RESEARCH HIGHLIGHTS

Pluripotency factors converge on Esrrb

Several signalling pathways and transcription factors have been implicated in the maintenance of the self-renewal properties of mouse embryonic stem cells. Two studies (*Cell Stem Cell* **11,** 477–490; 491-504; 2012) report that two transcription factors of the pluripotency network critically act on one common target, the orphan nuclear hormone receptor Esrrb.

It is known that inhibition of glycogen synthase kinase 3 (GSK3) signalling, by stabilizing β-catenin, relieves Tcf3 repressor function to maintain self-renewal of mouse embryonic stem cells. However, the critical targets of Tcf3 in the process were unclear. Smith and colleagues carried out an analysis of Tcf3 binding sites and combined it with a survey of genes upregulated in the absence of Tcf3 to identify 9 transcription factors that could be direct targets of Tcf3. They then showed that only one of them, Esrrb, is necessary and sufficient for self-renewal downstream of GSK3 inhibition. Chambers and colleagues also identified Esrrb while searching for the targets of Nanog, a transcription factor that has been linked to the maintenance of pluripotency. They found that Nanog directly stimulates the expression of Esrrb, and that Esrrb expression is sufficient to restore the loss of self-renewal and reprogramming properties associated with loss of Nanog. Both studies also show that Esrrb is not required for self-renewal in the presence of the signalling molecule LIF (leukaemia inhibitory factor), suggesting that several pluripotency modules may be acting in parallel. NLB

HSC regulation in the vascular niche

Haematopoietic stem cells (HSCs) reside in specialized microenvironments within the bone marrow, termed the endosteal and vascular niches. Winkler *et al.* report that E-selectin, an adhesion molecule expressed by endothelial cells, is a critical component of the vascular niche, where it controls HSC proliferation and chemosensitivity (*Nat. Med.* **18,** 1651-1657; 2012).

The authors observed that HSCs cycled more slowly in E-selectin-knockout mice, as a result of increased HSC quiescence and self-renewal capacity. Transplantation of wild-type fetal livers into E-selectin-deficient mice demonstrated that the E-selectin effects were not intrinsic to the HSCs, but were instead attributable to the absence of E-selectin from the endothelial cells of the bone marrow microenvironment. HSC damage, bone marrow suppression and neutropenia are among the adverse effects of cancer therapies. *In vivo* mouse experiments established that loss or inhibition of E-selectin renders HSCs more resistant to chemotherapy by inducing their quiescence and by increasing their self-renewal potential, and also allows faster blood leukocyte recovery following irradiation. Although the regulation of HSC proliferation by endothelial E-selectin was shown to be independent of its canonical ligands, the identity of the HSC molecule mediating these effects remains unclear.

Nevertheless, these findings contribute to our understanding of HSC regulation by the vascular niche, and highlight blocking of E-selectin as a potential strategy to alleviate the HSC-damaging side-effects of anti-cancer treatments. AIZ

Hedgehog signalling regulates autophagy

Autophagy, a degradative pathway for removal of cytoplasmic proteins and organelles through sequestration in autophagosomes and lysosomal degradation, has been suggested to be important for embryonic development. Rubinsztein and colleagues report in *Nature Communications* (http://doi.org/jrd) that autophagy can be controlled by the Hedgehog (HH) signalling pathway in mammalian cells and in *Drosophila melanogaster.*

Activation of HH signalling by a variety of means impairs autophagy; specifically, autophagosome formation. Known components of the HH signalling pathway — the receptors PTCH1 and PTCH2, the transmembrane protein SMO (which acts downstream of the receptors) and the transcription factor GLI2 in mammalian cells — are also required for HH effects on autophagy. Regulation of autophagy by the HH pathway was also conserved in *Drosophila.* In an effort to identify downstream targets of HH signalling that may directly modulate autophagy, the authors assessed changes in the expression patterns of an array of autophagy genes in response to HH signalling activation. They found that PERK (also known as EIF2AK3) and GABARAP1, both implicated in autophagy, were reduced following HH activation; however, additional effectors were also likely to be implicated in autophagy regulation by the HH pathway. The mechanistic details of how the HH pathway controls autophagy await future study. SS

Hedgehog rewires metabolism

Hedgehog signalling has been implicated in many physiological and pathological processes, including adipocyte differentiation, cancer, diabetes and obesity. Despite its involvement in these metabolic processes, a mechanism connecting Hedgehog signalling to metabolic reprogramming has been elusive. Pospisilik, Esterbauer and colleagues now reveal that Hedgehog activates Smoothened (Smo)–AMPK signalling to promote a Warburg-like transition to glycolytic metabolism (*Cell* **151,** 414–426; 2012).

Treatment of 3T3-L1 adipocytes with Smoothened agonist or Sonic Hedgehog ligand induced a metabolic shift towards aerobic glycolysis. Smoothened agonist treatment promoted phosphorylation of AMPK, and knocking down AMPK blocked Hedgehog-induced metabolic reprogramming. Hedgehog signalling depends on its localization to the primary cilium, and mouse epithelial fibroblasts (MEFs) that lacked these structures showed impaired AMPK activation and glucose uptake.

Surprisingly, the Hedgehog antagonist cyclopamine was found to activate this non-canonical Smo–AMPK pathway independently of canonical Hedgehog signalling. The authors found that cyclopamine treatment improved glucose tolerance in mice, promoted glucose uptake by muscle and brown adipose tissue, and also increased core body temperature. These findings suggest that Hedgehog partial agonism might have therapeutic benefit in metabolic diseases. Indeed, the authors found that an FDA-approved Hedgehog inhibitor, GDC-0449, promoted AMPK phosphorylation and glucose uptake. It will be important to determine whether this compound, or other Hedgehog inhibitors undergoing development, are useful reagents in treating cancer, obesity or diabetes. EJC

Written by Nathalie Le Bot, Emily J. Chenette, Sowmya Swaminathan, Alexia-Ileana Zaromytidou