MedicalXpress

DNA methylation shown to promote development of colon tumors

December 1 2007

Damaged or defective genes have long been known to be the cause of some cancers. Over the past decade, however, scientists have discovered that even healthy genes can be switched on or off and can cause cancer without any changes in the underlying DNA sequence—although how this happens has remained poorly understood.

Researchers in the laboratory of Whitehead Member Rudolf Jaenisch now have established a direct causal connection between hypermethylation (the accumulation of too many methyl molecules on regions of DNA) and the development of colon tumors in mice.

The research directly demonstrated that hypermethylation switches off tumor suppressor genes—the "housekeeping" genes that keep cancer cells in check. The study, published December 1 in *Genes and Development*, found that hypermethylation boosted the number of intestinal tumors by 60-100 percent and significantly increased the average size of microscopic early-stage tumors.

While DNA methylation has been correlated with tumor development in numerous studies of human cancers, this is the first in vivo work demonstrating a causal connection in mammals. Better understanding of the process is a promising pathway to the prevention, diagnosis and treatment of certain cancers with minimal side effects.

"Our research found a family of tumor-suppressor genes in mice that was silenced when methylated," says lead author Heinz Linhart. "This is

important because the same genes are known to be silenced by methylation in human colon cancer cells. If we can switch on the gene that creates this abnormal methylation pattern, the next step is to find out if we can reverse the abnormal pattern by simply switching it off, reactivating the genes that suppress tumors. This is the therapeutic hope."

DNA methylation and packaging of DNA by proteins and other molecules (often referred to epigenetic mechanisms) regulate the activity of certain genes and genetic regions, depending on what each cell needs to do. Since almost every cell of an organism has the identical DNA sequence the "packaging" of this DNA by these epigenetic mechanisms is a key element in determining cell identity and helps generate the wide variety of cell types that are found in the human body.

"If we tried to read a book that had the letters arranged in rows, we could not understand it," says Linhart. "We not only need the letters arranged in sequence, we need spaces and formatting to separate the letters into words, sentences and paragraphs. In the same way, we can imagine the human genome as a list of letters printed one after the other, without spaces or formatting. Methylation and protein “packaging” of DNA help the cell 'read' and make sense of the DNA sequence, determining which genes need to be active to perform a particular function, and which ones need to be switched off."

As cells renew and divide, their characteristic methylation and packaging pattern is usually maintained and transmitted to the new cells, ensuring that recently formed heart cells, for example, carry the same correct instructions for how to behave in order to contract and pump blood.

Trouble arises, however, when there is either too little methylation throughout the DNA (hypomethylation) or too much on specific regions of the strand (hypermethylation)—both of which are frequently

observed in cancer. In the last decade, scientists at Whitehead Institute and elsewhere demonstrated that the first phenomenon—too little methylation throughout the genome—is causally associated with the development of cancer.

The most recent Whitehead study established a direct causal connection between the second form of methylation imbalance—regional increases in methylation—and the development of colon tumors. The scientists did this by giving mice prone to developing intestinal tumors four variations of an enzyme that causes methylation. "We wanted to determine the impact of inducing methylation on tumor development," says Linhart. "Does it inhibit it, do nothing or promote it?"

Surprisingly and importantly, methylation appears to target specific regions of the DNA and the genes within them rather than being distributed randomly. "We found that key tumor-suppressor genes in certain DNA regions were silenced months before tumors appear," says Linhart. This specific targeting extends to organs as well: A given gene that is methylated in the colon, for example, does not become methylated in the spleen. The specificity of the process could prove a major advantage for diagnostic and therapeutic approaches based on DNA methylation.

"The enzymes that silence tumor-suppressing genes would be terrific targets for treatment," says senior author Rudolf Jaenisch. "If we can inactivate them and rescue the cancer-prevention functions of these genes, there would be predictably no side effects. And if we can examine circulating blood for signs of early methylation, we might be able to prevent tumors from developing."

Although this study focused on mice, Jaenisch notes that “current clinical trials using a drug to inhibit methylation in people with leukemia appear to delay the disease."

Source: Whitehead Institute for Biomedical Research