

IN BRIEF

CARDIOMYOPATHIES

Gene enhancer variation modifies cardiomyopathy

Genetic variation in non-coding regulatory regions for certain cardiac genes is associated with cardiomyopathy progression. McNally and colleagues used an approach that included analysis of epigenetic footprints and chromatin conformation to identify and validate multiple enhancer regions for two of the genes most frequently involved in inherited cardiomyopathies, *MYH7* and *LMNA*. In particular, the researchers identified an enhancer that regulates the switch from *MYH6* to *MYH7* expression and an enhancer-modifying variant upstream of *MYH7* that disrupts a binding site for the transcription factor *TBX5*. Removing the enhancer harbouring this variant markedly reduced *MYH7* expression in human cardiomyocytes in vitro. This variant was associated with a more dilated left ventricle over time according to echocardiographic data from a US biobank.

ORIGINAL ARTICLE Gacita, A. M. et al. Genetic variation in enhancers modifies cardiomyopathy gene expression and progression. *Circulation* <https://doi.org/10.1161/CIRCULATIONAHA.120.050432> (2021)

COVID-19

Microthrombi cause cardiac injury in COVID-19

Microthrombi are the most common cause of cardiac injury in patients with COVID-19, according to a systematic pathology analysis of 40 hearts from patients who died from COVID-19 in Bergamo, Italy. Pellegrini and colleagues found that 35% of the patients had evidence of cardiomyocyte necrosis, mainly of the left ventricle. The most common cause of the cardiomyocyte necrosis was microthrombi, found in 64% of hearts with necrosis. The microthrombi were different in composition (richer in fibrin and terminal complement) from intramyocardial thrombi from patients without COVID-19 and from coronary thrombus aspirates from patients with STEMI with or without COVID-19. Of note, the frequency with which viral RNA was detected in the heart was not significantly different in those with or without myocardial necrosis (14.3% versus 23.1%), suggesting that direct viral infection of the myocardium does not have a major role in the necrosis. The investigators suggest that tailored antithrombotic strategies might be useful to counteract the cardiac effects of microthrombi (which would not be detectable clinically owing to the lack of laboratory tests) and should be examined in future studies.

ORIGINAL ARTICLE Pellegrini, D. et al. Microthrombi as a major cause of cardiac injury in COVID-19: a pathologic study. *Circulation* <https://doi.org/10.1161/CIRCULATIONAHA.120.051828> (2021)

REGENERATION

Boosting stem cell vascular regenerative capacity

Mechanical and pharmacological conditioning of mesenchymal stem cells (MSCs) improves their vascular regenerative properties. Using a high-throughput screening combining a system for applying mechanical stretch to cultured cells with the administration of drug treatments, Lee and colleagues identified a combination of biomechanical stimulation and specific small-molecule inhibitors that synergistically increased the activation of pathways mediated by *SMAD2*–*SMAD3* and *YAP* and induced a vascular-cell-like phenotype in MSCs, with increased expression of pericyte and endothelial markers and increased angiogenic properties in vitro. The optimally conditioned MSCs also showed a higher capacity to induce the formation of blood vessels in mice after subcutaneous implantation and after implantation in ischaemic hindlimbs.

ORIGINAL ARTICLE Lee, J. et al. Mechanobiological conditioning of mesenchymal stem cells for enhanced vascular regeneration. *Nat. Biomed. Eng.* **5**, 89–102 (2021)

VASCULAR REMODELLING

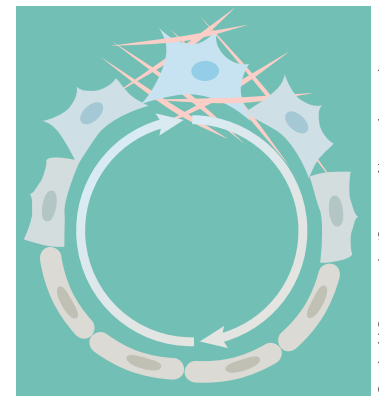
Transient mesenchymal activation of endothelial cells after MI

In the first week after a myocardial infarction (MI), endothelial cells can transition to a mesenchymal state but then return to baseline within 14 days; this transient mesenchymal activation is associated with metabolic remodelling and might contribute to the growth of new blood vessels in the heart.

Stefanie Dimmeler and colleagues used single-cell RNA-sequencing technology to explore the kinetics of individual endothelial cell responses in the heart in the 2 weeks after MI in mice. “We expected to identify endothelial cells that permanently acquire a fibroblast phenotype in this time course,” comments Dimmeler. “Surprisingly, we found that only a transient phenotypic switch occurred.”

In the first week after MI, the majority of endothelial cells in the heart had upregulation of mesenchymal, cell cycle, glycolysis

and proliferation genes and down-regulation of fatty acid uptake and endothelial marker genes. However, the number of endothelial cells with this mesenchymal gene-expression signature returned to baseline levels after 14 days, indicating that activation of the mesenchymal state was only transient and partial (the cells retained a low expression of endothelial genes, and levels of mesenchymal



Credit: V. Summersby/Springer Nature Limited

ATHEROSCLEROSIS

A novel cardioprotective function for DRP1 inhibition

New research shows that dynamin-related protein 1 (DRP1) can regulate PCSK9 secretion by the liver. Elena Aikawa, Maximilian Rogers and colleagues identify a role for DRP1 beyond mitochondrial fission that has important implications for cardiovascular disease (CVD).

“We have previously shown that DRP1, a mitochondrial fission protein, plays a role in select secretory events related to CVD pathology,” states Aikawa. “We were interested in understanding the mechanisms through which DRP1 regulates these select secretory events.” Treatment with the small-molecule DRP1 inhibitor mdivi-1 reduced PCSK9 secretion in human liver cells in vitro, and *Drp1*-knockout mice had a 78.5% reduction in PCSK9 secretion compared with wild-type mice. The researchers found that DRP1

mediates the remodelling of distinct endoplasmic reticulum (ER) microdomains to regulate PCSK9 proteasomal degradation. “DRP1 had not been previously associated with PCSK9, so this finding was highly novel,” states Rogers. “Our select ER microdomain remodelling finding provides a new function for DRP1 that is broadly applicable to studies outside of CVD,” he continues.

Injection of mdivi-1 into diabetic apolipoprotein E-deficient mice with advanced atherosclerotic plaques reduced the advanced atherosclerotic plaque area (–26%) and necrotic plaque area (–48%). Additionally, treatment with mdivi-1 reduced macrophage burden, oxidative stress and advanced calcified atherosclerotic plaque formation in the aortic roots of these mice.