MedicalXpress

Large DNA stretches, not single genes, shut off as cells mature

January 18 2009

Experiments at Johns Hopkins have found that the gradual maturing of embryonic cells into cells as varied as brain, liver and immune system cells is apparently due to the shut off of several genes at once rather than in individual smatterings as previous studies have implied.

Working with mouse brain and liver cells, as well as embryonic stem cells, Johns Hopkins University School of Medicine professor Andrew Feinberg, M.D., M.P.H., led an investigation of a kind of epigenetic modification to histones, the molecular "spools" that DNA winds around in the cell nucleus. This modification is a variety of the so-called epigenetic changes that alter the function of cells without directly altering the nuclear DNA in the cells.

Other scientists had previously found that histone modifications appear to silence individual genes in the DNA that coils around affected histones. But when Feinberg and his team compared the activity of thousands of genes in the liver and brain cells, they found that a particular modification — in which two methyl groups clip onto histones — seemed to silence long stretches of DNA containing many genes at once. The findings will publish in *Nature Genetics* online on Jan. 18.

Since the silenced stretches varied greatly between the different types of cells, Feinberg, postdoctoral fellow Bo Wen, and their colleagues wondered whether these sections — called large organized chromatin K9 modifications, or LOCKS — might be responsible for the transition from the "blank slate" quality of embryonic cells to the specialized

functions that mature cells take on. To find out, he and his team looked for LOCKs in mouse embryonic stem cells. Unlike mature, adult liver and brain cells, in which about 40 percent of the genome was silenced by LOCKs, the embryonic stem cells had no LOCKs.

Next, the researchers compared the regions of DNA affected by LOCKs between mouse liver and brain cells and their corresponding human cells. The same cell types in both organisms had remarkably similar regions of DNA silenced by LOCKs, suggesting that the same genes necessary to control cell function are affected in mice and people.

"These results suggest that LOCKs appear gradually during development, refining cells' functions as they differentiate into particular cell types," Wen says. "Our experiments suggest that the whole forest of genes is changing, but people have been looking at the individual trees."

Because epigenetic changes also are known to play a role in abnormal cell growth, the researchers suspected that LOCKs were involved in the development of cancer. When they looked for genes in several common cancer cell lines often used in research, they indeed found significantly fewer LOCKs than in normal liver and brain cells.

"In cancer, some of these LOCKs may become unlocked," says Feinberg. "Sections of DNA that were silenced in a cell type might become active, giving cancer cells characteristics of other cell types that they're not supposed to have."

Feinberg says this "unlocking" might cause cancer cells to revert to a more immature developmental state, explaining some of their unusual behavior, such as extreme proliferation or migration to different areas of the body.

Source: Johns Hopkins Medical Institutions