Cancer cells' universal 'dark matter' exposed

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Using the latest gene sequencing tools to examine so-called epigenetic influences on the DNA makeup of colon cancer, a Johns Hopkins team says its results suggest cancer treatment might eventually be more tolerable and successful if therapies could focus on helping cancer cells get back to normal in addition to strategies for killing them.

In a report published June 26 in Nature Genetics, the investigators focused on a particular epigenetic biochemical signature known as methylation, which silences genes. Although not part of a gene's central DNA sequence, it is copied when a cell divides, perpetuating its activity.

By comparing the epigenomes of eight human tissue samples -- three from noncancerous colon tissue, three from colon tumors and two from polyps (early-stage colon cancer) -- the team found that in all the colon tumors the defining characteristic was a universally "chaotic" pattern of methylation. In noncancerous tissue, they found methylation occurring in well-defined places, either as small "islands" of methylation or huge methylated "blocks" that collectively encompassed at least a third of the genome.

"In the cancer tissue we saw that the once-precise boundaries of the islands had shifted or disappeared altogether, and the start and end points of the sites appeared unregulated," says Andrew Feinberg, M.D., M.P.H., professor of molecular medicine and director of the Center for Epigenetics at the Johns Hopkins University School of Medicine's Institute for Basic Biomedical Sciences. "We also saw a loss of methylation, presumably increasing the randomness of gene function within them."

"What seems to define cancer at the epigenetic level may be simple and common, namely chaos that seems to be universal," he adds.

The researchers noted that cells in their normal colon tissue samples stayed methylated at around the 80 percent level for large (and previously unexamined) blocks of the epigenome. By comparison, cells from colon tumors comprising those same huge blocks had no such stability and were much more variable in terms of methylation levels.

Feinberg says the findings could mean that current efforts to simply identify methylation markers as signals of cancer or targets of cancer therapy may be misleading or worse, won't do the job at all. An alternative would be a new method that detects epigenetic chaos universally in any cancer epigenome.

The team designed a custom test to compare about 20 noncancerous tissue samples to 20 samples from each of a variety of tumors as they investigated thousands of methylation sites for colon, breast, lung, kidney and thyroid cancers. They found that, here again, methylation was well-regulated in the normal tissues, almost always occurring within a limited range of variability. However, in the very same specific places of the epigenome characterized by chaos in colon cancer cells, all the other cancerous tissues examined by the team showed distinctly variable and "chaotic" levels of methylation variation.

"Maybe the big lesson learned from our observation of this universal chaos is that we may need to think not so much about just killing cancer cells, but also about ways of helping cancer cells figure out how to be what they're supposed to be, and re-educate them so they can stay truer to their normal identities," Feinberg says.

From the cancer cells' "perspective," Feinberg says, the chaos is helpful, endowing tumors with the ability to turn genes on and off in an uncontrolled way, and making cancer cells adaptable enough to live in all different kinds of

environments, spread and thrive in foreign tissue.

"The regions of epigenetic chaos where methylation appears wildly variable in at least five different common cancers are -- not so coincidentally -- the very same as those that during normal development are important in controlling cell differentiation, or what particular cells are supposed to be, like normal colon cells," Feinberg says.

"The same epigenetic malleability that permits human cells with the same DNA to become different tissue types during development also confers vulnerability," adds Rafael Irizarry, Ph.D., a professor of biostatistics in the Johns Hopkins University Bloomberg School of Public Health, who with Feinberg, led this study. "The epigenome has these regions where change is easy in order for some cells to become kidney and others, brain and spleen, for example, but that very vulnerability to change may ultimately lead to cancer. Targeting those regions might help the cells become more normal."

Because the new study also identifies regions of the genome that appear to control this epigenetic chaos, Feinberg and his team say it may prove potentially fruitful in revealing new targets for cancer therapy or prevention.

More information:
www.nature.com/ng/index.html

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