p70S6K and AMPK converge for weight control

The hormone leptin translates information about fat stores to changes in food intake by activating signalling pathways including AMPK and PI(3)K–Akt–mTOR–p70S6K. How these pathways are integrated to elicit the appropriate physiological response has remained unclear. Kahn and colleagues now report that leptin stimulates inhibitory p70S6K-mediated phosphorylation of α2AMPK to decrease food intake and body weight (*Cell Metab.* **16,** 104–112; 2012).

Leptin treatment in mice promoted phosphorylation of α2AMPK at Ser 491 and concomitantly decreased AMPK signalling activity. Expression of a phosphorylation-deficient α2AMPK^{S491A} mutant in hypothalamic regions correlated with increased food intake and body weight. Moreover, leptin treatment, which usually results in weight loss, had no effect in mice expressing the phosphodeficient α2AMPK^{S491A} mutant. Treating mice with PI(3)K-pathway inhibitors, or expression of dominant-negative Akt, inhibited leptin-stimulated α2AMPK phosphorylation and increased AMPK activity. The authors next found that leptin increased p70S6K activity and, using *in vitro* kinase and immunoprecipitation assays, demonstrated that this kinase interacted with and phosphorylated α2AMPK on Ser 491. Conversely, expression of a dominant-negative p70S6K mutant blocked leptin-induced α2AMPK phosphorylation.

These data reveal another point of cross-talk between the mTOR and AMPK signalling pathways, and elucidate a mechanism by which leptin modulates food intake and body weight. EJC

Keeping warm with beige adipocytes

Brown adipocytes expess high levels of the mitochondrial uncoupling protein UCP1, have high mitochondrial respiration capacity, and are thought to protect organisms against hypothermia and obesity. Based on previous indications that UCP1-positive cells could arise in white adipose tissue, Spiegelman and colleagues have generated clonal cell lines from mouse subcutaneous white adipose tissue and identified 'beige' cells with brown adipocyte characteristics (*Cell* **150,** 366–376; 2012). Using an unbiased microarray approach to characterize their gene expression, they classified these cells as either classical white adipocytes or as cells more similar to brown adipocytes. They identified genes that are highly expressed in beige adipocytes compared with brown adipocytes, such as the genes coding for the transcription factor Tbx1, the lipid metabolic pathway component Slc27a1 or the surface proteins TMEM26 and CD137. These markers allowed the *in situ* identification of beige cells and their isolation from a subcutaneous stromal vascular fraction. Following cAMP stimulation, beige cells generated adipocytes with high UCP1 and mitochondrial respiration capacity *in vitro*. The authors also showed that irisin, a hormone that induces brown characteristics in white adipose tissue, triggered higher expression of UCP1 in CD137- or TMEM26-positive beige cells. Interestingly, analysis of brown adipose tissue biopsies revealed higher expression levels of these newly defined beige markers than of classical mouse brown adipocytes. NLB

Atg9 vesicles make up autophagosomes

Double-membrane autophagosomes sequester cytoplasmic material and target it for lysosomal degradation. Although more than 30 autophagy-related proteins (Atg) have been linked to the process in yeast, the origin of autophagosomal membranes has remained unclear. The sole multi-spanning transmembrane protein Atg9 labels cytoplasmic punctae and is required for autophagosome formation. Ohsumi and colleagues have used high temporal resolution fluorescence microscopy and single particle tracking, in combination with electron microscopy and biochemical characterization of Atg9-labelled vesicles, to investigate the role of Atg9 in autophagosome formation (*J. Cell Biol.* **198,** 219–233; 2012). They observed that Atg9–GFP labels single-membrane vesicles that are highly motile in the cytoplasm. Using the photoconvertible tag Kaede, they showed that Atg9 vesicles are generated *de novo* following autophagy induction by starvation. The authors extended previous findings indicating that these vesicles emerge from the Golgi apparatus, and also implicated Atg23 and Atg27 in their formation. By employing *atg* mutants blocked at distinct steps of autophagosome formation, they demonstrated that Atg9 vesicles assemble into the pre-autophagosomal structure. Only few of these vesicles were sufficient to trigger formation of an autophagosome that contained Atg9 on its outer membrane. It is thus likely that further sources of lipids are used for autophagosomal growth. NLB

Cancer stem cells revealed *in vivo*

Although the hypothesis that tumours are maintained by cancer stem cells is being intensively researched, it remains controversial. Three studies now use genetic lineage tracing to track cancer stem cells *in vivo*, providing support for this model of sustaining tumour growth.

Using elegant genetic lineage tracing approaches, Clevers and co-workers (*Science* **337,** 730–735; 2012) identified cells with stem cell characteristics in mouse intestinal adenomas. Distinguished by Lgr5, a marker of normal intestinal crypt stem cells, these cells displayed gene expression signatures, clonogenic properties and localization architecture similar to that of normal crypt stem cells. Simons, Blanpain and colleagues (*Nature* http://doi.org/h56; 2012) also employed lineage tracing to analyse the fate of genetically labelled tumour cells in mouse models of benign papilloma and squamous skin carcinoma. The authors' characterization of tumour growth modes demonstrated the existence of tumour cells with stem-cell-like properties. In a parallel study, Parada and colleagues (*Nature* http://doi.org/h57; 2012) showed in a glioma mouse model that tumour cells genetically labelled with Nestin–GFP, a marker of adult neural stem cells, have properties consistent with those of cancer stem cells. These cells were able to reinitiate tumour growth following chemotherapeutic inhibition of proliferation, whereas specific elimination of the cancer stem cells significantly impaired tumour growth.

These exciting findings will fuel studies to trace cancer stem cells in other tumour types, and to develop therapies to specifically target and eliminate them. AIZ

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