Pulmonary arterial hypertension (PAH) is a progressive and ultimately fatal disease characterized by elevated blood pressure in the pulmonary artery. The pathogenesis of PAH is driven by hyperproliferation of vascular smooth muscle cells in a hyperinflammatory environment, with local accumulation of innate immune cells, such as macrophages, and increased levels of inflammatory cytokines such as interleukin-6 (IL-6), IL-1β, and IL-18. Whereas we traditionally consider PAH a disease that selectively affects the precapillary arterioles, coronary artery disease (CAD) is reported to be 4x more prevalent in patients with PAH, suggesting possible common mechanisms of disease or risk factors. Indeed, PAH is associated with a higher prevalence of the metabolic syndrome, an observation that is particularly notable in patients who develop pulmonary vascular remodeling in the setting of heart failure with preserved ejection fraction.

How an Inflammation-Driven Epigenetic Regulator May Link Pulmonary Hypertension and Coronary Artery Disease

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Do BRD(4)S of a Feather Flock Together?

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enhancers is primed for activation in distinct cell types, and there is evidence supporting a critical functional role of enhancers in controlling cell differentiation and cell lineage identity.\textsuperscript{13,14} This raises the question whether BRD4 binds to specific subsets of enhancers and which target genes are upregulated in smooth muscle cells, endothelial cells, and immune cells, respectively.

The study by Meloche et al\textsuperscript{6} focused on the role of BRD4 in proliferation and apoptosis of smooth muscle cells in the coronary artery. However, aside from smooth muscle cells, endothelial cells can contribute to the vascular remodeling process in PAH and CAD. Endothelial dysfunction in CAD precedes adherence and extravasation of inflammatory monocytes, which differentiate into pathogenic foam cells in atherosclerotic plaques. Moreover, endothelial cells can indirectly aggravate disease pathogenesis by releasing inflammatory cytokines. Because endothelial dysfunction is a common pathogenic feature in PAH and CAD,\textsuperscript{15} BRD4 signaling in endothelial cells may play a role in CAD development in PAH patients. Interestingly, a recent article\textsuperscript{16} revealed the role of BRD4 in producing inflammatory cytokines, such as IL-6 and IL-8, by pulmonary endothelial cells. Clearly, future studies are warranted to investigate BRD4 signaling in coronary artery endothelial cells in patients with PAH and CAD. Moreover, because inflammatory macrophages and T cells are the major sources of IL-6 in tissues, it is possible that these inflammatory cells are recruited in the perivascular space and then induce smooth muscle cell proliferation by increasing BRD4 expression, suggesting a complex cross talk between these cell types (Figure).

Another hallmark of CAD is the presence of atherosclerotic plaques, but it is not currently known whether IL-6-mediated DNA damage and epigenetic modifications can mediate plaque development. It would also be interesting to know whether the drugs commonly used in CAD, such as statins and aspirin, or anti-inflammatory therapies currently tested in clinical trial like methotrexate\textsuperscript{17} (decreasing IL-6 levels) or canakinumab\textsuperscript{18} (anti-IL-1\textbeta antibody) can reduce BRD4 expression. As suggested by the authors, smooth muscle cell proliferation directly contributes to distal CAD by inducing vasoconstriction and reducing coronary perfusion. It is also widely assumed that proliferation of smooth muscle cell and their participation in the formation of a protective smooth muscle cell-rich, collagen-rich fibrous cap protects against plaque rupture in coronary arteries.\textsuperscript{19,20} Whether BRD4 contributes to these disparate properties of the atherosclerotic lesion remains to be studied.

In conclusion, this interesting study provides new evidence, suggesting that PAH is a systemic disease affecting other organs, such as the systemic vasculature and heart. Future studies will be required to untangle the interactions and clearly define causality and new therapies that capitalize on this new knowledge.

Disclosures

None.

References

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