■ METABOLISM

Eosinophils in energy homeostasis

Two recent studies in *Cell* have provided mechanistic insight into the interactions of adipose tissue and the immune system in the regulation of energy expenditure and glucose tolerance (*Cell* **157**, 1279–1291, 2014, and *Cell* **157**, 1292–1308, 2014).

In previous studies, Bruce Spiegelman and his colleagues showed that Pgc-1α4 is a unique isoform form of Pgc-1α that is expressed in mouse muscle during exercise and that exercise in mice induces 'beiging' of the white fat. In their new study, they link these previous findings by identifying meteorin-like (Metrnl) as a protein induced by Pgc-1α4 in skeletal muscle in mice and humans and one that promotes beiging and improved glucose tolerance—its expression is also induced by cold exposure in mouse adipose. Mechanistically, Metrnl expression is associated with recruitment to adipose tissue of eosinophils. This resulted in the Metrnl-dependent expression of the cytokines interleukin-4 (IL-4) and IL-13 in the adipose and promotion of the alternate activation of macrophages, thus possibly further explaining the increased insulin sensitivity upon Metrnl expression.

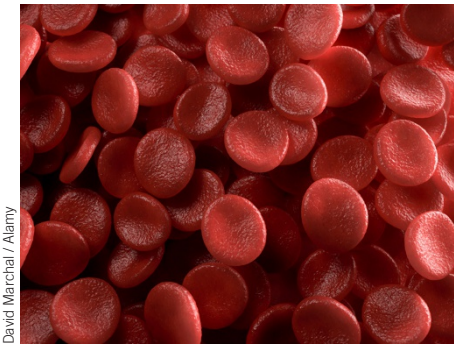
In a separate study, Ajay Chawla and his colleagues found that cold exposure of mice results in alternative activation of macrophages in white adipose tissue in response to eosinophil recruitment and their IL-4 secretion. They further found that these alternatively activated macrophages are a key source of catecholamines that result in beiging of the local white adipose tissue. At thermoneutrality, they could replicate the effects of cold exposure, including the increase in beige fat mass and the reversal of established diet-induced obesity and insulin resistance, by treating mice with IL-4. —*HS*

■ ANEMIA

Giving iron a boost

The surge in red blood cell production that occurs after hemorrhage requires an increased supply of iron. Tomas Ganz and his colleagues identify a new hormone in mice, named erythroferrone (ERFE), that suppresses expression of the iron-regulatory protein hepcidin and thereby promotes recovery from hemorrhage-induced anemia (*Nat. Genet.* **46**, 678–684, 2014).

Hepcidin, produced in the liver, causes degradation of the iron exporter ferroportin, leading to decreased flow of iron into blood plasma. The authors showed that after hemorrhage, the hormone erythropoietin acts on erythroblasts in the bone marrow and spleen to produce ERFE, a member of the tumor necrosis factor-α superfamily, which suppresses hepcidin expression in the liver of mice. Raising the levels of ERFE in mice, either by injection of recombinant protein or by lentiviral overexpression in the liver, suppressed hepcidin levels. In contrast, genetic deficiency of ERFE led to increased hepcidin levels after hemorrhage and impaired recovery from anemia.



David Marchal / Alamy

In β-thalassemia, the inappropriately low levels of hepcidin and the resulting iron overload might also be tied to ERFE. Thalassemic mice had very high levels of ERFE expression, and ERFE deficiency led to higher hepcidin levels and ameliorated iron overload. The contribution of ERFE to hepcidin suppression and iron overload in humans with inherited anemias will now need to be tested. —*MB*

■ NEURODEGENERATION

Mechanistic overlap in ALS

Several pathways perturbed in human motor neurons derived from individuals with amyotrophic lateral sclerosis (ALS) are described in a recent report in *Cell Stem Cell* (**14**, 781–795, 2014).

Mutations in the gene encoding superoxide dismutase 1 (*SOD1*) as well as hexanucleotide repeat expansions at the *C9orf72* locus have been associated with ALS. Kevin Eggan and his colleagues generated induced pluripotent stem cells (iPSCs) from two individuals with ALS harboring the same *SOD1* (A4V) mutation and differentiated them into spinal motor neurons. The authors observed an increase in apoptosis and altered morphology in these cells, which was corrected by restoration of wild-type SOD1 expression via zinc finger nuclease–mediated gene targeting. RNA sequencing analysis of iPSC-derived mutant motor neurons and isogenic control iPSC-derived motor neurons revealed transcriptional changes in mutant cells in several pathways, including oxidative stress, mitochondrial function and induction of endoplasmic reticulum stress and the unfolded protein response. Using iPSCs derived from individuals with expansions in the *C9orf72* locus, the authors identified a subset of genes that are commonly altered, including those encoding catalase, mitochondrial transporters and the protein chaperone DNAJC12.

Another study in the same journal also modeling ALS in iPSCs with *SOD1* mutations revealed neurofilament aggregation as an early event in ALS (*Cell Stem Cell* **14**, 796–809, 2014). Together, these studies indicate the promise of iPSCs for mechanistic understanding of ALS and potential identification of therapeutic targets. —*KDS*

■ IMMUNITY

Selective need for a CTP synthase

A new study by Martin *et al.* reports that deficiency in CTP synthase 1 (CTPS1), one of two CTP synthases involved in the *de novo* synthesis pathway of the nucleotide triphosphate CTP, impairs T and B cell function, resulting in impaired immunity against infection and cancer (*Nature* **510**, 51288–51292, 2014).

The researchers carried out whole-exome sequencing on DNA from three of eight patients (from five families) who experienced frequent viral and bacterial infections—and lymphoma in two cases—which is suggestive of a defect in adaptive immunity. They found all patients to be homozygous for a point mutation in *CTPS1* that resulted in loss of exon 18. The mutation inhibited expression of CTPS1 in patients' cells.

Martin *et al.* found that CTPS1 is strongly upregulated upon T cell or B cell stimulation *in vitro*. Moreover, CTPS1-deficient T cells had impaired T cell receptor–triggered cell proliferation and DNA and RNA synthesis. CTPS1-deficient B cell proliferation after stimulation was also reduced. T cell proliferation could be restored by supplementing cells with CTP or cytidine. Notably, the presence of CTPS2 did not compensate for the lack of functional CTPS1 in patient T cells, although it may act redundantly with CTPS1 in nonimmune cells, given the absence of other clinical phenotypes in the patients.

The authors suggest that this selective dependence of T cells on CTPS1 might be exploited to develop a more targeted immunosuppressant. —*AF*

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