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Gene switch sites found mainly on 'shores,' not just 'islands' of the human genome

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Scientists who study how human chemistry can permanently turn off genes have typically focused on small islands of DNA believed to contain most of the chemical alterations involved in those switches. But after an epic tour of so-called DNA methylation sites across the human genome in normal and cancer cells, Johns Hopkins scientists have found that the vast majority of the sites aren't grouped in those islands at all, but on nearby regions that they've named "shores."

"Our study suggests that the real jackpot for methylation isn't where we have all been looking, but in these shores located just nearby," says Andrew Feinberg, M.D., M.P.H., professor of medicine at the Johns Hopkins University School of Medicine.

Feinberg explains that the discovery is more than academic since it may shift the current focus away from the islands to thousands of new sites scattered throughout the genome, each with the potential to serve as novel targets for studying the development of tissues, organs and animals, and for treating diseases such as cancer already known to involve methylation chemistry.

Methylation is one of several so-called epigenetic modifications that affect which genes are expressed without changing the DNA sequence itself. Previous studies have suggested that DNA methylation plays an important role in guiding stem cells to mature into a variety of cell types such as hair, muscle and nerve cells. Methylation has also been implicated in the abnormal gene expression that cancer cells show.

The long-time focus in methylation has been CpG islands, regions of the genome rich in the DNA building-block molecules cytosine and guanine. The reason is that these islands tend to occur near the "start" signal of a protein-coding gene, a place with the potential to affect whether that gene is expressed or not and to what extent.

However, Feinberg and co-investigator Rafael I. Irizarri, Ph.D., of the Johns Hopkins University Bloomberg School of Public Health, and their colleagues wondered whether undiscovered methylated sites were hiding unnoticed elsewhere in the genome. The researchers performed their comprehensive survey in human brain, liver and spleen tissues obtained from five autopsies, identifying 16,379 methylated regions using a new method that searches all DNA, not just CpG islands.

To their surprise, the researchers discovered that about 76 percent of the genome's methylated sites occur a short distance away from the islands, between 200 and 2,000 kilobases away. In contrast, only 6 percent of methylated sites were situated inside CpG islands. Because of the newly discovered sites' proximity to the islands, the researchers named them CpG shores.

"This finding is so unexpected because CpG islands are the areas where scientists have really concentrated their research," Feinberg says.

Taking their research a step further, Feinberg, Irizarri and their colleagues searched for new methylated areas in colon tumors as well as normal colon tissue removed from 13 different cancer patients. The researchers identified 2,707 regions in both CpG islands and shores that were either more or less methylated between the two tissue types. Previous studies by other research groups, looking only at CpG islands, have suggested that the DNA in cancer cells tends to be more methylated compared to normal, healthy cells. However, comparing the tumor and healthy colon cells' entire genomes, including CpG islands as well as

shores, Feinberg's group found that cancer cells had a roughly equal number of more-methylated and less-methylated sites than the normal cells.

When the researchers looked at where these differently methylated sites were located in the cancer cells, they found that these regions matched up with many of the methylated areas they'd located in the normal brain, liver and spleen tissues they had examined.

"This suggests that the epigenetic changes we see in cancer are leading cells to look and behave like other cells they're not at all supposed to be like," Feinberg says. "For example, colon cells that become cancerous might start to act like brain, liver or spleen cells. They're losing the characteristics they should have and taking on those of other tissues."

He and his colleagues suggest in the study, published online on Jan. 18 in *Nature Genetics*, that their newly developed map of where these methylation sites differ in colon cancer and healthy tissue may eventually help researchers develop treatments for cancer by restoring normal methylation patterns or by targeting the gene pathways they have identified in this study.

For more information, go to:

www.hopkinsmedicine.org/ibbs/research/epigenetics/
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