■ MITOCHONDRIAL DISEASE

Rapamycin to the rescue

Inhibition of the mammalian target of rapamycin (mTOR) pathway with rapamycin attenuates neurological symptoms and extends lifespan in a mouse model of mitochondrial disease (*Science* doi:10.1126/science.1244360).

Leigh syndrome is a mitochondrial disease caused by mutations in NADH dehydrogenase (ubiquinone) Fe-S protein 4 (*Ndufs4*) characterized by stunted growth, myopathy and neurological symptoms, and ultimately death at an early age. Mice lacking *Ndufs4* shows many of these features, including neurodegeneration and early death.

Matt Kaeberlein and his colleagues report that daily treatment of these mice with rapamycin considerably extends lifespan, delays weight loss, improves motor function and reduces astrocyte and microglial activation in the central nervous system. Mice deficient for *Ndufs4* develop progressive metabolic abnormalities. Rapamycin treatment decreased accumulation of glycolytic intermediates and increased free fatty acid levels. As there are currently no treatment options for these patients, these findings suggest that targeting of the mTOR pathway could be used to treat Leigh syndrome and other mitochondrial diseases. —*KDS*

METABOLIC DISEASE

Obesity-associated mutations

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Kinase suppressor of Ras2 (*KSR2*) interacts with the cellular fuel sensor AMP-activated protein kinase (AMPK) and helps maintain energy homeostasis and glucose tolerance; its deficiency causes obesity and insulin resistance in mice. A new study reports numerous *KSR2* variants that are associated with obesity in humans and impair glucose and fatty acid oxidation (*Cell* 155, 765–777, 2013).

I. Sadaf Farooqi and her colleagues sequenced a large number of individuals with severe early-onset obesity and found several *KSR2* variants, which were associated with hyperphagia in childhood, reduced basal metabolic rate and insulin resistance. When mutations disrupting or possibly disrupting the highly conserved kinase domain were introduced in different cell lines, this blocked not only the interaction of KSR2 with the fuel sensor AMPK but also its interaction with members of the MAPK cascade, suggesting several pathways are altered by these variants.

Because reduced cellular fuel utilization was associated with *KSR2* mutations, the study suggests that *KSR2* mutations may promote obesity by increasing energy intake and reducing metabolic rate in humans. Although the antidiabetic drug metformin rescued the reduced fuel oxidation caused by *KSR2* mutants *in vitro*, other drugs may be developed to modulate KSR2 activity and treat obesity and type 2 diabetes. —*CP*

■ INFECTIOUS DISEASE

Blocking bacteria

Type I interferon is a key player in the host response to viruses, but its role during extracellular bacterial infections is less clear. LeMessurier *et al.* now report that type 1 interferon prevents the translocation of *Streptococcus pneumoniae* from the lung into the bloodstream, limiting systemic bacterial infections (*PLoS Pathog.* **9**, e1003727, 2013).

Intranasal infection with *S. pneumoniae* upregulated the expression of interferon-β1 (*Ifnb1*) mRNA in the lungs before bacteria were detected in the blood. Blockade of IFN-β signaling in mice resulted in earlier and more pronounced bacteremia following intranasal infection without affecting bacterial titers in the lungs. Pretreating mice with IFN-β reduced the titer of bacteria in the blood of wild-type mice infected with *S. pneumoniae*.

The effects of type I interferons may be attributable to two mechanisms. The expression of certain tight junction proteins in the lung was lower in *S. pneumoniae*–infected *Ifnar1*$^{-/-}$ mice (which lack the type 1 IFN receptor) as compared with wild-type mice, whereas treatment of mice with IFN-β increased the expression of these proteins. IFN-β also reduced epithelial cell expression of platelet-activating factor receptor, which is known to participate in receptor-mediated transmigration of *S. pneumoniae* across cell layers. Thus, the induction of *Ifnb1* expression in the lung during *S. pneumoniae* infection helps prevent systemic dissemination of bacteria by reducing their ability to migrate through or between alveolar cells and enter the vasculature. Taken together, these findings suggest that type 1 interferons may be used therapeutically to limit the development of invasive bacterial disease. —*AF*

■ INNATE IMMUNITY

HIV undercover

Detection of viral components, including nucleic acids, by pattern recognition receptors of the innate immune system, triggers the production of type 1 interferons that suppress viral replication. A new study shows that HIV-1 can replicate in human macrophages by recruiting host cofactors that help the virus avoid detection by the innate immune system (*Nature* doi:10.1038/nature12769).

Jane Rasaiyaah *et al.* show that two HIV-1 capsid mutants, N74D and P90A, which cannot interact upon entry with the host cofactors CPSF6 (cleavage and polyadenylation specificity factor subunit 6) and cyclophilins, respectively, stimulate IFN-β production upon infection and are unable to replicate in macrophages. Because blocking of the IFN receptor with an antibody allows replication to wild-type levels, IFN induction is probably involved in suppressing viral infection. Silencing of CPSF6 or pharmacological inhibition of cyclophilin with cyclosporine or a cyclosporine analogue reduce replication of wild-type virus and induce cell-autonomous IFN-β production in macrophages. These findings suggest that in the early stages of infection, the viral capsid conceals nucleic acids and recruits host cofactors, allowing HIV to escape detection by the innate immune system, preventing IFN production and allowing viral replication. —*KDS*

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