Hitched genes still independent

Transcribed genes move away from heterochromatin even if their silent neighbors do not, as shown by Zink et al. (page 815). Transcriptional status is closely related to nuclear positioning. Silenced genes, for example, are often associated with heterochromatin at the nuclear periphery, whereas active genes occupy different nuclear domains. The new results show that even close linkage to genes that are not transcribed does not prevent an activated gene from leaving heterochromatin.

The authors imaged three adjacent genes, CFTR (mutations in which cause cystic fibrosis), and its closest neighbors, GASZ and CORTBP2, in various cell types. When none of the genes were expressed, all three were closely associated with the nuclear envelope and peripheral heterochromatin. In cells that transcribed only one or two of the genes, only the active ones were found in the nuclear interior, separated from heterochromatin.

Repositioning might be controlled by histone modifications, which can be stably inherited through mitosis. Chemically induced histone acetylation pushed CFTR from the periphery into the interior. CFTR transcription was not activated, at least in the short term, but positioning may be important for maintaining transcriptional status. If so, gene therapy strategies for cystic fibrosis may need to overcome this additional layer of complexity.

Forced to bond

The bonds between leukocytes and endothelial cells last longer when under some strain, as shown by Yago et al. (page 913). The results explain why these white blood cells attach to and roll along the vasculature only when blood flow is strong enough.

Most explanations of this flow-enhanced adhesion suggest that flow increases the number of bonds that form between L-selectin on leukocytes and PSGL-1 or other ligands on vascular cells, possibly by rotating or deforming the blood cell. But some scientists believe that force generated from flow might also increase the lifetime of existing bonds.

The new results show that catch bonds—those whose lifetimes are lengthened by force—between L-selectin and PSGL-1 control leukocyte rolling. The authors correlated the lasting power of individual bonds with the rolling stability of the cells. As the force imposed on bonds increased, their lifetimes increased. The blood cells thus rolled more slowly on PSGL-1 substrates. Slow rolling allows leukocytes to respond to chemokines and traverse the endothelium. The force requirement probably prevents inflammation and leukocyte clumping at vascular blockages.

Above optimum shear, when blood cells roll most slowly, catch bonds became slip bonds, whose lifetimes are shortened by force. Rolling velocities thus increased, and the cells detached from the substrate. The transition to slip bonds may explain why leukocytes usually do not adhere in arteries, where blood flow is very strong.

Condensation by folding

To understand how chromosomes condense for mitosis, most researchers pick apart DNA’s most compact form: metaphase chromosomes. On page 775, Kireeva et al. work from the other end and watch condensation as it occurs. From this perspective, condensation looks like a folding continuum with intermediates that do not fit the favored radial loop model.

The authors used serial section microscopy to examine chromosomes at stages of prophase, when most condensation occurs. At even the earliest stages, 10- and 30-nm chromatin fibers are folded into larger ~100-nm fibers. In middle prophase, chromatids of 200–250 nm are present that appear to form from the folding of the 100-nm fibers. A further doubling in diameter occurs by late prophase.

Radial loop models propose that chromatin loops of fixed size are the repeating subunit of condensed chromosomes. Loops were imagined to be pulled together by a protein scaffold (including topoisomerase II and condensin), to which the loops were attached. But Kireeva et al. see that topoisomerase II and condensin are dispersed unevenly in foci on the chromosomes until condensation is nearly complete, at late prophase.

The authors do not contest that metaphase chromosomes decondensed in vitro show chromatin loops that likely result from the cross-linking of fibers by scaffold proteins. But they stress that formation of the scaffold axis and its cross-linking to chromatin occur after chromatid axis formation and most condensation, which they propose is driven by levels of folding. Topoisomerase II and condensin may lock these folds into a stable structure.