A chromatin twist to silencing choice

Although cells typically transcribe both copies of a particular gene, they sometimes flip off one copy and rely on the other. A histone-modifying protein might help determine which copies are turned on or off by tweaking the structure of chromatin, as Alexander et al. show.

This silencing—called monoallelic expression—reaches an extreme in female mammals, in which one X chromosome almost completely shuts down. Which copy a cell chooses to switch off appears to be random, and the selection mechanism remains unexplained.

Last year, the researchers showed that, in embryonic stem cells, would-be active and inactive X chromosomes differ even before one gets silenced. When the scientists tagged specific genes on the chromosomes using fluorescence in situ hybridization (FISH), one X chromosome typically carried two glowing spots (usually a sign that it will be shut down), whereas its counterpart had one (a sign of future expression). What structural differences between chromosomes this pattern reveals is unknown. Autosomal genes that don’t need to be silenced tend to show up as either two single dots or two double dots.

This single dot–double dot (SD) pattern also marked monoallelic genes on autosomes, Alexander et al. found when they examined embryonic stem cells, which haven’t yet picked which allele to close down. Before a stem cell made that choice, however, the alleles often flipped between single and double states, indicating that the cell is sometimes undecided about which allele to quiet. Switching also occurred on X chromosomes.

Suspecting that the SD arrangement might reflect a difference in chromatin structure, the researchers tested the effects of deleting the protein Eed, which helps tighten chromatin by methylating histone H3. Loss of Eed reduced the prevalence of SD cells and resulted in more double dot states. A single spot might indicate scrunched together sister chromatids, while a double spot might reveal standoffish sisters. But how Eed chooses which allele to target is unknown. The researchers now want to determine whether the single-spot-on—double-spot-off pattern shown by X chromosomes holds true for autosomes.

Reference: Alexander, M.K., et al. 2007. J. Cell Biol. 179:269–276.

A receptor with divided loyalties

The epidermal growth factor receptor (EGFR) is caught in a tug-of-war between two membrane domains, as Lajoie et al. reveal. Which domain wins the competition for this division-promoting protein helps determine whether a cell becomes cancerous.

Creating one of the domains is Caveolin1 (Cav1), which congregates in plasma membrane indentations called caveolae. Cav1 clusters pen in EGFR molecules and block them from relaying progrowth signals into the cell. Cav1 is faulty or absent in many tumors. Another domain, the galectin lattice, forms when galectin molecules interlink glycoproteins on the cell surface. The enzyme Mgat5 promotes these connections by modifying the ends of the glycoproteins. The researchers previously showed that the lattice holds EGFR at the membrane and increases cells’ sensitivity to growth stimulators such as epidermal growth factor (EGF).

In the current study, Lajoie et al. identified interactions between the two types of domains. The researchers found that in tumor cell lines that lack Mgat5, adding a little Cav1 squelched EGF signaling—and thus tumor growth—by trapping EGFR. Eliminating Cav1 from these cells restored their sensitivity to EGF. Tumor cells that make Mgat5 were also responsive to EGF. The results suggest that galectin lattices block Cav1’s inhibition of EGFR.

The lattices interfered by restricting EGFR movement. The authors tracked the receptor’s movements by photobleaching part of the membrane and following labeled EGFR molecules. If tumor cells had normal levels of Mgat5, EGFR was less likely to coexist with Cav1 clusters than in cells lacking the enzyme.

Overall, the study indicates that the galectin lattice speeds tumor growth by capturing EGFR and preventing Cav1 domains from ensnaring the receptor and shutting it down. Because the lattice gets first dibs on the receptor, Cav1 serves as a tumor suppressor only when the lattice is down. The work also explains the mysterious observation that some of the most dangerous cancers produce copious Cav1: other molecules can override its ability to block growth.

Reference: Lajoie, P., et al. 2007. J. Cell Biol. 179:341–356.