Genetic changes outside nuclear DNA suspected to trigger more than half of all cancers

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A buildup of chemical bonds on certain cancer-promoting genes, a process known as hypermethylation, is widely known to render cells cancerous by disrupting biological brakes on runaway growth. Now, Johns Hopkins scientists say the reverse process — demethylation — which wipes off those chemical bonds may also trigger more than half of all cancers.

One potential consequence of the new research is that demethylating drugs now used to treat some cancers may actually cause new cancers as a side effect.

"It's much too early to say for certain, but some patients could be at risk for additional primary tumors, and we may find that they need a molecular profile of their cancer before starting demethylating therapy," says Joseph Califano, M.D., professor of otolaryngology-head and neck surgery and oncology at Johns Hopkins.

The findings, based on studies of normal and cancer cells from human mouth, nose and throat tissue, provide more evidence that important regulators of gene activity occur outside as well as inside DNA in a cell's nucleus.

"While cancer-causing and other mutations alter vital protein-making pathways by rewriting the gene's DNA code, epigenetic changes affect

genes without changing the code itself. The new studies tell us that such changes occur not only when methyl groups bond to a gene's on-off switch, but also when they come unglued," says Califano.

Califano says sporadic reports of demethylation as a tool in activating cancer-promoting genes led his team to develop a systematic way to discover these epigenetic changes and show how the process is linked to cancer.

To gather their evidence, Califano and his group treated two cell lines from normal oral tissue with the demethylating drug 5-azacytidine and collected a list of genes that were activated as a result. They used special silicon chips carrying pieces of genetic material that allow thousands of genes to be analyzed at one time to locate genes activated by demethylation.

The list was cross-referenced with genes "turned on" in 49 head and neck cancer samples and 19 normal tissue samples. In all, Califano and his team found 106 genes specific to head and neck cancer that were activated by the demethylation process. "Some of the genes regulate growth, others metabolize sugars and some have already been linked to cancer development," says Califano, who is director of head and neck cancer research at the Milton J. Dance Jr. Head & Neck Center at Greater Baltimore Medical Center. A report on this work appears on March 23 in *PLoS One*.

Further analysis by the Johns Hopkins team revealed a single connection among 106 genes: methylation within them is regulated by another gene called BORIS. BORIS acts as a "master regulator," recruiting other proteins to demethylate a coordinated set of genes and signaling the development of cancer. According to the scientists, nearly 60 percent of a wide range of cancers, including head and neck and lung cancer, have high levels of BORIS expression.

He envisions that agents like 5-azacytidine may need to be combined with a "BORIS blocker," a drug that has yet to be developed to protect patients who need demethylating therapies.

More information: www.plosone.org

Source: Johns Hopkins Medical Institutions