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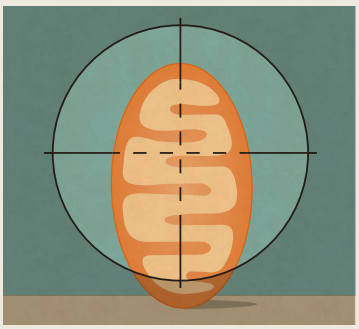
HYPERTENSION

Promising mitochondria-targeting drug for PAH

Accumulating evidence indicates that metabolism and mitochondria are critical in the pathogenesis of pulmonary arterial hypertension (PAH). Mitochondrial glucose oxidation is suppressed in the pulmonary arteries of patients with PAH and glycolysis is upregulated to compensate, all of which leads to inhibition of apoptosis and promotion of proliferation. A new study now shows that dichloroacetate (DCA), an inhibitor of the mitochondrial enzyme pyruvate dehydrogenase kinase (PDK), improves haemodynamics and functional capacity in genetically susceptible patients with PAH. "This work proves that the 'metabolic theory of PAH' is clinically relevant," say lead investigators Evangelos Michelakis and Martin Wilkins. "Our work opens a new window in PAH therapeutics, because it identifies other potential therapeutic targets that are involved in the biology of mitochondrial inhibition and its downstream signalling."

Previous work from the research team showed that PDK, an inhibitor of pyruvate dehydrogenase, a crucial enzyme in glucose oxidation, could be a therapeutic target in PAH. Using *ex vivo* assays in explanted lungs from patients with PAH, Michelakis *et al.* now show that treatment with the PDK inhibitor DCA activated PDH and increased mitochondrial respiration. Furthermore, in a 4-month, phase I trial in patients with idiopathic PAH who were already taking approved PAH therapy, DCA treatment led to a reduction in mean pulmonary arterial pressure and pulmonary vascular resistance as well as an improvement in functional capacity. However, the response to DCA varied in both the *ex vivo* assays and the clinical trial. The investigators show that the presence of functional inactivating variants in *SIRT3* and *UCP2* were associated with a poor clinical response to DCA.

> "dichloroacetate … improves haemodynamics and functional capacity in genetically susceptible patients with PAH"



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"We show that gene variants can be used as novel biomarkers of the metabolic remodelling in this disease and specifically predict the resistance to DCA and other metabolic modulators targeting mitochondria," comment Michelakis and Wilkins, who remark that future clinical trials should have a precision medicine design that considers patient genotype to maximize a beneficial response.

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ORIGINAL ARTICLE Michelakis, E. D. *et al.* Inhibition of pyruvate dehydrogenase kinase improves pulmonary arterial hypertension in genetically susceptible patients. *Sci. Transl Med.* **413**, eaao4583 (2017)
FURTHER READING Lau, E. M. T. *et al.* Epidemiology and treatment of pulmonary arterial hypertension. *Nat. Rev. Cardiol.* **14**, 603–614 (2017)