IN THIS ISSUE

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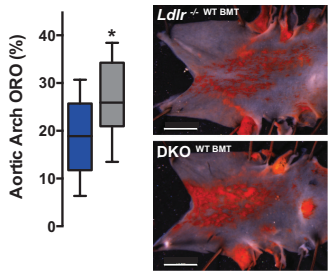
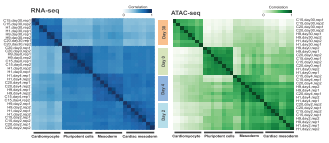


MiR-146a Regulates Atherogenesis (p 354)

Cheng et al discover that unleashing inflammatory signaling can, paradoxically, reduce atherosclerosis.

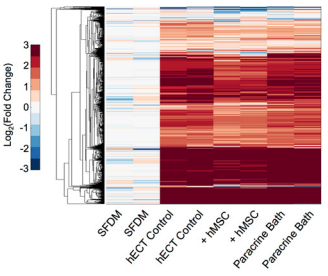
Atherosclerosis develops when fatty deposits in the blood vessels cause endothelial cell (EC) activation and leukocyte recruitment, with subsequent inflammation, mediated largely by the activation of NF-κB signaling. The microRNA miR-146a is known to suppress NF-κB, and injection of miR-146a into atherosclerosis-prone mice has been shown to suppress plaque development. However, the role of NF-κB is complex: suppression of this transcription factor in ECs reduces atherosclerosis; while its suppression in macrophages increases lesion formation. Indeed, Cheng and colleagues have now found that removing miR-146a (thus activating NF-κB), specifically in bone marrow cells (BMs), reduced atherosclerosis in mice, while in ECs miR-146a removal increased atherosclerosis. Paradoxically, while miR-146a depletion in BMs reduced plaque burden in the animals, there was an increase in systemic inflammatory signaling, which, the team suggests, appears to cause hematopoietic cell exhaustion. Indeed, the miR-146a depletion in BMs seems to suppress atherogenesis by over-activating the BMs so much they essentially burn out. In agreement with previous work, these results suggest that a general therapeutic augmentation, rather than suppression, of miR-146a may slow atherosclerosis.



Omics Profiling of Early Cardiac Differentiation (p 376)

Liu et al analyze the early stages of in vitro human cardiomyocyte differentiation.

The ability to differentiate human induced pluripotent stem cells (hiPSCs) and embryonic stem cells (hESCs) into cardiomyocytes (CMs) in vitro is valuable for the study of heart cell development, disease processes, and other myocardial systems. A thorough understanding of the molecular details of this in vitro differentiation is essential, but while transcriptional regulation at late stages of the process has been well studied, analysis of earlier phases has been lacking. Liu and colleagues used both RNA sequencing and chromatin accessibility assays to determine the transcription and chromatin dynamics throughout CM differentiation. Using 2 hiPSC lines and 2 hESCs lines, the team found that patterns of both transcription and chromatin accessibility were highly similar between the 4 cell lines, and identified a number of novel factors specific for particular stages. They also showed that one such factor, ZEB1, upregulated at the cardiac mesoderm stage, was required for early differentiation—knock down of ZEB1 caused a number of essential CM differentiation factors to be downregulated. These results provide novel insights into the early stages of in vitro cardiomyoctye differentiation that will help to frame future investigations into heart development and disease.



hMSC Effects on Contraction and Arrhythmogenesis (p 411)

Mayourian et al distinguish between the different effects of mesenchymal stem cells on heart tissue.

Human mesenchymal stem cells (hMSCs) have therapeutic potential for the treatment of damaged heart tissue. But despite encouraging preclinical results, trials with hMSCs have provided modest benefits, at best. To improve such therapies, a thorough understanding of the interactions between MSCs and cardiomyocytes is essential. It has been suggested that the benefits come mainly from paracrine signaling. Indeed, hMSC-conditioned media can modulate ion channel activity and action potentials in rodent cardiomyocytes. MSCs can also form gap junctions with cardiomyocytes, however, and these heterocellular couplings might also impact cardiomyocyte physiology. Using computational modeling, together with studies of human-engineered cardiac tissue, Mayourian and colleagues have begun resolving the independent effects of paracrine signaling and heterocellular coupling. They showed that paracrine signaling had a greater ability to increase contractility of cardiac tissue than heterocellular coupling and was, in fact, protective against the potential proarrhythmic effects of such coupling. The research, which also included proteomic analyses of MSC and cardiac tissue interactions, provides greater insight into how the stem cells influence the heart and suggests that future studies into how paracrine signaling improves cardiac contractility could lead to more effective therapies.

Written by Ruth Williams

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