Cdk1 boosts mitochondrial energy production

The energy demands of the cell increase during the G1/S and G2/M transitions in the cell cycle, but it was not known whether this is regulated by the main mitotic kinase, the cyclin B1/Cdk1 complex. Li and colleagues have found that Cdk1-mediated phosphorylation of complex I (C1) subunits of the mitochondrial respiratory chain promotes increased respiration for cell cycle progression (*Dev. Cell* **29**, 217–232; 2014).

The authors initially found that a pool of cyclin B1/Cdk1 localizes to mitochondria. Further, a proteomics approach identified 52 potential mitochondrial substrates, among which 12 were components of respiratory complexes. Five subunits of the C1 complex were confirmed to be Cdk1 substrates *in vitro* and *in vivo*, and mutation of the Cdk1 phosphorylation site in any of these subunits reduced cellular C1 activity. The authors also found that C1 activity peaks at G2/M, as does that of cyclin B1/Cdk1. Targeting cyclin B1/Cdk1 to mitochondria increased C1 activity and mitochondrial respiration in a manner dependent on Cdk1 activity. Interestingly, constitutive overexpression of mitochondrial cyclin B1/Cdk1 caused an acceleration of the cell cycle that was most prominent at the G1 phase, but also seen at G2/M.

Thus, mitochondrial respiration can be counted as one of the many nuclear and cytoplasmic events coordinated by the cyclin B/Cdk1 complex.

CKR

A fountain of youth for stem cells

Ageing leads to a decrease in the functioning of stem cells in tissues, such as adult neural stem cells and muscle satellite cells (which participate in regeneration in mouse skeletal muscle). Adult neural stem cells lie in close contact with endothelial cells, which provide signals modulating stem cell proliferation and differentiation, and which also deteriorate with ageing. Previous studies have shown that systemic factors from the circulation of a young mouse placed in parabiosis with an older animal can rescue the function of satellite cells. Two studies (*Science* **344**, 630–634, 649–652; 2014) have identified a specific factor that alone restores satellite cell function in aged muscle and improves neural stem cell and endothelial cell function in the aged brain.

Wagers and colleagues showed that aged satellite cells display DNA damage and regeneration defects in response to irradiation. Injection of GDF11 (growth differentiation factor 11), which is known to reverse age-related hypertrophy and whose systemic levels decline with age, restored genomic integrity and improved satellite cell muscle regeneration capacity in old mice. Likewise, Rubin and colleagues found that young blood from parabiotic animals increased the proliferation and differentiation of neural stem cells and their progenitors. They also described remodelling events in the vasculature and, in particular, an increase in endothelial cell proliferation. They too found that GDF11 injection can

have effects similar to those of exposure to young blood in parabiotic animals, ultimately resulting in a functional improvement of neurogenesis, as measured by improved olfactory functions.

NLB

Cellular hierarchies in glioblastoma development

During development, master regulatory transcription factors and their transcriptional programs drive the hierarchical organization of stem and progenitor cells and their differentiated progeny. Some cancer types also rely on similar cellular hierarchies. Suvà *et al.* now characterize the transcriptional networks that govern the hierarchical cellular organization of glioblastoma (*Cell* **157**, 580–594; 2014).

The authors cultured distinct populations of tumour-propagating cells (TPCs) and differentiated glioblastoma cells (DGCs) from patient-derived glioblastoma cells. Combining epigenetic mapping of active gene promoters with computational identification of transcription factor binding sites and gene expression profiles, they identified 19 transcription factors that were enriched in TPCs. Ectopic expression of these factors, alone or in combination, demonstrated that combined induction of POU3F2, SOX2, SALL2 and OLIG2 provided DGCs with tumour-propagating capacity *in vitro* and *in vivo*, and reprogrammed their epigenetic state to resemble that of TPCs. These four transcription factors were expressed in a subset of primary human glioblastomas and were essential for the tumour-propagating abilities of TPCs *in vitro* and *in vivo* in mice. Chromatin immunoprecipitation and gene expression data allowed the reconstruction of the gene networks regulated by these transcription factors, and identified the RCOR2 co-repressor as a critical factor downstream of OLIG2 that could replace OLIG2 in the reprogramming cocktail.

These analyses provide important insights into the transcriptional and epigenetic determinants that control the tumour-propagating potential of glioblastoma cells.

AIZ

Confining stress to the mother

Regardless of whether they bud from young or old mothers, *Saccharomyces cerevisiae* daughter cells are capable of undergoing roughly the same number of subsequent divisions. This resetting of daughter cells' biological clocks is attributed to the formation of a diffusion barrier at the bud neck that contains ageing factors in the mother cell. Barral and colleagues provide insight into the nature and function of this barrier (*eLife* **3**, e01883; 2014).

Misfolded proteins formed as a result of endoplasmic reticulum (ER) stress were specifically retained in the mother cell by a sphingolipid-rich ER diffusion barrier. Intriguingly, proteins involved in bud site selection — including the GTPase Bud1, the GEF Cdc24 and the GTPase Cdc42 — were essential for diffusion barrier formation and the retention of misfolded proteins in the mother cell. ER stress reduces replicative lifespan, but *bud1Δ* cells were largely protected from this effect, suggesting that the diffusion barrier normally acts to contain toxic misfolded proteins within the mother cell.

The authors also found that the sphingolipid diffusion barrier forms downstream of the known barrier components septin and Bud6, and that sphingolipids help to define a discrete ER membrane subdomain in the bud neck. These findings add complexity to the composition and function of diffusion barriers, and suggest that the ER barrier has a fundamental role in keeping daughter cells young.

EJC

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