Two pathways in the cell interact to spur tumor growth: study

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The researchers describe how the two pathways interact to produce their combined effect in a study in the journal Genes and Development that is available online.

Tumor growth occurs upon disruption of the regulation of the cell cycle, the cascade of events that result in the division and duplication of a cell. One critical pathway regulating the cell cycle is the retinoblastoma (Rb) tumor suppressor pathway. The Rb pathway is found to be mutated or functionally inactivated in nearly all human cancers.

Maxim Frolov, UIC associate professor of biochemistry and molecular genetics, models development of human cancer by studying inactivation of Rb in fruit flies. In flies, a deficiency in the Rb pathway alone, he says, surprisingly causes only subtle defects in cell proliferation, but does not result in a full-blown tumor.

"We wanted to understand why," he said.

One possible explanation was that other regulatory pathways were working together with the Rb pathway. In their previous studies, the researchers had found a pathway called Hippo, which seemed to work with Rb in regulation of cell proliferation.

In the new study, Frolov and his colleagues showed that simultaneously inactivating both pathways led to a marked enhancement of tumor growth. The researchers were able to trace the mechanism responsible for the synergy between these two pathways. They found that inactivation of the Hippo and Rb pathways results in an up-regulaton of a unique set of genes.

"We saw that the genes important to cell proliferation and cell cycle regulation are inappropriately expressed in these cells," Frolov said. The genes were not up-regulated when either the Rb or Hippo pathway alone was inactivated.

"We found that transcription factors -- proteins that turn genes on and off -- involved in each of the two pathways cooperate in inducing expression of these cell-cycle specific genes, resulting in inappropriate cell proliferation," he said.

The way Hippo is able to cross-talk with the Rb pathway and disrupt cell-cycle regulation to grow tumors may have important implications for understanding the complexity of mutations in human cancers, Frolov said. The finding suggests that there may be other factors that work with Rb to promote tumor growth.

"We should be looking for more cooperating mutations in human cancers," he said.

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