Mutant gene identified that causes abnormal chromosome count, leading to cancer

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Cells with too few or too many chromosomes have long been known to be a hallmark of cancer - but the cause of this abnormal number of chromosomes has been little understood. Now, in the August 19th issue of *Science*, researchers at the Georgetown Lombardi Comprehensive Cancer Center, a part of Georgetown University Medical Center, have identified a gene that is commonly mutated in human cancers and have demonstrated its direct role in causing aneuploidy, an abnormal number of chromosomes.

The researchers found that 20 percent of the brain cancer (glioblastoma multiforme), skin cancer (malignant melanoma), and bone cancer (Ewing's sarcoma) samples they examined made no STAG2 protein, often due to a missing or mutated STAG2 gene. The STAG2 gene encodes a component of a protein structure known as the "cohesin complex" which regulates the separation of replicated chromosomes during cell division.

What this means is that if the STAG2 gene has been inactivated by a mutation, chances increase that a cell undergoing division will distribute an uneven number of chromosomes to the two new "daughter" cells being created. These cells, which now have too few or too many genes, are significantly more likely to develop into cancer.

"Scientists have long been searching for the genetic basis of aneuploidy in cancer cells, and our study provides substantial new insight into that process," says the study's senior investigator, cancer geneticist Todd Waldman, M.D., Ph.D., an associate professor at Georgetown Lombardi.

"In the cancers we studied, mutations in STAG2 appear to be a first step in the transformation of a normal cell into a cancer cell," he says. "We are now looking at whether STAG2 might be mutated in breast, colon, lung, and other common human cancers."

The study may also provide a new direction for cancer therapy, says the study's lead author, David Solomon, Ph.D., a student in the M.D./Ph.D. program at Georgetown University School of Medicine. "We are now attempting to identify a drug that specifically kills cancer cells with STAG2 mutations," says Solomon, who received his Ph.D. in May, 2010. "Such a drug would be of clinical benefit to the many patients whose tumors have inactivation of STAG2."

The study was a product of Solomon's work on a doctoral thesis. Waldman, who heads the M.D./Ph.D. program at Georgetown, mentored Solomon in his cancer genetics lab. Solomon's thesis was to search for genes that are mutated in glioblastoma multiforme, the most common and lethal form of brain cancer.

Using advanced gene chip technology, Solomon and Waldman identified regions of the human genome that were missing in aneuploid brain cancer cells. "One day, we found the gene STAG2 was deleted in one of our brain cancer samples," says Waldman. "It was easy to imagine that this gene might play a role in aneuploidy and that got us excited."

During the hunt for STAG2 mutations, Solomon recalls a "eureka" moment. "I had first identified mutations of STAG2 in a few brain tumors but was unsure of its importance as a broad spectrum cancer gene in tumor types other than brain. The day that I did a Western blot of 10 Ewing's sarcoma tumors, a bone tumor most common in adolescents, and found that 6 out of 10 Ewing's sarcoma tumors had mutations or deletions of STAG2," he says. "I knew then that STAG2 was indeed an important tumor suppressor gene in several tumor types. That day I wrote EUREKA! in my lab notebook."

What was also intriguing is that the STAG2 gene is located on the X chromosome, Waldman says,

adding, "this is only the second cancer-causing gene ever found on the human sex chromosome." Men have only a single copy of the X chromosome, and women have only one functional copy (their other copy is dormant due to a process known as X-inactivation). "Therefore, unlike most genes which require mutations of two copies for complete inactivation, inactivation of STAG2 requires only a single mutational event," He says. "This may help explain the unusually high prevalence of STAG2 mutations in cancer."

After identifying the mutations of STAG2, the researchers then used a technique known as "human somatic cell gene targeting" that makes it possible to correct mutant genes in their normal chromosome location. Using this technique, Waldman and Solomon were able to correct the STAG2 mutation in glioblastoma cells, essentially replacing a bad gene with a good one. "When the STAG2 mutations were corrected, the chromosome count stabilized," Solomon says. "This offers compelling evidence that the STAG2 mutation was the cause of aneuploidy in these cells."

Waldman says STAG2 likely functions as a "caretaker" tumor suppressor gene. "It's not like most tumor suppressor genes, which when mutated lead to either enhanced cell proliferation or decreased cell death. Instead it's a tumor suppressor gene with a different function - maintaining normal chromosome number and structure."

Provided by Georgetown University Medical Center