CELL CYCLE

Here comes the cycling squad!

Multiple protein kinases regulate different phases of the cell cycle in metazoans. In turn, these kinases are themselves regulated by phosphorylation events and cooperate with other protein kinases. Bettencourt-Dias, Glover and colleagues have tested the complete set of *Drosophila melanogaster* protein kinases for their involvement in the cell cycle by knocking down their gene expression by RNA interference. The results are reported in *Nature*.

Each of the genes encoding the 228 predicted kinases was downregulated in S2 cells and the resulting cell lines were screened for cell-cycle defects. Flow-cytometry analysis revealed delays in cell-cycle progression for 42 protein kinases. Certain mitotic defects could not be detected by flow cytometry, so by quantifying 20 parameters the authors concluded that 60 kinases had a mitotic phenotype. In total, 80 kinases showed defects in cell-cycle progression and/or mitosis.

Reassuringly, Bettencourt-Dias, Glover and co-workers identified most previously known cell-cycle kinases, including the G1–S regulators Cdc2c and Cdk4, the mitotic kinase Cdc2, the Cdc2-inactivating kinases Wee and Myt1, and Trbl kinase (which induces proteolysis of String, the Cdc2-activating protein phosphatase). As predicted, depletion of Polo kinase and Aurora kinase gave rise to mitotic defects. Together, these findings validated the authors' approach, although some effects might have been cell-type specific.

During the course of their analysis, the authors identified new cell-cycle protein kinases and assigned new cell-cycle functions to known kinases. Some of the latter were putative regulators of the actin cytoskeleton, including integrin-linked kinase (Ilk), Src64B and genghis khan (Gek) — for example, knockdown of *gek* caused the formation of abnormal spindles that produced defective chromosome alignment. Knockdown of other kinases with cytoskeletal functions was associated with defects in the G2–M transition. So, these results indicate a possible role for the actin cytoskeleton in early mitotic events.

The study also assigned new cell-cycle functions to known kinases that function in external signalling from growth factors, stress signalling or the regulation of cell growth. For example, the depletion of certain protein kinases that function in the nuclear factor (NF)-κB , JNK (Jun N-terminal kinase) or JAK–STAT (Janus-kinase–signal-transducer-and-activator-of-transcription) pathways resulted in an increased number of G1-phase cells. Downregulation of the PDGF and VEGF (platelet-derived growth factor and vascular endothelial growth factor)-related receptor, Pvr, caused an increase in the number of cells in G2 phase. S6k, the effector kinase in the Tor (target of rapamycin) nutrient-sensing signalling pathway, as well as several other kinases in this pathway, caused an increased proportion of small G1 cells after downregulation. Knockdown of Gcn2, a protein kinase in a different nutrient-sensing signalling pathway, caused spindle and chromosomal defects.

Altogether, this genome-wide survey highlights the interconnections between the regulation of cellular physiology and that of cell-cycle progression by protein-phosphorylation events. Given the high level of conservation of cell-cycle regulators, these findings provide an interesting starting point for the study of their human counterparts.

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References and links

ORIGINAL RESEARCH PAPER Bettencourt-Dias, M. *et al.* Genome-wide survey of protein kinases required for cell cycle progression. *Nature* **432**, 980–987 (2004)

WEB SITE
David M. Glover's laboratory: http://www.gen.cam.ac.uk/newdept/research/labs/glover.htm