Multilevel omics: A next step on the way to understanding pulmonary arterial hypertension?

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Pulmonary arterial hypertension (PAH) remains a major cause of morbidity and mortality despite continuous efforts to increase our understanding of the underlying pathophysiology.[1] As a matter of fact, little has changed in terms of our ability to treat this deadly disease since the introduction of the first vasodilator treatment two decades ago.[2 3] Although three different classes of drugs are currently available, all converge on the same downstream event (ie, vasodilation). The fact that mortality is still high despite current therapy suggests that there are hitherto unknown mechanisms that determine the outcome. Omic approaches provide an unbiased method, and—being both inclusive and hierarchical—omics may help to prioritise candidate targets for development of novel drug classes.

In the current issue of *Thorax*,[4] Harbaum *et al* have combined metabolomic and proteomic studies to assess whether a specific lipoprotein composition is associated with clinical endpoints in patients with PAH. Using nuclear MR spectroscopy, 105 different lipoproteins were measured in the plasma of patients with idiopathic or hereditary PAH and correlated with survival. The study demonstrated association of PAH survival with three lipoproteins of the high-density lipoprotein (HDL) subclass 4, of which HDL-4-apolipoprotein A-2 (HDL-4-Apo A-2) showed the strongest association. Higher levels of HDL-4-Apo A-2 were associated with better survival, both in the discovery and in the validation cohort. The association was independent of markers of inflammation, other lipoprotein classes, clinical parameters of PAH, concomitant cardiovascular disease and the use of PAH-specific medication or statins. To elucidate the link between the HDL-4 subfraction and PAH survival and to find intermediate mechanisms, the authors elegantly combined lipoprotein data with proteome data of 1124 plasma proteins measured in the same patients. By means of this analysis, they identified nine proteins that were statistically associated with HDL-4-Apo A-2. Although statistical association does not prove physical or functional interaction, the study provides evidence for the presence of 2 out of 9 of the proteins (prekallikrein and neuropilin-1) in the HDL-4 subfraction. As 5 out of 9 of these proteins have previously been shown to be present in HDL subfractions, there is support for a functional substrate of the statistical association. In network analysis, 3 out of 9 proteins (prekallikrein, coagulation factor XI and alpha-2-antiplasmin) were functionally linked to fibrinolysis, suggesting a role of the fibrinolytic system in PAH survival.

Pointing to the HDL-4 subclass as strongest associate, it is interesting to see that the unbiased approach of Harbaum and colleagues revives the debate on the role of HDL in PAH. While independent groups have linked low HDL-cholesterol with worse survival in PAH,[5 6] other groups were not able to reproduce the prognostic value of HDL-cholesterol.[7] It is interesting to see that the study of Harbaum *et al* takes its own position in the debate, by confirming that total HDL-cholesterol does not correlate with PAH survival,[7] but that the composition of the smallest HDL particles (HDL-4 subfraction) does associate with adverse outcomes among the patients with PAH. Although inclusion of incident[7] versus prevalent[5] patients may contribute to observed differences in the debate, the current study demonstrates that a similar trend is observed in both incident and prevalent cases. The current study therefore validates the importance of HDL particles in PAH, but also suggests a nuance that needs further exploration in PAH. Next steps in this exploration could be guided by atherosclerosis studies, where the classic idea of HDL-cholesterol as a causative factor of cardiovascular disease was challenged by Mendelian randomisation studies[8] and clinical trials where HDL-cholesterol increasing agents were tested.[9 10] Nowadays, HDL parameters like HDL-cholesterol efflux capacity and HDL particle concentration rather than HDL-cholesterol levels per se are considered to drive the vasculoprotective effects.[11 12] To explore the potential modifier role of HDL and HDL particles in the course of PAH, it might be interesting to see how changes in HDL and HDL particles over time associate with disease survival.

In expectation of future studies on the exact role of HDL and the HDL-4 subclass in PAH, it is tempting to speculate how this class of lipoproteins may modify the course of disease. An explanation that comes at first hand is the role of HDL in the activation of endothelial Nitric Oxide Synthetase (eNOS). The HDL/Apo A-1 complex directly stimulates nitric oxide production by direct eNOS activation and prevention of eNOS uncoupling.[12] As Apo A-1 was also shown to be present in the HDL-4 subfraction, this may suggest that the increase in the HDL-4 subfraction of lipoproteins serves as an endogenous vasodilator that delays disease progression. However, the current study indicates that not only vasodilation, but also the fibrinolytic system is of importance in PAH. Impaired fibrinolytic activity has been reported to be present in patients with PAH,[13 14] but our current understanding of the exact role is limited. The association of prekallikrein, coagulation factor XI and alpha-2-antiplasmin with the HDL-4 subfraction may contribute to a better understanding of the role of fibrinolysis in PAH and provide novel targets for therapy. Looking beyond idiopathic and hereditary PAH, it would be interesting to see this metabolomic approach repeated in patients with chronic thromboembolic disease and chronic thromboembolic pulmonary hypertension, in which disturbed fibrinolysis is anticipated to play an even bigger role.

Overall, this study provides a hypothesis-generating association between the HDL-4 subclass of lipoproteins and PAH survival. Although the complexity of the technique to measure the HDL-4 fraction hampers use of HDL-4 as clinical prognostic tool in clinical setting, the unbiased and inclusive approach provides a number of clues that direct future investigation into the role of HDL-4-associated proteins in PAH. In addition, the methodology of a combined

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metabolomics and proteomics approach may set an example for future studies in and outside the field. This is likely to result in an increase in our understanding of the pathophysiology of PAH and may ultimately lead to additional targets for therapy.

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