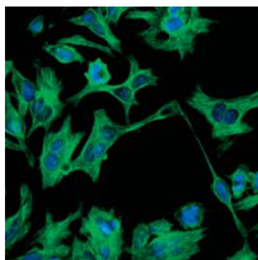
Aurora B gone



The Aurora B kinase is found at centromeres during mitosis. Among other functions, it phosphorylates histones H3 and CENP-A, thus playing a crucial part in cell division. Peter and colleagues now provide a model for the eviction of Aurora B from chromosomes after mitosis. This model implicates ubiquitination of the kinase in the completion of cytokinesis and also suggests Aurora B may be a target of the Cul3-based E3 ligase substrate–specific adaptors KLHL9 and KLHL13. Cul3 depletion by RNA interference results in incomplete cytokinesis. The authors found not only that Cul3 associates and copurifies with KLHL9 and KLHL13, but that these in turn are required for cytokinesis. In addition, depletion of any of these three factors results in mislocalization of Aurora B across the chromosome (beyond its usual centromeric location) as well as persistent Aurora B chromosomal association and histone H3 phosphorylation into the later stages of mitosis. These results suggest that the three ubiquitination factors somehow affect the cell cycle–dependent targeting and function of Aurora B. Peter and colleagues go on to show that a Cul3–KLHL9–KLHL13 E3 ligase is able to ubiquitinate Aurora B *in vitro* and *in vivo*. Although the site of ubiquitination, and its mechanistic effect on Aurora B's localization and function, remain to be explored, this study provides an initial clue as to how a Cul3-type E3 ligase might be involved in cell division. (*Dev. Cell* **12**, 887–900, 2007) *SL*

Change for Tolls

Toll-like receptors (TLRs) sense subtle differences between 'self' and microbial molecules. TLR3 and TLR7–9, located in the endosome, are sensitive to the distinctive DNA methylation pattern of microbes. TLR9 activation by microbial DNA, rich in unmethylated CpG motifs, triggers the adaptive immune response. TLR9 overactivation or activation by self DNA can lead to chronic inflammatory disorders and autoimmune diseases, so mechanistic insights may prove useful for drug development. Espevik, Golenbock and coworkers investigated CpG DNA–mediated activation of TLR9 using a series of biochemical and fluorescence techniques. They found that although both stimulatory and nonstimulatory DNA sequences bind the ligand-binding ectodomain of the receptor, only the stimulatory CpG DNA induces large conformational changes in the ectodomain. Cross-linking and immunoprecipitation studies suggested that TLR9 dimerizes in the unstimulated state and that ligand binding does not induce higher-order aggregation of the receptors. The authors next used a green fluorescent protein (GFP) fragment reconstitution assay, in which the cytoplasmic Toll interleukin-1 receptor (TIR) signaling domains were replaced with the GFP N- and C-terminal domains. Fluorescence at the endosomes was observed only when CpG DNA was added, indicating that the cytoplasmic domains come together upon ligand stimulation. Altogether, the studies indicate that TLR9 exists as a preformed dimer under nonstimulatory conditions and that ligand binding induces conformational changes in the ectodomain, which may promote a reorientation of the intracellular TIR domains favorable for downstream signaling events. Whether these conformational changes are common to all TLRs remains to be tested. (*Nat. Immunol.* **8**, 772–779, 2007) *MM*

Akt-ing on insulin stimulation

Decreasing liver glucose production is a normal response to increased glucose levels. Insulin signaling is known to decrease transcription of genes involved in gluconeogenesis by inhibiting expression of the FOXO1 transcription factor. However, some insulin-inhibited genes are FOXO1 independent, and insulin also regulates hepatic fatty acid metabolism. Birnbaum and colleagues now help elucidate a second pathway that, in response to insulin signaling, not only inhibits transcription of genes involved in gluconeogenesis such as *G6Pase* (encoding glucose-6-phosphatase), but also affects transcription of fatty acid–oxidation genes such as *MCAD*. The authors essentially define a phosphorylation site in the transcriptional coactivator PGC-1α that can be targeted by Akt, a kinase activated by insulin signaling and previously implicated in inhibitory phosphorylation of FOXO1. PGC-1α is phosphorylated on Ser570 in cells, and the importance of this site is indicated by mutation studies. S570A mutation leads to upregulation of both *G6Pase* and *MCAD*, an effect resistant to expression of a constitutively active Akt variant in cell lines and in transfected mice. Increased *G6Pase* and *MCAD* transcription correlates with the presence of PGC-1α at the promoters of these genes. Indeed, neither glucose production nor β-oxidation of fatty acids can be downregulated by Akt if unphosphorylatable PGC-1α is expressed. While further insight into whether PGC-1α regulates other lipid metabolism genes, aberrant hepatic lipid production is a feature of the type 2 diabetic state and may be linked to cardiovascular disease. (*Nature*, advance online publication 6 June 2007, doi:10.1038/nature05861) *SL*

Dancing around Drosha

MicroRNAs are 21–23 nucleotides in length and are involved in regulating the expression of many genes. These RNAs are processed in two steps: the nuclear RNase III Drosha cleaves primary miRNAs to release hairpin-shaped precursor miRNAs (pre-miRNAs), which are subsequently cut by the cytoplasmic RNase III Dicer to generate a miRNA-miRNA duplex. The mature miRNA from this duplex is then incorporated into the silencing complex. Bartel and coworkers have now discovered an alternative pathway for miRNA biogenesis that bypasses the need for Drosha-mediated cleavage. They identified certain introns that act as pre-miRNAs, or 'mirtrons', from flies and worms. These pre-miRNAs arise from splicing rather than Drosha cleavage: they are spliced as introns and then diced as pre-miRNAs. The authors show that mirtrons generate functional miRNAs in *Drosophila* S2 cells and that mirtron processing depends on splicing and debranching. The abundance of pre-miRNA–sized introns could allow miRNAs to emerge in any organism that performs splicing and post-transcriptional RNA silencing but lacks the specialized Drosha RNase III enzyme. (*Nature*, advance online publication 24 June 2007, doi:10.1083/nature05983) *BK*

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