Transient silencing made permanent

All cancers have genes that are permanently silenced by DNA methylation. Yeshayahu Schlesinger, Howard Cedar (The Hebrew University, Israel), and colleagues, and Martin Widschwendter (UCL, London, UK), Peter Laird (USC, Los Angeles, CA), and colleagues inspect these irreversibly silenced genes. In normal tissues, they find, these genes carry transient repression signals, which are inappropriately made permanent in cancer.

Large parts of the genome get methylated and thus permanently silenced in the early embryo, but genes associated with CpG islands are spared. Some are instead transiently repressed by a complex called polycomb. This prevents inappropriate expression during development, but allows repression to be reversed when needed.

Irreversible silencing by DNA methylation occurs at many CpG island genes during cancer progression. Schlesinger et al. now show that >60% of genes that are methylated in colon cancer are marked by polycomb in normal tissues. In an accompanying paper, Widschwendter et al. calculated from previously published data that polycomb target genes are 12-fold more likely than nontargets to be methylated in cancer.

Different sets of CpG island genes get methylated in different cancers, but both groups found that, regardless of cancer type, the correlation between methylation and polycomb tagging is consistent.

No causal link between transient repression and permanent silencing marks, or between methylation of genes and cancer, has been established. Cedar speculates, however, that methylation of polycomb-tagged CpG genes could be an early, even causative, event in cancer. “Polycomb target genes are required for differentiation,” he explains. “Therefore, cells have a mechanism for getting rid of polycomb. If, prior to that, these genes get abnormally methylated, the cell gets stuck in a state of proliferation, unable to differentiate.”

The model suggests that cancer might originate from adult stem cells rather than from cell dedifferentiation. Perhaps an abnormally active DNA methyltransferase in certain stem cells incorrectly targets transiently repressed loci. JCB

References: Schlesinger, Y., et al. 2007. Nat. Genet. doi:10.1038/ng1950.
Widschwendter, M., et al. 2007. Nat. Genet. doi:10.1038/ng1941.

Pom1p prevents a spreading middle

Cells often take on a perfect hourglass figure as they divide into two equal daughter cells. Precise positioning of the cytokinetic waistline in fission yeast requires inhibitory signals from the cell poles, Neal Padte, Fred Chang (Columbia University, New York, NY), and colleagues now report.

The waistline in Schizosaccharomyces pombe is positioned by a belt-like ring of mid1p at the cell’s midpoint. Mid1p, located in the plasma membrane, then recruits myosin and other contractile ring proteins to separate the cell into two.

Padte and colleagues predicted by computer simulation that mid1p is in the middle because its diffusion to the poles is forbidden. They found that, in yeast cells lacking a polar kinase called pom1p, mid1p was no longer in a band around the middle, but was instead spread out. This in turn caused misplaced or multiple myosin contractile rings to form and the yeast to divide asymmetrically.

Spreading of mid1p in pom1p-deficient cells was only seen in one direction, however. Although pom1p is located at both poles, it is usually enriched at one. What prevents mid1p from creeping toward the other pole is currently under investigation. JCB

Reference: Padte, N., et al. 2006. Curr. Biol. 16:2480–2487.

Clustered creates a spindle

Individual lobbyists might have a hard time promoting their cause, but get a large group of like-minded individuals together, and there’s action. Similarly, the spindle assembly action of Aurora B starts only once this kinase comes together with other chromosomal passenger complex (CPC) members, according to a new study by Alexander Kelly, Hironori Funabiki, and colleagues (Rockefeller University, New York, NY).

Spindle assembly at the chromosomes is controlled by the Aurora B kinase, which deactivates microtubule-destructing proteins MCAK and Op18. The CPC member Dasra A is required for the rest of the CPC to assemble on chromosomes. Kelly et al. now show that this chromosomal loading serves to cluster the CPC components. It is this clustering that then kicks off the Aurora B pathway.

The team induced clustering of the CPC proteins in cell extracts devoid of chromatin using antibodies to a CPC component. This clustering was sufficient to phosphorylate downstream targets of Aurora B and to generate spindles lacking chromosomes.

Clustering, the team showed, allowed the CPC components to effectively phosphorylate each other and ultimately activate Aurora B. They suggest that cytoplasmic phosphatases would dampen the activity of Aurora B that is not bound to chromosomes. Thus, clustering of CPC components by loading onto chromatin provides a “very simple mechanism to spatially control the kinase activity,” says Funabiki. JCB

Reference: Kelly, A., et al. 2007. Dev. Cell. 12:31–43.