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Metabolic origins for pulmonary hypertension

By Kai-Jye Lou, Staff Writer

Researchers at the **University of Alberta** and **Metabolic Modulators Research Ltd.** have shown that a pathological shift toward glycolysis could be responsible for the deleterious vascular remodeling seen in pulmonary arterial hypertension.[1] The findings highlight key molecules in well-known metabolic pathways that could be targeted to prevent and treat the root cause of the disease as opposed to just its symptoms.

The vascular remodeling seen in PAH is caused by greater proliferation and resistance to apoptosis in vascular cells. This remodeling is typically limited to pulmonary vascular tissues and leads to obstruction of the pulmonary arterial lumen, right ventricular failure and eventual death. Systemic vascular tissues usually remain normal.

Earlier studies from the Alberta group and MMRL-affiliated researchers showed that use of dichloroacetate (DCA) to shift cellular metabolism toward glucose oxidation and away from glycolysis could reverse PAH in rats by reducing cell proliferation and promoting apoptosis in the pulmonary issue.[2,3] DCA is a small molecule pyruvate dehydrogenase kinase (PDK) inhibitor.

However, despite the pharmacological data highlighting the potential therapeutic benefits of PDK inhibition and DCA in PAH, the researchers lacked the molecular and genetic evidence to prove that a pathological shift toward glycolysis is indeed responsible for the vascular remodeling that characterizes the disease.

The group's new study not only supports the rationale for targeting PDK but also highlights additional targets in the pathway that could be explored for PAH (*see* **Figure 1, "Targeting pulmonary hypertension through metabolic pathways"**).

PDK inhibition is known to reduce pyruvate dehydrogenase (PDH), a key enzyme that promotes glucose oxidation.

Increased fatty acid oxidation is also known to inhibit PDH. Thus, the researchers reasoned that reducing fatty acid oxidation could be expected to activate PDH and increase glucose oxidation.

The team selected malonyl-CoA decarboxylase (MLYCD; MCD) as a candidate target because it is a key regulatory enzyme needed for fatty acid oxidation.[4] Moreover, MCD inhibition has been shown to decrease fatty acid oxidation, activate PDH and increase glucose oxidation.[5]

In mice, the Canadian researchers showed that genetic knockout of MCD prevented hypoxia-induced PAH and the associated vascular remodeling in pulmonary artery smooth muscle cells. Under hypoxic conditions, the pulmonary artery of mice with functional

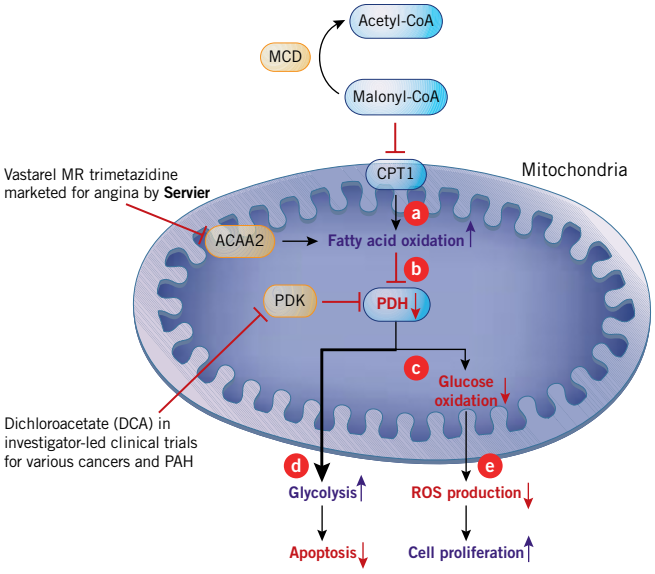

Figure 1. Targeting pulmonary hypertension through metabolic pathways. Increased cell proliferation and resistance to apoptosis in pulmonary arteries result in the deleterious vascular remodeling seen in pulmonary arterial hypertension (PAH). **University of Alberta** researchers propose that this remodeling is due to a shift in cellular metabolism from glucose oxidation toward glycolysis.
Specifically, carnitine palmitoyltransferase 1 (CPT1) activity along the mitochondrial membrane increases fatty acid oxidation [**a**]. This increase leads to a decrease in pyruvate dehydrogenase (PDH) activity [**b**], which results in a shift toward glycolysis from glucose oxidation [**c**]. Upregulation of glycolysis is associated with resistance to apoptosis[10] [**d**], whereas lower glucose oxidation leads to less production of reactive oxygen species (ROS) in mitochondria and greater cell proliferation [**e**]. Researchers showed that they could block the vascular remodeling in PAH by reversing this shift in cellular metabolism. In particular, they suggest that fatty acid oxidation can be inhibited by blocking malonyl-CoA decarboxylase (MLYCD; MCD). This blocks the conversion of malonyl-CoA into acetyl-CoA, resulting in more malonyl-CoA around to inhibit CPT1.

The researchers also showed that trimetazidine (TMZ), which is marketed by **Servier** as Vastarel MR to treat angina, could reverse this metabolic shift and block vascular remodeling. TMZ inhibits 3-ketoacyl-coA thiolase (ACAA2), a molecule normally known to promote fatty acid oxidation.

Additionally, they showed that dichloroacetate (DCA), a compound that is in investigator-led clinical trials for various cancers and PAH, could achieve a comparable therapeutic effect by inhibiting pyruvate dehydrogenase kinase (PDK) to promote PDH activation.

Mcd showed a shift toward glycolysis and away from glucose oxidation compared with the artery of control mice housed under normoxic conditions. In contrast, the pulmonary artery of *Mcd* knockout mice did not show this metabolic shift in response to hypoxia.

In mice expressing *Mcd*, treatment with DCA and trimetazidine (TMZ) mimicked the metabolic effects of knocking out *Mcd* and reduced PAH symptoms compared with vehicle control treatment. Moreover, cellular assays showed that both drugs also increased apoptosis and reduced proliferation in remodeled rat pulmonary arteries compared with vehicle.

TMZ is an 3-ketoacyl-CoA thiolase (ACAA2) inhibitor. **Servier** markets it as Vastarel MR to treat angina.

Results were published in *Science Translational Medicine*.

"It was previously thought that pulmonary hypertension is caused by vasoconstriction, but now we have molecular evidence showing that disease pathogenesis could be due to metabolic remodeling in pulmonary vascular cells that causes resistance to apoptosis and increased proliferation," said Evangelos Michelakis, professor of medicine in the Division of Cardiology of the University of Alberta. He is Canada Research Chair in Pulmonary Hypertension and corresponding author on the paper.

"The novelty of this work is in showing that fatty acid metabolism could be targeted to increase mitochondrial metabolism and prevent the remodeling of smooth muscle cells in the pulmonary artery," said Rubin Tuder, a professor of medicine in the Division of Pulmonary Sciences and Critical Care Medicine and director of the Program of Translational Lung Research at the **University of Colorado Denver**.

"The results make a very strong case for targeting proliferation to treat the disease, and the mechanistic data support the concept that in pulmonary hypertension, ATP generation in vascular smooth muscle cells is shifted towards glycolytic pathways and away from mitochondria," he added.

"This study provides another potential indication for PDK inhibitors, which MMRL is already developing for heart diseases and diabetes," noted Gary Lopaschuk, a coauthor on the paper and president and CEO of MMRL. "While we have already licensed our MCD inhibitors to Eli Lilly, the current findings also suggest that such compounds could have a therapeutic effect in pulmonary hypertension."

MMRL has rights to MCD inhibitors from **Chugai Pharmaceutical Co. Ltd.**, and **Eli Lilly and Co.** has rights from MMRL to the MCD inhibitors for use in all indications.

Lopaschuk, who also is a professor in the Department of Pediatrics and scientific director of the Mazankowski Alberta Heart Institute at the University of Alberta, added that stimulating glucose oxidation is known to have beneficial effects in heart failure and ischemic heart disease.[6,7]

"The pathways highlighted in our work suggest that compounds that stimulate glucose oxidation, which are already being developed for other indications like cancer and metabolic diseases, could potentially be repurposed for treating pulmonary hypertension," said Michelakis. "For example, there are already companies developing PDK inhibitors with greater potency than DCA for other diseases like cancer."

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Indeed, Michelakis and colleagues have previously shown that using DCA to reverse the metabolic shift toward glycolysis in cancer can promote apoptosis and reduce tumor growth in animal models, and DCA showed signs of therapeutic efficacy in an ongoing Phase II trial in patients with glioblastoma.[8,9]

MMRL has DCA mimetics that inhibit PDK in preclinical development for diabetes and heart disease. Lopaschuk said these compounds have not been evaluated in PAH.

Targeting the root

Researchers contacted by *SciBX* agreed that targeting the metabolic pathway could improve upon the current treatments for PAH because they have the potential to reverse disease pathology.

The three drug classes currently used to treat PAH—prostaglandin analogs, endothelin receptor antagonists and phosphodiesterase-5 (PDE-5) inhibitors—primarily work by promoting vasodilation or relieving vasoconstriction. Although these drugs alleviate symptoms and increase patient lifespan, they do not reverse disease pathology. Moreover, such drugs act on both systemic and pulmonary vascular tissues, thus limiting the amount of drug that can be given to the patient.

"Compounds like DCA and TMZ appear to target the heart of the problem by specifically preventing the metabolic remodeling and resistance to apoptosis in affected vascular tissues and thus could have fewer nonspecific effects," said Michelakis. "The idea is that this metabolic remodeling is intrinsic to the smooth muscle cells in affected blood vessels, so if you attack what is abnormal, you could treat the problem at its root and avoid targeting normal cells."

However, Tuder noted that the current study only evaluated PAH models that primarily involve pathology in smooth muscle cells. He said it would be important to show that a compound could affect both pulmonary smooth muscle cells and endothelial cells, the two major cell populations involved in disease pathology.

"The results from the current study will be much more compelling if they could show that these effects also translate into a pulmonary hypertension model with endothelial cell pathology," he told *SciBX*.

Although stimulating glucose oxidation has been shown to have beneficial effects in heart disease, diabetes and now PAH, Lopaschuk noted that there is still no consensus over how the effects occur. "It will be important to understand why stimulating glucose oxidation has these beneficial effects in pulmonary hypertension," he said.

Targeting decisions

Michelakis said his group at the University of Alberta and collaborators at **Imperial College London** already have an ongoing investigator-led Phase I trial evaluating DCA in patients with PAH. The university is also running a Phase II trial evaluating DCA in patients with anaplastic astrocytoma and glioblastoma.

MMRL's Lopaschuk said it will be important to now show that DCA has a therapeutic effect in PAH patients but added he is still ambivalent about whether the compound would be appropriate for a chronic indication like PAH. He suggested DCA's potency and short half-life "could make it challenging to deliver a therapeutic level of the compound to the patient."

Michelakis, who has no direct affiliation with MMRL, disagreed. He noted that multiple clinical studies, including the ongoing Phase II trial in brain cancer, have shown it is possible to achieve a therapeutic level of DCA with oral dosing.

In any case, Lopaschuk thinks PDK inhibitors with greater potency and a better pharmacokinetic profile than DCA also should be tested in PAH.

In addition to MCD, PDK and ACAA2, Colorado's Tuder said the detailed dissection of the metabolic pathway in the new study also implicates the activation or stabilization of glycogen synthase kinase 3β (GSK3B) and inhibition of the transcription factor nuclear factor of activated T cells cytoplasmic calcineurin-dependent 2 (NFATc2) as potential therapeutic strategies for treating pulmonary hypertension.

He added that it will be important to also study the involvement of the identified metabolic pathways in additional PAH settings.

"Pulmonary hypertension is frequently found in patients with lung and heart disease, and when present, is a major factor of morbidity and mortality in these diseases. However, most of the present knowledge of pulmonary hypertension has been based on studies in which the disease occurs due to a primary involvement of the pulmonary arteries," he told *SciBX*.

The University of Alberta has issued composition-of-matter patents covering the PDK inhibitors and their use in all indications. The patents have been licensed to MMRL, and the PDK inhibitors are available for licensing from the biotech.

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COMPANIES AND INSTITUTIONS MENTIONED

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