IN THIS ISSUE

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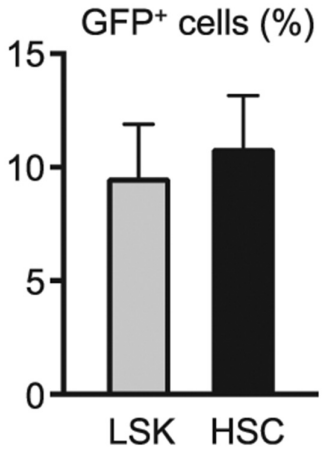
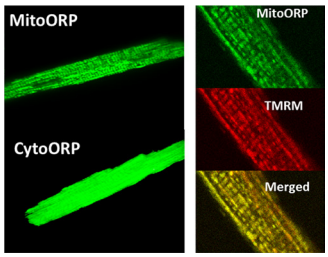


Hematopoietic Tet2, Dnmt3a, and Heart Failure (p 342)

Sano et al use CRISPR editing to investigate genes involved in clonal hematopoiesis.

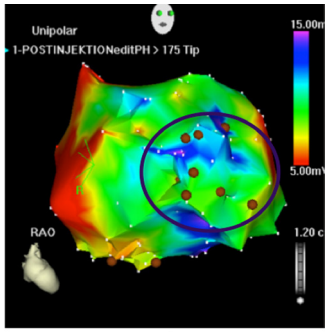
Accumulation of somatic mutations with age not only increases a person's risk of cancer, but also of clonal hematopoiesis, which is excessive production of hematopoietic cells from one mutant stem or progenitor cell. Clonal hematopoiesis can be caused by mutations in any one of ≈40 genes, and it could lead to cardiovascular disease (CVD). But to date, just one gene—*Tet2*—has been confirmed to cause CVD in mice. Now, Sano and colleagues have used a CRISPR gene-editing approach to examine the role other such genes in CVD. As proof of principle, the team first showed that bone marrow cells carrying CRISPR-induced *Tet2* mutations promoted clonal hematopoiesis and CVD in hypertensive mice. Next, they examined CRISPR-mutated *Dnmt3a*—a gene that has been linked to clonal hematopoiesis in old mice and humans. While bone marrow cells carrying the mutation caused CVD symptoms, clonal hematopoiesis was not observed—possibly because the mice were too young. The *Dnmt3a* mutant cells also differed from *Tet2* mutant cells in the repertoire of inflammatory cytokines produced. Collectively, these findings suggest that clonal hematopoiesis-linked mutations have gene-specific pathologies and that CRISPR may be a useful tool for studying them.



mROS Drive Sudden Death and Heart Failure (p 356)

Antioxidant therapy rectifies the proteome changes associated with heart failure, report Dey et al.

In the US, heart failure (HF) causes some 300 000 deaths per year, many of which are due to arrhythmia-induced sudden cardiac death (SCD). Among the several factors that contribute to HF and arrhythmia, the role of mitochondrial dysfunction leading to excessive production of reactive oxygen species (ROS) may be particularly critical. Indeed, approaches aimed at reducing mitochondrial ROS and oxidative stress have been found to attenuate HF in both mice and dogs. However, the molecular mechanisms that link ROS to heart failure remain unclear, and it is not known whether antioxidants can prevent SCD. In a guinea pig model of HF, which has a high rate of SCD, Dey and colleagues found that HF was associated with an increase in ROS levels in cardiac myocytes, and, importantly, treatment with a mitochondria-targeted antioxidant attenuated HF and prevented SCD. The team also identified a number of changes in the proteome and phosphoproteome of animals with HF, which were reversed by antioxidant treatment. Taken together, these results support the potential use of mitochondrial-targeted antioxidants for HF and identify novel proteins that are misregulated in HF, which could be additional target for therapeutic interventions.



Baseline

Repetitive CD34+ Cell Therapy in Cardiomyopathy (p 389)

Double-dose cell therapy is not beneficial for dilated cardiomyopathy patients, report Vrtovec et al.

Trials of cell therapy for nonischemic dilated cardiomyopathy (DCM)—the most common cause of advanced heart failure—have produced limited benefits. However, the results of these trials suggest that conditions such as assessing patients soon after therapy, giving high doses of cells, and administering cells over large areas of myocardium, were associated with the greatest measurable improvements. Vrtovec and colleagues reasoned that repeated doses of cells might potentially address all three of these conditions. And, encouragingly, preclinical evidence also suggests that repeated doses may be more effective than a single dose. The team, therefore, performed a randomized trial with 60 DCM patients—30 receiving 2 doses of autologous stem cells and 30 receiving just 1. After 6 months, both groups displayed similar improvements in left ventricle function, NT-proBNP levels, and exercise capacity. However, after an additional 6 months (and the repeat dose), no further improvements were seen in either group. A second dose of cells, therefore, does not appear to improve outcomes in DCM. The researchers did note a small electrophysiological improvement in 10 patients who received 2 doses, but since there was no functional improvement, additional trials would have to be done to assess the significance of this finding.

Written by Ruth Williams

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