IN THIS ISSUE

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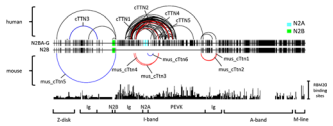
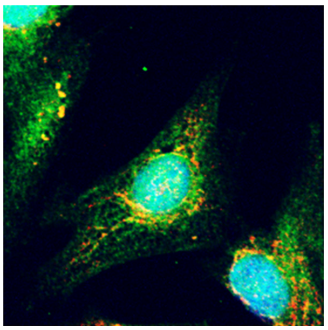


circRNAs in the Human Heart (p 996)

Aberrant circular RNA production could contribute to dilated cardiomyopathy, suggest *Khan et al.*

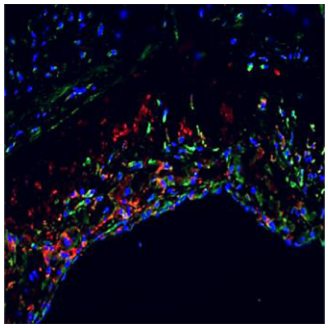
Circular molecules of RNA (circRNAs) were originally discovered around 20 years ago, but until recently they were largely ignored and assumed to be artifacts. However, it is now becoming clear that certain pre-mRNAs can form circRNAs (via splicing between exons located toward the beginnings and ends of transcripts), and that these unusual circular molecules have important functions. Khan and colleagues examined circRNAs in the hearts of healthy people and those with cardiomyopathies. They found several circRNAs that were differentially expressed in healthy and diseased hearts and also discovered that the gene tintin, which encodes a critical structural and mechanical protein of the sarcomere, is a hotspot for circRNA production. Tintin is known to display aberrant splicing in dilated cardiomyopathy (DCM) patients who carry mutations in the splicing factor RBM20. The team found that in a mouse model of DCM lacking RBM20, the production of certain tintin circRNAs was diminished. The production of titin was also abnormal in a DCM patient with an RBM20 mutation. These results suggest that RBM20 mutations may cause DCM not just via incorrect splicing of tintin RNA, but possibly also via the aberrant production of tintin circRNAs.



Role of RING1A S-Nitrosylation (p e129)

Transdifferentiation of fibroblasts to epithelial cells requires nitric oxide synthase, report *Meng et al.*

Transdifferentiation of one cell type to another could be potentially beneficial for therapeutic tissue regeneration. For instance, switching the identity of fibroblasts into cardiomyocytes or endothelial cells could reduce scarring while simultaneously building heart muscle or promoting vascularization. Transdifferentiation generally requires the overexpression of specific transcription factors, but it has been shown that activation of the innate immune response could also faciliate a change in cell identity. Inducible nitric oxide synthase (iNOS) is a major effector of innate immune signaling, and now Meng and colleagues report that abundance of the iNOS protein and nitric oxide (NO) production are increased during fibroblast to epithelial transdifferentiation. By inhibiting iNOS or eliminating NO, the team showed that NO production was required for this identity switch. They discovered that iNOS induction led to the S-nitrosylation of RING1A—a chromatin-binding protein that stabilizes repressive epigenetic marks. S-nitrosylation of RING1A reduced the ability of the protein to bind chromatin, which in turn released epigenetic repression at endothelial-specific genes. The findings suggest that boosting NO or iNOS during fibroblast to epithelial transdifferentiation could enhance this transformation and therefore improve the process for therapeutic applications.



Resolving Atheroprogression (p 1030)

Anti-inflammatory lipid mediators halt progression of atherosclerosis in mice, report *Viola et al.*

Atherosclerosis is a condition of chronic non-resolving vascular inflammation. After an acute inflammatory response, its resolution is driven by a reduction in immune cell traffic, removal of apoptotic cells and by changes in the balance of lipid mediators—from proinflammatory mediators, such as leukotriene B4 and prostaglandin E2, to anti-inflammatory lipid mediators, such as Resolvin D2 (RvD2) and Maresin 1 (Mar1). However, the role of lipid mediators in atherosclerosis was unknown. Viola and colleagues hypothesized that an imbalance in the levels of lipid mediators within atherosclerotic plaques may favor continued inflammation. To test this hypothesis, the team examined lipid mediator levels in atherosclerosis-prone mice fed a high-fat diet. They found that during early stages of atherogenesis, there was an increase in the levels of inflammatory lipid mediators, which was accompanied by a decrease in resolving lipid mediators. The team went on to show that repeated injections of the resolving lipid mediators RvD2 and Mar1prevented atherosclerosis progression in the mice. Comparisons of the plaques from the treated and untreated animals showed that macrophages in the treated mice adopted an anti-inflammatory phenotype. These findings suggest that administration of resolving lipid mediators could be a potential therapy for preventing the formation of atherosclerotic lesions.

Written by Ruth Williams

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Ruth Williams

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