFN1) and optic atrophy-1 were not different when pulmonary arterial smooth muscle cells from humans with PAH were compared with cells from control humans who were not hypertensive. In contrast, the profusion protein MFN2 was decreased in human PAH pulmonary arterial smooth muscle cells under conditions in which increased phosphorylation on serine-616 of the fission protein DRP1 was observed. Interestingly, it was observed in the present study that inhibition of DRP1 with Mdivi-1 reversed the fragmented phenotype and increased the MFN2. Increased MFN2 previously has been associated with promoting apoptosis in vascular smooth muscle cells. Recent studies in mice having conditional MFN1 deficiency results in small spherical mitochondria; however, the mice show rather normal cardiac and mitochondrial respiratory function. A cardiac MFN2 deficiency was actually associated with enlarged spherical mitochondria and some cardiac and mitochondrial respiratory dysfunction. Interestingly, both of these deficiencies were associated with a resistance to oxidant exposure promoting a mitochondrial transition pore response. In contrast, a combined ablation of cardiac myocyte MFN1 and MFN2 and its associated mitochondrial fragmentation resulted in mitochondrial respiratory dysfunction and rapid progression into a fatal dilated cardiomyopathy. Thus, mitochondrial fission and fusion are not specifically linked to a disruption of mitochondrial energy metabolism or highly energy-dependent processes like cardiac function. However, activation of DRP-1 and perhaps decreased MFN2 appear to contribute to promoting proliferative remodeling of vascular smooth muscle.

The HIF-1α–controlled mitochondrial fission regulatory pathway illustrated in the Figure, which is reported in the article by Marsboom et al in the current issue of Circulation Research, is likely to be of great importance in physiological and pathophysiological processes involving vascular smooth muscle remodeling. Hypoxia sensing and oxidant mechanisms regulating HIF-1α provide pathways for its regulation by many types of stress-type conditions existing in vivo. Regulation of mitochondrial fission and other processes such as promoting aerobic glycolysis appear to enable the progression through mitosis that is needed for the stem cell–associated remodeling seen in pulmonary hypertension. Interestingly, Archer et al also recently have reported the 18F-fluorodeoxyglucose positron emission tomography tracer diagnostic method for imaging the enhanced glycolytic metabolism and its therapeutic reversal by dichloroacetate associated with controlling the hyperproliferative changes seen in small pulmonary arteries in PAH. Thus, the DRP1-regulated mechanism controlling mitochondrial fusion and proliferation described in the current issue of Circulation Research opens a new metabolism-associated target for therapies to treat pulmonary hypertension and perhaps other vascular remodeling-associated disease processes.
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References

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