## Evading the defence against brain metastasis

To colonize the brain, cancer cells need to evade the defence mechanisms of this organ against metastasis. Massagué and colleagues report that cancer-cell-secreted serpins counteract the protective effects of plasmins in the reactive brain stroma, resulting in cancer cell survival, vascular co-option and metastasis (*Cell* **156,** 1002–1016; 2014).

The authors observed that the plasminogen activator (PA) inhibitors, serpins, were upregulated in brain metastatic cancer cell lines and human patient samples, and detected components of the plasmin production cascade, which serpins act to inhibit, in the brain metastasis microenvironment. Plasmin activity decreased parental, but not brain-metastatic, cancer cell survival in co-culture assays with astrocytes and microglia, and when seeding cancer cells on mouse brain slices. Brain metastatic cell survival depended on the PA inhibitory function of serpins: by preventing plasmin production, serpins blocked the plasmin-mediated cleavage of the FasL cytokine into a diffusible death signal that would otherwise cause cancer cells to apoptose when exposed to it in the brain. Serpins were also shown to protect the L1-CAM adhesion molecule (which was expressed in brain metastatic cancer cells) from cleavage by plasmin. This allowed L1-CAM-mediated adhesion of cancer cells to each other and to endothelial cells, and promoted vascular co-option and metastatic outgrowth.

By revealing how serpins antagonize the dual anti-metastatic function of plasmin in the brain, these findings provide exciting insights into the process of brain metastatic colonization. AIZ

## Tight control of HSC protein synthesis

Little is known about the regulation of translation in somatic stem cells, although mutations affecting ribosomal functions and translation in humans have been associated with haematopoietic defects, including cancers. Morrison and colleagues (*Nature* http://doi.org/rt9; 2014) have monitored protein synthesis in haematopoietic stem cells (HSCs) and progenitors *in vivo*, taking advantage of the incorporation of a fluorescently labelled O-propargyl-puromycin in nascent polypeptides. By analysing mouse haematopoietic cells one hour after injection of the analogue, they find that HSCs synthesize less protein per hour than other cells in the bone marrow. When induced to undergo self-renewing divisions, HSCs also produced less protein. A mutation in the Rpl24 ribosome subunit decreases protein synthesis in multiple cell types, and the authors show this mutation further reduces protein synthesis in HSCs, without any apparent adverse effect on the bone marrow *per se*. However, these HSCs have impaired proliferative potential *in vitro* and in transplantation assays, indicating a requirement for a specific level of protein synthesis in these cells. Authors have previously found that deletion of *Pten* in mice caused depletion of HSCs and leukaemia. They now show that protein synthesis is increased in HSCs from *Pten*-deficient mice. Combining the *Rpl24* mutation and the *Pten* deletion restored protein synthesis to low levels and suppressed leukaemic development. How the tight control of protein translation level is maintained in HSCs is a question for future studies. NLB

## RIPK3 kinase activity determines death pathway

Receptor-interacting protein kinase 1 (RIPK1) and RIPK3 promote necroptosis in cells and mice in response to inflammatory signalling. Dixit and colleagues wished to explore the role for RIPK3 kinase activity in this process *in vivo* by generating knock-in mice expressing a catalytically inactive version (*Science* http://doi.org/rvc; 2014). Surprisingly, the authors found that mice expressing kinase-dead RIPK3 D161N — in contrast to RIPK3 knockouts, which are viable — died at embryonic day 11.5, displaying severe apoptosis in the yolk sac vasculature. The authors argue this is not due to a dominant-negative effect of the mutation, given that mice expressing only one mutant allele are viable. Further mouse genetics showed that the observed apoptosis was dependent on caspase-8 and RIPK1, and, in cells, RIPK3 D161N but not wild-type RIPK3 associated with RIPK1, FADD and caspase-8. Similarly, inducible expression of RIPK3 D161N in adult mice caused caspase-8-dependent apoptosis in the small intestine. Mice expressing catalytically inactive RIPK1 D138N, on the other hand, were viable but could not rescue the embryonic lethality in RIPK3 D161N mice — suggesting that a scaffolding function, rather than the kinase activity of RIPK1, is required for activation of caspase-8 by RIPK3 D161N. These experiments indicate that whereas RIPK3 kinase activity promotes necroptosis, loss of this activity causes apoptosis. CKR

## Generating energy with mitochondrial fission

Brown adipose tissue (BAT) undergoes mitochondrial uncoupling and expends energy in response to adrenergic stimulation. Mechanistically, norepinephrine promotes the release of free fatty acids (FFAs), which activate Ucp1 to mediate thermogenesis. Shirihai and colleagues report that norepinephrine also induces mitochondrial fragmentation in BAT to promote thermogenesis (*EMBO J.* **33,** 418–436; 2014).

Norephinephrine and FFA treatment in mouse primary brown adipocytes synergistically induced energy expenditure, indicating that adrenergic signalling promotes thermogenesis through FFA-independent pathways. Indeed, norephinephrine, but not FFA alone, induced mitochondrial fragmentation. Norepinephrine promoted protein kinase A (PKA)-mediated phosphorylation of the pro-fission protein Drp1, and its localization with the mitochondria. Intriguingly, inhibiting FFA release by treating cells with Orlistat blocked depolarization but did not affect mitochondrial fragmentation, suggesting that Drp1-mediated fragmentation is stimulated by norephinephrine but not FFA.

Overexpressing a dominant-negative Drp1 mutant blocked norephinephrine-stimulated energy expenditure and mitochondrial depolarization, revealing the importance of mitochondrial fission in thermogenesis. Consistent with this observation, knocking down the pro-fusion protein Mitofusin 2 (Mfn2) caused mitochondrial fragmentation and depolarization, and increased oxygen respiration. Mfn2 knockdown also synergized with FFAs to promote energy expenditure in brown adipocytes. Thus, adrenergic signalling promotes thermogenesis by promoting FFA release and mitochondrial uncoupling, and by activating Drp1 and stimulating mitochondrial fission. EJC

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