Scientists uncover role of cancer stem cell marker: controlling gene expression

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Scientists at Jefferson's Kimmel Cancer Center in Philadelphia have made an extraordinary advance in the understanding of the function of a gene previously shown to be part of an 11-gene "signature" that can predict which tumors will be aggressive and likely to spread. The gene, USP22, encodes an enzyme that appears to be crucial for controlling large scale changes in gene expression, one of the hallmarks of cancer cells.

As a result, USP22 immediately becomes a potential target for new anti-cancer drugs, says Steven McMahon, Ph.D., associate professor of Cancer Biology at Jefferson Medical College of Thomas Jefferson University, who led the work. And it solves a bit of a biological mystery.

Researchers knew that the gene USP22 was part of a group of 11 genes that are overexpressed in a variety of cancers and that overexpression of USP22 predicts which tumors can go on to spread elsewhere in the body. This group of genes is collectively called the "cancer stem cell signature."

"Such cancers that have those properties – going on to be metastatic and resistant to therapy – are referred to as having cancer stem cell-like features," Dr. McMahon explains. "The genes in the signature are in a family of genes implicated as cancer stem cell markers. Many of them code for critical components of signaling pathways that are altered in cancer, making proteins that play roles in tumor growth." But unlike the othergenes in the stem cell signature, the exact function of USP22 was

not known.

Reporting January 18, 2008 in the journal Molecular Cell, Dr. McMahon and his co-workers have shown that not only is USP22 overexpressed in cancer cells, its enzymatic activity is necessary for some of the global changes in gene expression patterns that occur in these cells.

In one example, they looked at the relationship between MYC and USP22. MYC, which is among the most commonly overexpressed genes in cancer, encodes a protein that controls the expression of thousands of other genes. The scientists showed that USP22 is a critical partner of MYC and that by depleting cells of USP22, they could prevent MYC from working properly, stopping it from inducing the invasive growth of cancer cells.

“We’ve shown that the MYC pathway is among the transcriptional programs that require USP22,” Dr. McMahon says. “Identifying USP22 as a global transcription regulator helps explain why it is part of this aggressive stem cell signature.”

Dr. McMahon and his group determined how USP22 works at the biochemical level and found that it is part of a large complex of proteins called human SAGA. According to Dr. McMahon, these proteins are responsible for turning on genes, helping them get expressed more efficiently. This suggests that the genes that are turned on by the USP22 complex are important for altering cancerous cells in such ways that they become more aggressive and metastatic.

Source: Thomas Jefferson University