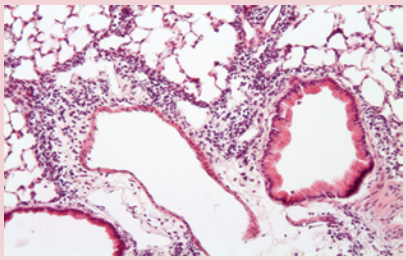
MTOR ablation: a stressful situation for the heart

Inhibitors of mechanistic target of rapamycin (MTOR) are used as anticancer therapeutics. Data generated in mice and reported in this issue by Zhang and colleagues (2805–2816) suggest that such therapeutics might have adverse effects on heart function in patients with ongoing cardiac dysfunction. Specifically, Zhang and colleagues found that adult mice in which *Mtor* was ablated in the myocardium developed a fatal, dilated cardiomyopathy. Disease was associated with accumulation of eukaryotic translation initiation factor 4E–binding protein 1 (4E-BP1), an inhibitor of translation initiation that is normally held in check by MTOR-containing multiprotein complex-1 (MTORC1). Further analysis indicated that when subjected to pressure overload, *Mtor*-ablated mice demonstrated an impaired hypertrophic response and accelerated progression to heart failure. Importantly, deletion of the gene encoding 4E-BP1, under these conditions, improved heart function and survival in the *Mtor*-ablated mice. Thus, decreased MTOR activity impairs the protective myocardial response to stress by enhancing 4E-BP1 activity, providing a potential new therapeutic strategy for improving heart function in patients with heart failure and a warning to clinicians using mTOR inhibitors.

TIM(-1)ely intervention for asthma

The T cell, immunoglobulin, mucin receptor molecule 1 (*TIM1*) gene is a susceptibility gene for asthma. It encodes a cell surface protein that is expressed by T cells upon activation and that is thought to promote Th2 cell–dependent inflammation, the type of inflammatory response underlying the pathogenesis of asthma. To investigate further the role of TIM-1 in human disease, Sonar and colleagues generated a panel of mouse antibodies specific for human TIM-1 (2767–2781). An antibody specific for a cleft formed within the IgV domain of human TIM-1 blocked binding to dendritic cells and had therapeutic activity in a humanized SCID model of experimental asthma, ameliorating inflammation and airway hyperresponsiveness. Further analysis indicated that the protective effects of this antibody were mediated by its ability to block dendritic cell–dependant Th2 cell proliferation and cytokine production. This report describes functional data that support the genetic study linking TIM-1 to asthma and that lead the authors to suggest that TIM-1–specific antibodies targeting the appropriate region of the molecule might have therapeutic benefit in the treatment of asthma.



Young and old differ in energy homeostasis regulation

Understanding how energy homeostasis is regulated is an area of intense research because of the current "epidemic" of obesity and its related diseases. Leptin contributes to this regulation by acting on neurons in different brain regions, but exactly what effects each region mediates has not been clearly determined. To address this issue, Laurence Ring and Lori Zeltser have generated mice in which leptin signaling is disrupted in only the hypothalamus ($Lepr^{Nkx2.1}$ KO mice) (2931–2941). At a young age, the mice were similar to mice lacking leptin signaling in all cells ($Lepr^{db/db}$ mice), showing increased weight gain and adiposity. However, after 8 weeks of age, the $Lepr^{Nkx2.1}$ KO mice maintained stable adiposity, while $Lepr^{db/db}$ mice became more and more obese. These data indicate that leptin signals in the mouse hypothalamus are required to prevent the development of adiposity up to 8 weeks of age, while leptin signals in other regions of the brain are able to limit further increases in adiposity after this time, although they cannot reverse established adiposity. This demonstration that regulation of energy expenditure in young and adult mice differs markedly has implications for combating childhood obesity if it holds true in humans.

Protecting preimplantation embryos: a dead Sirt(3)

Infertility affects approximately 10% of couples worldwide. Although assisted reproductive technologies such as in vitro fertilization are commonly used in developed countries to treat infertile couples, the processes remain relatively inefficient. Moreover, 60% of naturally fertilized embryos do not survive to delivery, mainly because of early developmental failure before and during implantation. Better understanding of events such as preimplantation embryo development could help improve the efficiency of assisted reproductive technologies. In this context, Kawamura and colleagues have now determined that Sirt3, a member of the sirtuin family of NAD^+-dependent protein deacetylase/ADP-ribosyltransferases, helps protect preimplantation mouse embryos against stress conditions during in vitro fertilization and culture (2817–2828). Mouse embryos in which Sirt3 was inactivated showed increased generation of mitochondrial ROS and a decreased ability to form blastocysts in vitro. Furthermore, they showed decreased implantation and fetal growth rates upon transfer into pseudopregnant mice. Mechanistic analysis indicated that p53 expression was upregulated by the increased levels of ROS induced upon Sirt3 inactivation and that this was key to the negative effects of Sirt3 inactivation. Of potential clinical significance, the in vitro negative effects of Sirt3 inactivation on mouse embryos were overcome by culture in the presence of either an antioxidant (*N*-acetyl-*L*-cysteine) or low-oxygen conditions.