ATHEROSCLEROSIS

Active LDL trafficking drives atherosclerosis

Accumulation of LDL in the artery wall is critical to atherosclerosis initiation and progression. However, the precise mechanisms controlling LDL entry into the artery wall are not fully understood. A study published in *Nature* shows that scavenger receptor class B member 1 (SRB1) in endothelial cells mediates active transcellular transport of circulating LDL into the artery wall and thereby fosters the accumulation of LDL in macrophages, which become foam cells and promote the development of atherosclerosis. "These findings challenge the long-held concept that the LDL entry into the artery wall that drives atherosclerosis occurs passively at sites of injury or disruption of the endothelial barrier," says lead investigator Philip Shaul.

To gain insight into the role of endothelial SRB1 in atherosclerosis, Shaul and colleagues deleted the SRB1-encoding gene *Scarb1* specifically in endothelial cells in three mouse models of atherosclerosis, and using confocal fluorescence microscopy, they visualized LDL entry into arteries in vivo. The research team had shown previously that SRB1, which is a receptor for both HDL and LDL, mediates many potential protective, anti-atherosclerotic actions of HDL in endothelial cells. "Therefore, at the outset of the studies, we expected that the loss of SRB1 from endothelial cells in mice with hypercholesterolaemia would result in worse atherosclerosis," explains Shaul. "To our initial surprise, deletion of *Scarb1* from endothelial cells yielded considerably less atherosclerosis than in control mice," he adds. By contrast, mice with specific deletion of *Scarb1* in hepatocytes had increased atherosclerosis, indicating that SRB1 in endothelial cells and hepatocytes has contrasting effects on cardiovascular health.

SRB1 deficiency in endothelial cells had no effect on circulating lipids or vascular inflammation in mice, but resulted in lower LDL delivery to the artery wall than in control mice. In addition, the investigators found that LDL particles co-localized with SRB1 in intracellular vesicles within endothelial cells in vivo. Mechanistically, the researchers determined that trafficking of LDL into and across endothelial monolayers requires direct binding of LDL to SRB1 and SRB1 recruitment of dedicator of cytokinesis protein 4 (DOCK4). DOCK4 in turn promotes SRB1 internalization and LDL transport by activating the RHO GTPase RAC1. SRB1 and DOCK4 levels were higher in atherosclerosis-prone regions than in atherosclerosis-resistant regions of the mouse aorta prior to lesion formation, and in human atherosclerotic arteries compared with normal arteries.

Shaul comments that they are now exploring the possibility of using gene therapy or pharmacological intervention to reduce the function of SRB1 or DOCK4 in endothelial cells as a strategy to prevent atherosclerosis.

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ORIGINAL ARTICLE Huang, L. et al. SR-B1 drives endothelial cell LDL transcytosis via DOCK4 to promote atherosclerosis. *Nature* https://doi.org/10.1038/s41586-019-1140-4 (2019)

CARDIOMYOPATHIES

Genetics of cancer therapy-induced cardiomyopathy

Cardiomyopathy is an adverse effect of chemotherapy that can affect long-term prognosis. In a study published in *Circulation*, Garcia-Pavia and colleagues report an increased prevalence of rare variants of cardiomyopathy-related genes in patients with chemotherapy-induced cardiomyopathy (CCM).

Anthracyclines can mediate cardiac damage in a dose-dependent manner. Although several risk factors, such as advanced age, female sex and a history of heart disease, predispose individuals to CCM, predicting individual susceptibility to CCM remains challenging. Garcia-Pavia and colleagues sought to determine the genetic risk factors for CCM among both adult and paediatric patients with cancer.

In total, 213 patients with CCM were assessed, including 99 adults with haematological or solid tumour cancer retrospectively recruited from heart failure clinics, 73 adults prospectively enrolled from breast cancer clinics and 41 paediatric patients with acute myeloid leukaemia. The prevalence of rare variants across nine genes previously found to be mutated in patients with dilated cardiomyopathy was significantly higher in the combined CCM cohort than in the unselected participants in The Cancer Genome Atlas (TCGA), ancestry-matched reference populations and healthy volunteers. In particular, titin-truncating variants (TTNtv) were identified in 7.5% of patients with CCM, compared with 1.1% in the TCGA cohort, 0.7% of the healthy individuals and 0.6% of the reference population. Patients with CCM expressing TTNtv were more likely to be hospitalized with heart failure than those without the variants.

To corroborate these clinical findings, the investigators assessed

HEART FAILURE

Balancing stress signalling in the heart

New research on the direct effects of stress on the heart highlights the importance of the balance of stress hormone signalling through glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) in cardiomyocytes to maintain cardiac health. "Alterations that favour less GR signalling and more MR signalling promote heart disease, whereas alterations that favour more GR signalling and less MR signalling are cardioprotective," explain study investigators Robert Oakley and John Cidlowski.

The research team had previously shown that mice with GR deficiency in cardiomyocytes spontaneously develop heart disease and die prematurely from heart failure. However, glucocorticoids can bind to both the GR and MR; therefore, the phenotype in these mice could be due to the loss of the GR and/or to unopposed MR signalling in cardiomyocytes. To assess the specific and coordinated GR and MR response in the heart, the researchers generated mice with cardiomyocyte-specific deficiency of GRs, MRs or both receptors. Mice lacking cardiomyocyte MRs had normal hearts. Simultaneous deficiency of GRs and MRs in cardiomyocytes, despite inducing myocardial stress, reduced the cardiac remodelling, left ventricular dysfunction and early death observed in mice with GR deficiency alone. In addition, double-knockout hearts showed gene-expression changes associated with cardioprotection, but not the gene-expression changes associated with impaired Ca^{2+} handling and increased oxidative stress and cell death observed in hearts with cardiomyocyte GR deficiency alone. Re-expression of the MR in double-knockout hearts partially reversed the cardioprotective changes and led to the development of heart failure. These findings indicate that MR signalling