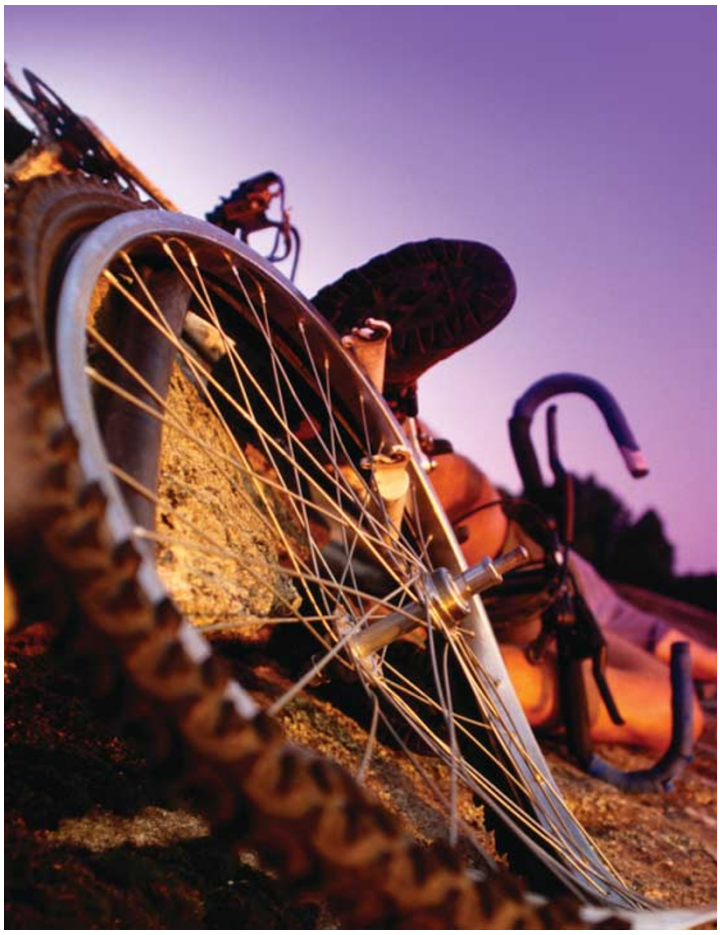
CELL CYCLE

Cycling is an E2Ffort



In *Cell*, Reis and Edgar shed light on the regulation of cell-cycle timing by showing that the E2F1 transcription factor can modulate cell-cycle-phase length in *Drosophila melanogaster* wing-disc cells.

The regulation of cell-cycle-control proteins has been studied extensively, but how the rate of progression through cell-cycle phases is coordinated to control overall cell-cycle length is poorly understood. Overexpression of the cell-cycle regulators Cyclin E (CycE) and Cdc25 (known as String (Stg) in *D. melanogaster*) shortens G1 and G2 phases, respectively. However, the overall rate of cell division is maintained by making other cell-cycle phases longer. If an active mechanism that monitors, and maintains, the overall duration of the cell cycle is responsible for this regulation, then experimentally lengthening cell-cycle phases would similarly result in the maintenance, rather than the elongation, of the rate of cell division.

The authors lengthened G1 phase in larval tissues by overexpressing the CycE–Cdk2 inhibitor *dacapo* (*dap*; the *D. melanogaster* homologue of $p21^{CIP1}$ and $p27^{KIP1}$). Analysis of wing-disc cells showed no overall lengthening of the cell cycle due to a compensatory shortening of the subsequent S and G2 phases. Transcription of *stg*, which is the rate-limiting factor for the G2–M transition, was upregulated in the *dap*-overexpressing cells, which explained the increase in the rate of G2–M progression. *stg* transcription is affected by E2F1 activity and other E2F1 target genes, *ribonucleotide reductase-2* (*rnr2*) and *cycE*, were also upregulated in these cells. Immunostaining of these cells showed increased amounts of E2F1 protein, which correlated with the upregulation of E2F1 target genes.

Next, the authors overexpressed *wee1*, which lengthens G2 phase by inhibiting Cdk1. Messenger RNA and protein levels of the E2F1 targets *stg*, *rnr2* and *cycE* were increased in these cells, which, again, correlated with increased amounts of E2F1 protein. The overall cell-cycle length was maintained by shortening G1 phase, an effect that is attributable to the increased amounts of CycE. Similar results were observed in cells in which G2 phase was lengthened by overexpressing another cell-cycle regulator, *Tribbles*. So, a reduction in Cdk activity extends a specific gap phase, increases E2F1 levels and results in the compensatory truncation of the complementary gap phase.

Manipulating Cdk activity by overexpressing activators or inhibitors of Cdks confirmed that Cdk activity regulates the levels of the E2F1 protein. Double labelling of wing-disc cells for E2F1 protein and for markers that are specific for different cell-cycle phases also showed that the level of E2F1 oscillates with the cell cycle — it is present in G1, G2 and M phases but absent in S phase. However, the cell-cycle-specific distribution of E2F1 was not affected by Cdk activity. Furthermore, when *e2f1* was artificially expressed throughout the cell cycle, the E2F1 protein was still absent during S phase, which indicates that E2F1 protein is removed from S-phase cells.

Next, the authors manipulated the cell cycle in cells that lacked E2F1 activity due to a mutation in DP, which is an essential coactivator of E2F1. They found that E2F1 activity is required for *stg*, *rnr2* and *cycE* gene upregulation in Cdk2-inhibited cells and cycle compensation in Cdk1- and Cdk2-inhibited cells. Moreover, the overexpression of proteins that promote cell growth (such as Rheb or Myc) normally accelerates the G1–S transition and elongates G2 phase, but in *DP*-mutant cells the effect was much less pronounced. These cells also had high rates of apoptosis, which indicates that, in the absence of E2F1 activity, cells cannot tolerate changes in cell-cycle phasing that are induced by physiological growth promoters.

The authors conclude that "…in *Drosophila*, E2F1 is a central component of a regulatory circuit that allows cells to sustain alterations in the lengths of individual cell cycle phases without compromising overall cell cycle timing." And, they propose that the phosphorylation of E2F1 by Cdks might be responsible for targeting E2F1 for protein degradation.

Lesley Cunliffe

References and links

ORIGINAL RESEARCH PAPER Reis, T. & Edgar, B. A. Negative regulation of E2F1 by cyclin-dependent kinases controls cell cycle timing. *Cell* **117**, 253–264 (2004)

IN THE NEWS

Fat starved to death

Obese people could be one step closer to a slimmer life, thanks to researchers at the University of Texas and Baylor College of Medicine, Texas, USA.

The treatment — dubbed 'molecular liposuction' — is based on a cancer therapy that destroys the blood vessels that supply the nutrients needed for tumour growth. It starves fat cells of the nutrients needed for their growth, by destroying "those blood cells that served white adipose or fatty tissue" (*The Guardian*, 10 May 2004).

Reporting in *Nature Medicine*, Mikhail Kolonin and colleagues found that prohibitin, which regulates blood-vessel growth, is present only on the surface of fat cells, so they "took a fragment of a protein that binds to prohibitin, and attached it to another protein fragment that is used in cancer therapy to kill blood vessels" (*Nature Science Update*, 10 May 2004). In just 4 weeks, this composite molecule succeeded in producing a 30% reduction in the body weight of mice that had been fed a high-calorie diet.

One of the authors, Renata Pasqualini said, "If even a fraction of what we found in mice relates to human biology, then we are cautiously optimistic that there may be a new way to think about reversing obesity" (*BBC News Online*, 10 May 2004). Peter Carmeliet, from Flanders Interuniversity Institute for Biotechnology in Belgium, agrees. "It is an approach with great potential" that "could potentially work even better against obesity than cancer" (*Nature Science Update*, 10 May 2004).

More research is needed, but encouragingly "the drug didn't seem to cause any toxic side effects and the lost fat did not accumulate in other organs or in the circulation" (*NewScientist.com*, 10 May 2004).

Natalie Wilson