Hyperhomocysteinemia and Vascular Inflammation (p 37)

Genetically engineered mice created by Zhang et al reveal how hyperhomocysteinemia contributes to atherosclerosis.

It has been known for some time that hyperhomocysteinemia—a condition in which blood plasma levels of the amino acid homocysteine are significantly raised—is a risk factor for cardiovascular disease and stroke. How the condition contributes to cardiovascular problems has not been clear, partly because treatments aimed at lowering blood homocysteine in humans have given mixed results. To resolve the confusion, Zhang et al created genetically engineered, atherosclerosis-prone mice in which raising and lowering homocysteine levels could be tightly controlled by diet. They showed that hyperhomocysteinemia was not just a biomarker of cardiovascular disease but a cause. High homocysteine levels were associated with an increase in proinflammatory monocyte numbers in the blood, which in turn resulted in the accumulation of these cells in vessel walls and systemic vascular inflammation. The team also showed that lowering homocysteine levels, by increasing folate in the diet, could prevent both hyperhomocysteinemia-induced monocyte differentiation and atherosclerosis. The results suggest that a similar vitamin fix might be a preventative measure against cardiovascular disease in humans with hyperhomocysteinemia.

Fibroblast Reprogramming by GMT Is Inefficient (p 50)

Contrary to previous findings, Chen et al find it difficult to reprogram fibroblasts into cardiomyocytes.

In 2010, an article by Ieda et al appeared in Cell that claimed transfecting mouse fibroblasts with 3 transcription factors—Gata4, Mef2c, and Tbx5—could reprogram the cells to become spontaneously beating cardiomyocytes. Not only that, but the reprogrammed cells could survive when transplanted into mouse hearts in vivo. Given the immense potential of such a technique for future heart reparative therapies, Chen et al hoped to establish the methods in their own lab. The team successfully transfected mouse fibroblasts with the 3 factors, which were expressed robustly. However, signs that the cells were converting to cardiomyocytes were distinctly lacking. Some cardiac genes were induced in some cells, whereas many other important genes were not induced. Furthermore, even cells that did switch on certain cardiac genes remained morphologically indistinguishable from fibroblasts and exhibited no spontaneous beating activity. Transplanting the transfected cells into mouse hearts, in the hope that the in vivo environment would support transformation, was also unsuccessful. The authors say that much more work must be done to improve transformation efficiency by this strategy.

Pim-1 Bone Marrow Cells Improve Cardiac Structure (p 77)

Pim-1 gives bone marrow cells a boost to help fix injured hearts, reports Quijada et al.

Researchers have analyzed a number of different stem and progenitor cell types for their abilities to mend injured heart tissues after myocardial infarction. The hope is that either the cells themselves will give rise to new myocardial tissue in the injured heart or that they will secrete factors that promote endogenous cells to do so. Bone marrow stem cells (BMCs) are believed to do the latter and are a popular choice for use in therapies because of the relative ease with which they are acquired. They have also been shown to be safe and relatively efficacious in promoting myocardial repair. However, the majority of BMCs transferred to injured hearts are rapidly lost. Therefore, researchers must find a way to make the cells stick around and prolong their beneficial effects. Quijada et al now suggest that BMCs genetically engineered to express Pim-1 might be just the solution. Pim-1 is a kinase that promotes cell proliferation and survival, and, when introduced into BMCs, it improved not only their survival in culture but also their persistence in injured mouse hearts. This persistence translated to better hemodynamic performance and increased anterior wall thickness in the injured hearts compared with hearts that received normal BMCs. Thus, boosting Pim-1 levels in BMCs might be a beneficial approach for enhancing the clinical efficacy of these cells.
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