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EDITORIAL COMMENT

Heart Failure in Pulmonary Arterial Hypertension Is Just a WNK1 Away*

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Although heart diseases are the leading cause of death worldwide, and much is known about heart failure associated with atherosclerosis or diabetes, less is known about the mechanisms underlying the cardiac dysfunction that results from pulmonary arterial hypertension (PAH). One unique distinction between these heart failure etiologies is that PAH primarily leads to right ventricular dysfunction (RVD) as opposed to left ventricular dysfunction. Despite this difference, many of the molecular changes within the tissue are similar, with a metabolic substrate switch from fatty acid to glucose utilization in heart failure. This increase in glucose uptake and utilization can, in part, be shunted to the pentose phosphate pathway or fuel the hexosamine biosynthetic pathway leading to increased protein post-translational modifications via the addition of UDP-*N*-acetylglucosamine to serine and threonine residues (O-GlcNAcylation [1]). Although the glucose can also be used for ATP synthesis, this is often less efficient than oxidative phosphorylation of fatty acids, which may result in signaling AMP-kinase (AMPK) activation highlighting an energy deficit state. Furthermore, it is known that hypochloremia is associated with adverse outcomes in patients with PAH. This latter observation may be linked to the changes in glucose metabolism. A potential mechanism by which hypochloremia may affect molecular function is via signaling through the With No Lysine (WNK) family of protein kinases. However, the link between these 2 pathways has not been fully defined.

That was, until now. In this issue of *JACC: Basic to Translational Science*, Prisco et al (2) show that in a rat model of PAH using monocrotaline (MCT), WNK1 is induced and, more importantly, small molecular inhibition of WNK1 via WNK463 is sufficient to attenuate much of the metabolic remodeling associated with PAH as well and the molecular signaling via O-GlcNAcylation. More specifically, this study explores 2 different aspects of this glucose-mediated signaling in PAH as potential targets for therapy. One is by regulating protein function through O-GlcNAcylation and glycosylation, while the other is through regulation of right ventricular (RV) mitochondrial metabolism.

Protein O-GlcNAcylation is a well-defined mechanism related to cardiovascular diseases (1); its addition is regulated by O-GlcNAc transferase whereas its removal is regulated by O-GlcNAcase. The current study provides evidence for a direct molecular mechanism in RV cardiomyocyte by protein O-GlcNAcylation. Interestingly Prisco et al (2) find that despite no change in O-GlcNAc transferase protein levels and an induction of O-GlcNAcase protein, total protein O-GlcNAcylation is paradoxically increased. They provide supporting evidence to suggest that this is a result of increased flux through the hexosamine biosynthetic pathway, as shown by their metabolomics data. To find the mechanism linking these 2 changes, they examined another important connection between protein O-GlcNAcylation and metabolic alteration through O-GlcNAcylation of AMPK, which alters signaling of several pathways in response to changing energy status of an organ. Inhibition of AMPK signaling is well elucidated in cardiac hypertrophy (3), and the authors of the current study show that AMPK phosphorylation is markedly reduced in their MCT-induced PAH model. This is further supported by a complete remodeling of the

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mitochondrial proteome for the citric acid cycle, β-oxidation enzymes, and several of the subunits across the entire oxidative phosphorylation respiratory pathway. To support a direct link of the changes to WNK1, the authors show that most of the alterations are reversed, or at least attenuated, with WNK463 treatment. These new findings also suggest a novel role for WNK1 in the previously mentioned connection between AMPK signaling and protein O-GlcNAcylation. This molecular remodeling was accompanied by changes in both mitochondrial and peroxisomal density and several functional characteristics of heart hypertrophy and contractility, without altering severity of pulmonary vascular disease. Finally, in an attempt to link their findings to RVD in human PAH, they show a correlation between hypochloremia, which is predicted to activate WNK1, and RV function.

Outstanding questions include the fact that the primary known role of WNK1 is regulating sodium chloride cotransporter (NCC), and WNK1 sequence variant is closely related to hypertension and consequently PAH. To validate the usefulness of the proposed pathway for PAH treatment, the WNK1 inhibitor should also alleviate the adverse effect on ion channels in addition to NCC. Because sodium and chloride are major water-soluble minerals, with chloride neutralizing the positive charge of sodium, this change might impact molecular function, in turn resulting in body fluid retention; as such, this endpoint should also be assessed in future studies. As these ions can have multiple effects, specifically, calcium can affect chlorine channels and vice versa, the effect of WNK1 inhibition and its consequences on NCC regulation should be noted as both a potential therapeutic target as well as a potential complication for treatment of underlying arrhythmias. Although Prisco et al (2) clearly show a protective effect of WNK1 inhibition on PAH, the precise ion channel affected should be determined in future studies.

It is noteworthy that several other targets have been identified as potential avenues for treatment of RVD in PAH (4). The new possibilities opened by the current study highlight further areas that should be considered. One aspect of the regulation of glucose metabolism not defined in the current study was that of regulation between glycolysis and citric acid cycle. Specifically, a growing number of investigators are examining regulation of the pyruvate dehydrogenase complex. This complex regulates the conversion of pyruvate to acetyl-CoA, effectively coupling glycolysis and glucose oxidation from other glucose utilizing pathways, and could explain some of the metabolic changes observed in the current study. The pyruvate dehydrogenase complex is inhibited by phosphorylation via a family of pyruvate dehydrogenase kinases (PDKs), which in turn can be inhibited by treatment with dichloroacetate (DCA). Studies in ischemic heart failure suggest that inhibition of PDK, and the resulting changes in glucose metabolism, provide an enticing therapeutic target in cardiovascular disease. However, their role in PAH and how this might relate to WNK1 signaling remains to be determined. Along these lines, it is important to note that either DCA or genetic ablation of PDKs prevent effects of various cardiovascular diseases. More important to the current study is the finding that DCA treatment can work as an idiopathic PAH treatment, which has progressed to a phase 1 clinical trial, but to date has only provided partial improvement of hemodynamics and functional capacity with PDK-independent and DCA nonresponder patients (5). Also, long-term treatment of DCA reported peripheral neuropathy, highlighting potential complications of pursuing it as a patient treatment option. The current paper suggests another promising target of glucose and fatty acid oxidation regulation mechanism via WNK1 inhibition in RV, which may overcome the limitations of these other previous approaches.

Finally, a few additional limitations for future study do exist. The authors suggest that WNK463 will work specifically through cardiomyocyte inhibition of WNK1. However, the WNK family has many roles, including heterodimeric effects and cellular localization, with diverse distribution of isoforms depending on the tissue type (6). To define the precise mechanism and specific isozyme role in the RV as well as cardiovascular diseases, further cell- and isozyme-specific studies must be performed. It is also noteworthy that the MCT model of PAH can induce hypoxic signaling. This is important as the glucose metabolism alterations seen by MCT-induced PAH may also induce the hypoxia inducible factor 1 α axis. This supports that additional studies on the effect of WNK1 in PAH may lead to uses in different disease etiologies, such as angiotensin II hypertension, deoxycorticosterone acetate and salt hypertension, and pulmonary artery banding models. This highlights that the current findings may only be the tip of the iceberg in our molecular understanding of metabolic control and disease progression.

Despite some of these minor limitations, Prisco et al (2) clearly show a new link between the induction of WNK1 in PAH and a mechanism by which this can signal to metabolic remodeling, contributing to changes in RV cardiac structure, function, proteomics, and post-translational regulation. Altogether

the results support that WNK1 inhibition is a promising new avenue for treatment of PAH-induced RVD.

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