p107 Skps from S phase

Pocket proteins find multiple routes to stop cell proliferation, according to results on page 55 from Rodier et al.

The well-known antiproliferative route taken by pocket proteins, including pRb and p107, is through interaction with E2F. When bound to pRb, E2F cannot initiate the transcription of cell cycle progression genes, and cells thus linger in G1.

But pocket proteins are also able to block proliferation by less well-characterized E2F-independent pathways. The new results reveal that, for p107, this pathway operates by interfering with protein degradation. The end result is a low level of Cdk activity that prevents S phase.

Serum addition or p107 deletion led to stabilization of high levels of Skp2, the substrate recognition component of an E3 ubiquitination complex. The resulting complex could degrade the CDK inhibitor p27, leaving cells free to transition from G1 to S phase. Overexpressed p107 (open boxes) makes Skp2 unstable.

The only pocket protein that is a proven tumor suppressor is pRb. pRb was also recently shown to inhibit Skp2 function (Ji et al. Mol. Cell., 16:47–58), although through a different mechanism involving direct binding to Skp2. If the Skp2 effect is the tumor suppressor function of pRb, it is likely that p107 is also a tumor suppressor, whose loss is offset by other pocket proteins.

Freedom in condensation

Even highly condensed mitotic chromatin allows for the comings and goings of transcription factors, according to Chen et al. on page 41. Their measurements of the dynamics of RNA polymerase I (Pol I) transcription factors show that mitotic transcriptional silencing is not due to inaccessible chromatin.

RNA polymerases II and III stay off chromatin during cell division, but RNA pol I is found at rDNA sites throughout mitosis. The new fluorescence recovery experiments show that pol I subunits and the transcription initiation factor UBF1 are not trapped within the condensed DNA during this time, but instead come and go. By keeping RNA pol I at rDNA, transcription activation may begin as soon as sister chromatids separate, thus maximizing ribosome synthesis, which is so fundamental to survival. Indeed, the earliest detectable RNA synthesis was that of rRNA at late anaphase.

Dynamic exchange was also seen for histone H1 throughout mitosis and for core histones at late anaphase and telophase. Core histone exchanges coincided with H3 lysine 9 acetylation (a hallmark of transcriptionally active chromatin), pol II association, and the first hints of transcription. Chromatin remodeling therefore takes place before widespread DNA decondensation and the bulk of transcription activation at mitotic exit.

Thinning microtubules

Centrosomes spindle out microtubules to thin out their load at the end of mitosis, as illustrated by Rusano and Wadsworth on page 21. This reorganization helps reestablish the interphase microtubule array and may contribute to localizing the cytokinetic ring.

Centrosomes nucleate many more microtubules during mitosis than they do in interphase. The new results show that the extra load is lightened in mammalian cells at late anaphase, when microtubules were released both individually and in clusters. The clusters carried with them centrosomal proteins such as γ-tubulin, the microtubule nucleator. The release of microtubules is prevented by CDK activity, as nondegradable cyclin B inhibited the disassembly after chromosome separation.

Microtubules were released and actively transported outwards in the direction of the cell poles (away from the chromosomes), where microtubules were previously scarce. Because the freed microtubules are not protected at their minus ends, they are more dynamic and turn over more rapidly than attached microtubules. The microtubules or their subunits are probably used to reform the interphase array.

The bias in turnover also creates an asymmetry in the array that might be important for directing cytokinesis to a central location. The attached, stable microtubules (those pointing inward) are more likely to transport signals that might stimulate the formation of the cytokinetic ring.

During anaphase, microtubules (green) are released from the centromere and move toward the poles.

Overexpressed p107 (open boxes) makes Skp2 unstable.