IN THIS ISSUE

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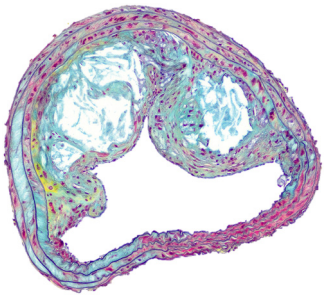
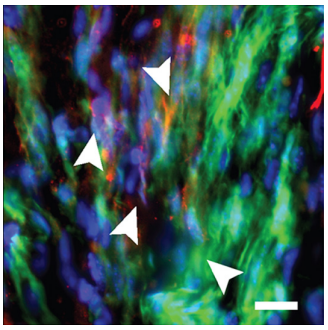


Novel Mouse Model of Atherosclerosis Regression (p 560)

Basu et al develop a method for studying atherosclerosis regression in mice.

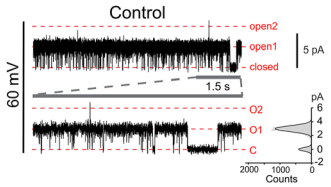
Mice genetically engineered to be deficient in either apolipoprotein E (ApoE) or the LDL receptor (LDLR) are models of choice for studying atherosclerosis. Such models have enabled researchers to gain a detailed understanding of how diet, genetic background, and other factors affect the development of atherosclerotic lesions. However, there are few animal models that mimic regression of the disease, and those that do require either complicated surgeries or time-consuming breeding. To address this, Basu and colleagues have developed an alternative model. First, the researchers induce atherosclerotic plaques in wild-type mice using a combination of high-fat diet and repeated injections (1 per week for 16 weeks) of an LDLR-suppressing antisense oligonucleotide. Then, they give the animals injections of an LDLR sense oligonucleotide to restore receptor expression. This both reduces plasma cholesterol and diminishes the immune cell content of the plaques. With the benefit of using normal laboratory mice, this simple yet effective approach should expedite research into both development and regression of atherosclerosis, say the authors.



Bone Marrow Lineages and Infarct Fibroblasts (p 583)

Moore-Morris et al investigate the origins of scar fibroblasts after myocardial infarction.

Large numbers of cardiac myocytes can be destroyed by a myocardial infarction, and because these cells are not readily replenished, functional muscle is replaced with a collagen-rich, fibrous scar created by fibroblasts. But it is unclear where these fibroblasts come from. Some reports suggest they are derived from endothelial-to-mesenchymal transition, while other investigators suggest that circulating fibroblast progenitors from bone marrow are the source. Yet others suspect that the fibroblasts arise from the epicardium of the heart itself. To find out, Moore-Morris and colleagues performed a series of lineage-tracing experiments in mice subjected to myocardial infarctions. Their results showed that fibroblasts within the infarcted myocardium were not derived from endothelial-to-mesenchymal transition, and were not of either bone marrow or hematopoietic origin (with the exception of a small number of fibroblasts on the surface of the injured heart). Indeed, within the scar tissue itself, the authors discovered that 96% of the fibroblasts were of epicardial origin. Identifying the fibroblast source could provide insights into how to modulate the fibrotic process to reduce scarring and maximize heart function.



Spironolactone Inhibits Panx1 (p 606)

Good et al identify spironolactone as a potent inhibitor of pannexin 1.

Hypertension is a major risk factor for cardiovascular disease, and it affects ≈40% of adults worldwide. In many cases, first-line therapies do not adequately control hypertension. Identifying alternative clinical targets is, therefore, a major research goal. One potential druggable target is pannexin 1—a nucleotide release channel implicated in many physiological and pathophysiological processes, including vasoconstriction via α-adrenergic-induced ATP release. Good and colleagues performed an unbiased screen of small molecule pannexin 1 inhibitors and, in so doing, identified the known antihypertensive drug spironolactone. Interestingly, spironolactone, which is a diuretic, was believed to have antihypertensive effects not explained by its known mechanism of action. Thus, its inhibition of pannexin 1 may be such an off-target effect. The team went on to confirm that spironolactone could inhibit α-adrenergic-induced vasoconstriction in arterioles from hypertensive mice and humans, and could reduce blood pressure in mice. Both effects depended upon smooth muscle expression of pannexin 1. Together, these results bolster the idea that pannexin 1 inhibition could be an effective pharmacological strategy for the management of treatment-resistant hypertension.

Written by Ruth Williams

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