Mutations in STAP1 Associate With ADH (p 552)

Fouchier et al discover a new gene associated with autosomal dominant hypercholesterolemia.

In most afflicted individuals, autosomal dominant hypercholesterolemia (ADH) is caused by a mutation in one of three genes—LDLR, APOB or PCSK9, but in others the causative mutation is unknown. Fouchier and colleagues have now performed genetic linkage analysis and exome sequencing on members of a family who have ADH without mutations in LDLR, APOB or PCSK9. In such individuals, they identified a new mutation in the gene STAP1. They found that this mutation was absent from 400 healthy controls of similar ancestry as well as numerous other control exome and genome sequences—thus suggesting the mutation is not merely a harmless variation. Indeed, analysis of STAP1 coding sequences in a cohort of ADH patients revealed another individual with the same mutation and three individuals with alternative mutations in STAP1—one of which were found in the 400 healthy controls. The team observed that carriers of the STAP1 mutations had higher levels of both total and LDL cholesterol compared with non-carriers, while levels of HDL were unaltered. Figuring out STAP1 function, which is currently unknown, should provide novel insight into the pathological pathways of hypercholesterolemia and might even suggest new treatment modalities.

Heart cells derived from human induced pluripotent stem cells can be used to study viral infection, report Sharma et al.

Between 30 and 50 percent of cases of myocarditis—heart inflammation—are caused by Group B coxsackieviruses. Infections with the viruses can cause heart failure, arrhythmia, and even sudden death, however, at present clinical options for treating the disease are limited. Hence, more in-depth understanding of the underlying mechanism is needed to develop new therapies. But for this, a steady supply of human heart cells is needed. Unfortunately, obtaining heart cells from patients is invasive and expensive, so Sharma and colleagues set out to develop these cells from skin cells, which are relatively easy to get and maintain. Using cells from tiny scraps of skin from healthy people, they induced these cells to become pluripotent stem cells and were then directed them to differentiate into cardiomyocytes. The differentiated cells expressed cardiomyocyte markers including the receptor used by coxsackieviruses for gaining entry. They also exhibited spontaneous regular contractions. Upon infection with a specially constructed luminescent coxsackievirus, the cells began beating erratically and, after approximately 12 hours, they ceased beating altogether. The luminescent coxsackievirus, the cells began beat- ing erratically and, after approximately 12 hours, they ceased beating altogether. The luminescent virus allowed the researchers to track infection, to gauge viral replication and also to observe the effects of antiviral agents. As such, these cells represent a powerful resource for studying coxsackievirus infection and for high-throughput testing of novel antiviral therapeutics, say the authors.

Somanathan et al create degradation-resistant LDLR variants to improve the chances of successful gene therapy in familial hypercholesterolemia.

Loss-of-function mutations in the LDL receptor gene cause familial hypercholesterolemia. Indeed, patients who carry two copies of the mutant gene develop early-onset, life-threatening cardiovascular disease. It has been suggested that these patients may benefit from gene therapy using an LDLR-expressing viral vector, but researchers fear that the transfected receptor may be rapidly degraded by PCSK9 and IDOL, proteins that naturally degrade LDLR in the body, thereby minimizing any potential benefits of LDLR gene therapy. Hence to generate a more stable, and less degradable LDLR, Somanathan et al created vectors expressing PCSK9- and IDOL-resistant variants of LDLR. They screened a panel of mutant LDLRs to find one that escaped PCSK9 degradation. They also mutated two amino acids in LDLR known to be required for IDOL-induced degradation. Then they incorporated all three mutations into one LDLR gene, cloned the gene into a viral vector, and administered the vector to mice that expressed both human PCSK9 and IDOL. Compared with wild-type LDLR, the mutated LDLR protein avoided both PCSK9 and IDOL degradation in the mice. Levels of intact LDLR were increased and, more importantly, levels of serum cholesterol were suppressed in transfected mice. Based on these data, the authors suggest that inclusion of these mutations in clinical-grade versions of LDLR-containing vectors might increase the efficacy of LDLR gene therapy for familial hypercholesterolemia.

Human iPSC-CMs as a Model for Viral Myocarditis (p 556)

Heart cells derived from human induced pluripotent stem cells can be used to study viral infection, report Sharma et al.

Gain-of-Function LDLR for Treating FH (p 591)

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