New melanoma tumor suppressor gene uncovered

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National Institutes of Health (NIH) researchers have identified a gene that suppresses tumor growth in melanoma, the deadliest form of skin cancer. The finding is reported today in the journal *Nature Genetics* as part of a systematic genetic analysis of a group of enzymes implicated in skin cancer and many other types of cancer.

The NIH analysis found that one-quarter of human melanoma tumors had changes, or mutations, in genes that code for matrix metalloproteinase (MMP) enzymes. The findings lay the foundation for more individualized cancer treatment strategies where MMP and other key enzymes play a functional role in tumor growth and spread of the disease.

Tumor suppressor genes encode proteins that normally serve as a brake on cell growth. When such genes are mutated, the brake may be lifted, resulting in the runaway cell growth known as cancer. In contrast, oncogenes are genes that encode proteins involved in normal cell growth. When such genes are mutated, they also may cause cancer, but they do so by activating growth-promoting signals. Cancer therapies that target oncogenes usually seek to block or reduce their action, while those aimed at tumor suppressor genes seek to restore or increase their action.

The new study may help to explain the disappointing performance of drugs designed to treat cancer by blocking MMP enzymes. Because members of the MMP gene family were thought to be oncogenes and many tumors express high levels of MMP enzymes, researchers have

spent decades pursuing MMPs as promising targets for cancer therapies. However, when MMP inhibitors were tested in people with a wide range of cancers, the drugs failed to slow -- and in some cases even sped up -- tumor growth.

Now, it turns out that one of the most often mutated MMP genes in melanoma is not an oncogene at all. In its study, the team led by researchers from the National Human Genome Research Institute (NHGRI) found that MMP-8 actually serves as a tumor suppressor gene in melanoma. Consequently, in the estimated 6 percent of melanoma patients whose tumors harbor a mutated MMP-8 gene or related tumor suppressor(s), it may not be wise to block all MMPs. The study suggests that a better approach may be to look for drugs that restore or increase MMP-8 function or for drugs that block only those MMPs that are truly oncogenes.

"This research is an illustrative proof of concept that shows the value of genomic strategies for understanding cancer and possible therapies," said NHGRI Scientific Director Eric Green, M.D., Ph.D. "It is gratifying to see that genomic technologies are guiding scientific discovery, advancing cancer research, especially melanoma research."

Melanoma is the most serious form of skin cancer. In the United States and many other nations, melanoma is becoming more common every year. A major cause is thought to be overexposure to the sun. The ultraviolet radiation in sunlight can damage DNA and lead to cancer-causing genetic changes within skin cells.

MMP enzymes help the body to break down and recycle proteins, playing a crucial role in the process of remodeling skin after sunburns, cuts or other injuries. The MMP gene family has been associated with tumor growth in a variety of cancers, including breast, colon and melanoma.

To explore the role of MMP genes in melanoma, the NHGRI researchers studied a bank of tumor and blood samples collected from 79 patients with aggressive melanoma by collaborator Steven Rosenberg, M.D., Ph.D., chief of surgery at the National Cancer Institute (NCI). Specifically, they compared the sequence of MMP genes in tumors and normal DNA from the same patients, looking for mutations in all 23 members of the MMP gene family.

The researchers identified 28 different mutations in eight MMP genes in the melanoma tumors studied. These mutations were found to be distributed in different frequencies and patterns among the tumor samples. Nearly one-quarter of the tumors analyzed had at least one MMP gene mutation. Some mutations were found in as few as 3 percent of tumors, while more than 6 percent of tumors had mutations in MMP-8 and more than 7 percent had mutations in MMP-27, which codes for an enzyme very similar to MMP-8.

"We often talk about cancer as though it is one disease, and cancers do have many common denominators. But when we look at the DNA level, we see that different cancers have different genetic profiles, and so do different patients who have the same cancer," said the study's senior author, Yardena Samuels, Ph.D., an investigator in the Cancer Genetics Branch of the NHGRI's Division of Intramural Research.

Dr. Samuels and her collaborators followed up their DNA sequencing work with cell and animal studies to see whether MMP-8 mutations affect enzyme function. Strikingly, the researchers showed that five of the mutations reduced activity of the MMP-8 enzyme. The researchers next studied whether MMP-8 mutations promote activities related to cancer. Indeed, cells with MMP-8 mutations showed increased ability to multiply outside the constraints of normal cells, a hallmark of cancer development known as anchorage-independent growth. Likewise, cells with MMP-8 mutations had a greater ability to migrate -- a key aspect of

cancer metastasis -- than normal cells.

The researchers found that mice injected with cells expressing normal MMP-8 did not develop skin ulcers, which are one of the most important measures of cancer aggression in melanoma. In contrast, mice injected with cells expressing mutated MMP-8 went on to develop ulcerations and metastases in their lungs.

Source: NIH/National Human Genome Research Institute