

Researchers find gene function 'lost' in melanoma and glioblastoma

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Researchers at Georgetown University Medical Center have found a gene they say is inactivated in two aggressive cancers – malignant melanoma, a form of skin cancer, and glioblastoma multiforme, a lethal brain tumor. They add that because this gene, known as PTPRD, has recently been found to be inactivated in several other cancers as well, their discovery suggests that PTPRD may play a tumor suppressor role in a wide variety of different cancers.

The findings are published in the December 15 issue of *Cancer Research*.

"Over the past decade several dozen tumor suppressor genes have been identified, but only a minority of them is important in causing many different tumor types. PTPRD seems to be one of these broad spectrum tumor suppressor genes," says the study's lead investigator, Todd Waldman, MD, PhD, an associate professor of oncology at Georgetown's Lombardi Comprehensive Cancer Center.

If the hypothesis is true – and Waldman and his team are now investigating loss of PTPRD in a number of additional cancers – then it may be possible to design a therapy that has wide applicability in oncology, he says.

"Most targeted cancer drugs today work by inhibiting gene products that are overactive in cancer cells. In this case, it is loss of the PTPRD gene that leads to cancer," Waldman says. "Therefore, we are trying to discover the molecules that PTPRD's protein controls, and then we plan to target these downstream molecules with a novel agent."

Waldman found that when the researchers restored production of the gene's protein in cancer cells that harbored PTPRD deletions or mutations, these tumors stopped growing and initiated a program of cell suicide.

The researchers also discovered PTPRD mutations in both the blood and in tumors of a patient with multiple different kinds of cancers. "This suggests that the gene could be responsible for an inherited predisposition to cancer," Waldman says

PTPRD produces a receptor protein tyrosine phosphatase that bisects the outer membrane of a cell. The part that protrudes outside the cell body is thought to be involved in helping cells stick to each other to form a tissue as well as in cell-to-cell communication. The part that juts into the cell is an enzyme that removes phosphates from other proteins – in other words, it changes the activity of proteins either by activating or deactivating them, Waldman says.

"In the absence of PTPRD, there are as yet unknown proteins floating around inside the cell with more phosphate residues than they should have, and it is a well known fact that the presence of these residues activates cellular growth pathways," he says. But it is not yet known which specific proteins PTPRD regulates, Waldman says.

Deletions of PTPRD in human cancer cells were first discovered in 2005, and since then, deletions or mutations of the gene have been discovered in several cancer types, including those of the colon and lung.

In this study, Waldman and his research team, which includes investigators from the National Cancer Institute, the University of Iowa and Duke University, used a laboratory technique known as copy number analysis to look for PTPRD in melanoma cell lines and in samples of human glioblastoma multiforme, the deadliest of brain cancers.

This technique uses a gene microarray that contains millions of probes that can stick to different regions of the human genome. The researchers purified DNA from tumors and then used the

microarray chip to quantify genomic copy number. They found that PTPRD was deleted or mutated in 12 percent of melanoma tumors and in 14 percent of glioblastoma tumors examined. "That makes PTPRD one of the most commonly mutated genes discovered yet in melanoma," Waldman says.

"Before this study, no single tyrosine phosphatase was thought to play a generally important role as a tumor suppressor gene in multiple tumor types," Waldman says. "Now we have provided the first functional evidence that PTPRD is a tumor suppressor gene, and potentially an important one at that."

Source: Georgetown University Medical Center

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