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MIT IDs role of key protein in tumor growth

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MIT researchers have identified how a missing protein causes tissue to become precancerous--a finding that could help doctors identify patients at high risk to develop tumors.

Most breast and prostate tumors are missing the protein, known as 14-3-3 sigma, but until now it has not been clear what role it plays in tumor growth. The MIT researchers report in the March 15 issue of Nature that when the protein is knocked down, dividing cells fail to separate fully and become precancerous.

"The cells try to divide and try to divide, and they just give up. They can't finish cytokinesis (the final stages of cell division)," said Michael Yaffe, associate professor of biology and biological engineering and leader of the research team. Failing to divide completely, the cells recombine into a single cell with two nuclei.

Such fused, or binucleate, cells have recently been shown to be precursors to cancer cells. They are often found in so-called "dysplastic" tissue, which consists of cells that are not fully normal but are not cancerous, said Yaffe.

Comparing tumors to weeds, Yaffe explained that those tissues act as fertile "soil" for tumor development. "Tumors grow in epithelial tissues that are already deranged for some reason, and something about that soil makes it better able to grow weeds," he said.

Loss of 14-3-3 sigma in dysplastic tissue could serve as a marker to help

doctors predict whether tumors will develop. "Our hope is that it will be possible to monitor 14-3-3 expression in these 'benign' conditions, a subset of which may not be so benign," said Yaffe, who is also affiliated with MIT's Center for Cancer Research, the Broad Institute of MIT and Harvard, and Beth Israel Deaconess Medical Center.

The researchers were initially intrigued by the fact that 14-3-3 sigma is missing in normal tissue that surrounds tumors, which suggested that its function is lost very early in tumor development. Once the researchers started investigating the protein, they eventually unraveled a complex signaling pathway whose disruption leads to the failure of cell division.

They discovered that 14-3-3 sigma is most active during mitosis, when it helps control production of proteins necessary for division. Although 14-3-3 sigma interacts with many proteins, the research team focused on its relationship with a single protein, a translation factor known as eIF4B.

Translation factors are proteins that help determine the mix of proteins that a cell produces. Translation occurs when a messenger molecule known as mRNA carries information encoded by DNA to a cell organelle called the ribosome, which "translates" the mRNA sequence into a protein.

The translation factor eIF4B forms part of an enzyme that allows mRNA to unwind so the ribosome can read its sequence. When 14-3-3 sigma is knocked out, eIF4B is not produced, and mRNA for the protein p58 cannot be translated. p58 plays a critical role in the final splitting of one cell into two during mitosis, so when it is missing, the cells cannot fully divide.

When p58 function is restored, the cells resume normal division.

The work demonstrates the importance of studying translation factors and the cell signaling pathways that affect them, Yaffe said. Most research on gene regulation focuses on transcription factors, which control which DNA sequences are transcribed into mRNA, but now "we're at the beginning of understanding another wave of regulation," which takes place at the translation level, he said.

The lead author of the paper is former MIT postdoctoral fellow Erik Wilker. Other authors are Marcel van Vugt, a postdoctoral fellow at the Center for Cancer Research (CCR); Steven Artim of the CCR and MIT's Department of Biology; Paul Huang, a professor in the Harvard-MIT Division of Health Sciences and Technology and Department of Biological Engineering; Christian Petersen, a former MIT postdoctoral associate; Christian Reinhardt, a postdoctoral fellow in the CCR and biology; Yun Feng of the CCR and biology; MIT Institute Professor Phillip Sharp; Nahum Sonenberg of McGill University; and Forest White, an assistant professor of biological engineering.

Source: MIT