ApoE Suppresses Atherosclerosis via miR-146a (p e1)

Li et al uncover a second pathway by which the cholesterol transporter ApoE reduces atherosclerosis.

The protein ApoE suppresses atherosclerosis through its cholesterol transporting activity. However, ApoE also has anti-inflammatory effects, which may further contribute atherosclerosis suppression. To learn more about this secondary action of ApoE, Li and colleagues studied the effects of the protein in macrophages and monocytes. In these cells, inflammatory processes generally start with activation of the transcription factor NF-κB. Li’s team found that Apo E suppresses the expression of NF-κB. Indeed, in mice lacking ApoE, the expression of NF-κB was increased, while expression of the negative regulator of NF-κB—the microRNA miR-146a—was decreased. The team also found that the expression of miR-146a was driven by activation of the transcription factor PU1. Remarkably, the team discovered that Apo E-null mice, repeated injections of miR-146a-containing liposomes reduced both macrophage activation and atherosclerosis. These injections also reduced atherosclerosis in animals with functional ApoE, though the effect was less dramatic. Together, the findings suggest that the miR-146a-NF-κB axis may be a useful target for resolving inflammation in atherosclerosis.

Functional Genomics of iPSC-Macrophages (p 17)

iPSC-derived macrophages are just like their natural isogenic counterparts, say Zhang et al.

Induced pluripotent stem cells (iPSCs) made from a patient’s own cells can be differentiated into various cell types. In principle, this technique could be used to generate an unlimited source of patient-specific cells that could be used for studying disease pathology, screening potential drugs and developing cell-based therapies. But just how similar are iPSC-derived cells to the real thing? Zhang and colleagues discovered that iPSC-derived macrophages, like their isogenic counterparts, can be polarized in culture to become either M1 or M2 cells. They found also that the iPSC-derived macrophages were similar to native macrophages in their morphology, expression of characteristic markers, secretion of cytokines, phagocytic and cholesterol efflux capacity, as well as their transcriptional profiles. The team generated iPSC-derived macrophages from patients with Tangier disease (TD)—a rare autosomal recessive condition in which patients exhibit defective cholesterol transport from macrophages and premature atherosclerosis. The TD iPSC macrophages recapitulated the known defects of the patient’s own macrophages, but also displayed a novel enhanced inflammatory response. These findings are encouraging and suggest that iPSC-derived macrophages may be useful in studying the pathology of not only TD but many other macrophage-based disorders.

Cardiac Reparative Potential of ESC Exosomes (p 52)

Embryonic stem cell-derived exosomes promote heart repair after myocardial infarction, report Khan et al.

The heart has a limited repair capacity. As a result injury caused by myocardial infarction can be catastrophic—if not immediately then in the long-term. Consequently, stem cell therapy aimed at boosting the innate regenerative potential of the heart is the subject of intensive research. While the approach is promising, its efficacy is limited. For example, most stem cells, when injected, do not survive at the site of injury. A large part of the beneficial effects of stem cells is thought to be driven by cell-free components—such as exosomes. Khan and colleagues therefore examined the effects of injecting exosomes directly. They found that in mice subjected to myocardial infarction, embryonic stem (ES) cell-derived exosomes consistently increased left ventricle contractility and ejection fraction. Treatment with exosomes also decreased infarct size, and increased capillary density, cell proliferation and the survival of cardiomyocytes and progenitor cells. The team went on to show that the exosomes were enriched for an ES-specific microRNA, which alone could mimic the effect of the exosomes on cardiac progenitors in culture. Together the results suggest that the benefits of cell therapy for cardiac repair may ultimately be achieved without injecting the cells themselves.
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