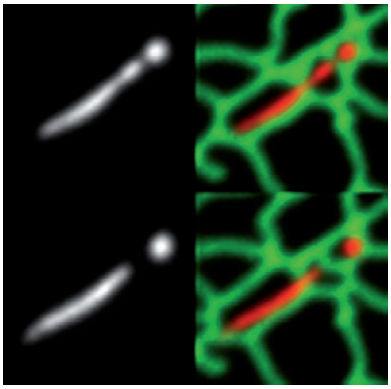
RESEARCH HIGHLIGHTS

Coordinating cell cycle with neurogenesis

During development of the central nervous system, a lengthening of the cell cycle marks the change from maintenance of progenitor cells to differentiation and neurogenesis. However, the molecular mechanism underlying this process was unclear. Ali *et al.* (*Development* **138,** 4267–4277; 2011) now demonstrate that this response may be coordinated by multi-site phosphorylation of the transcription factor neurogenin 2 (Ngn2).

Ali *et al.* found that Ngn2 phosphorylation is dependent on the cell cycle. Nine sites were identified in Ngn2 that could potentially be phosphorylated, and mutation of all nine resulted in a loss of significant phosphorylation, which was found to be dependent on cyclin-dependent kinases (cdks). Expression of this mutant in *Xenopus* embryos also led to a significant increase in neurogenesis. The authors found that preventing phosphorylation of Ngn2 increased its stability and enhanced its ability to interact with DNA. Interestingly, rather than some of the specific phosphorylation sites being essential or a threshold level of phosphorylation being required, the authors showed that each phosphorylation has an additive effect on the ability of Ngn2 to bind to its promoters. This could allow fine-tuning of the Ngn2 response to the increasing cell length and the inhibition of cdks that accompanies neurogenesis. GD

Mitochondrial fission: ER marks the spot



Mitochondrial homeostasis requires the coordination of fusion and fission events. The mammalian dynamin-related protein Drp1 (called Dnm1 in yeast) forms coils around mitochondria and mediates fission, but how fission sites are selected was unclear. Voeltz and colleagues now show that fission preferentially occurs at sites of endoplasmic reticulum (ER)–mitochondria contact (*Science* http://dx.doi.org/10.1126/science.1207385).

High-resolution microscopy of ER–mitochondria contact sites revealed that the ER wraps tightly around the mitochondria to form constrictions in the mitochondrial network. Intriguingly, Drp1/Dnm1 accumulation, and mitochondrial fission, occurred preferentially at these contact sites in both mammalian and yeast cells. The outer mitochondrial protein Mff is essential for Drp1 localization and mitochondrial fission, and ER–mitochondria contact and mitochondrial constriction occurs even when Mff or Drp1 are depleted.

The authors propose that ER-mediated constriction of mitochondria might facilitate the formation of Drp1/Dnm1 coils and subsequent fission, but also acknowledge that the ER might participate in mitochondrial fission directly — possibilities that will be important and interesting to address. EJC

Sticking to the TCA cycle

Detachment of epithelial cells from the extracellular matrix (ECM) can induce profound changes in cellular metabolism, including decreased glucose uptake and ATP production. However, the mechanism by which ECM detachment affects metabolism is less well defined. Brugge and colleagues now provide fresh insight into how ECM detachment reduces ATP production and suggest a mechanism by which cancer cells avoid these metabolic changes (*Genes Dev.* **25,** 1716–1733; 2011).

Acetyl-CoA is consumed by the tricarboxylic acid (TCA) cycle to produce ATP and other biosynthetic compounds. Pyruvate dehydrogenase kinases (PDKs) inhibit the conversion of pyruvate to acetyl-CoA by phosphorylating and inactivating the responsible catalyst — pyruvate dehydrogenase (PDH). The authors found that flux through the TCA cycle and ATP production was impaired in detached normal mammary epithelial cells, but not in those overexpressing the growth factor receptor ErbB2. Decreased PDH flux was ascribed to detachment-induced upregulation of PDK4 in normal cells. However, ErbB4 overexpression blocked PDK4 upregulation and restored PDH flux via Mek–Erk activaton. Indeed, Mek inhibition decreased PDH flux even in attached cells.

The authors went on to show that PDK4 overexpression blocked PDH flux in attached cells independently of ErbB2 expression, and inhibited cellular proliferation. These data show that TCA flux is exquisitely sensitive to ECM attachment, and suggest that hyperactive Mek–Erk signalling might protect cancer cells from detachment-induced changes in cellular metabolism and proliferation. EJC

Tumour microenvironment: Cytokines signal for invasion

The interaction between tumour and stromal cells and their signalling output mould the microenvironment to support tumorigenesis and metastasis. In this context, actomyosin contractility is important for carcinoma-associated fibroblasts (CAFs) to promote cancer cell migration through matrix remodelling, and for the rounded 'amoeboid' motility of cancer cells themselves. Sanz-Moreno *et al.* now delineate the cytokine-controlled pathways regulating these processes (*Cancer Cell* **20,** 229–245; 2011).

Previous findings implicated Janus kinase (JAK) signalling in CAF-induced matrix remodelling. Using *in vitro* organotypic invasion assays and *in vivo* imaging of xenografted tumours, the authors showed that JAK1 activation through the GP130-IL6ST receptor promotes actomyosin contractility in both CAFs and tumour cells, leading to matrix remodelling, tumour cell amoeboid motility and invasion. The authors pinpointed oncostatin M and IL6 as the cytokines regulating actomyosin contractility in CAFs and tumour cells, respectively. They further showed that high contractility affected the activity of the JAK effector STAT3, which altered expression of upstream JAK-STAT pathway components, in support of previous reports of positive feedback regulation in this network. Finally, STAT3 activation was found to correlate with a rounded morphology in tumour xenografts and human melanoma samples, demonstrating the importance of the cytokine-dependent control of actomyosin contractility in tumour and stromal cells *in vivo*. AIZ

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