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Renegades of cell biology: Why K-Ras gene mutations prove so deadly in cancer

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Cells with a mutation in the gene called K-Ras—found in close to 30 percent of all cancers, but mostly those with worst prognosis, such as pancreatic cancer, colon cancer, and lung cancer—behave in ways that subvert the normal mechanisms of cell death, according to a cell-culture study by researchers from Huntsman Cancer Institute (HCI) at the University of Utah.

Normal cells need survival signals from the tissue that surrounds them to remain alive. Other research has shown cells with the K-Ras mutation can survive and direct their own fate without these signals.

"Epithelia act as a skin that coat and protect most organs and are the sites where most solid tumors arise. Our previous studies showed that cells making up epithelia turnover at high rates due to mechanical pressure. When cells become too crowded (due to cells dividing), some cells pop out and die. The surprising thing we found in this study is that cells with the K-Ras mutations pop into the tissue and instead live," said Jody Rosenblatt, PhD, an HCI investigator and associate professor in the Department of Oncological Sciences at the University of Utah who co-authored the study.

The process of popping cells from epithelia is called extrusion, and in normal cells, this leads to cell death to keep the number of cells under control. "Our new study suggests that this oncogene subverts the mechanism of normal cell death to promote invasion."

Another characteristic of cells with K-Ras mutations is that they consume parts of themselves (a process called autophagy) to keep up with the energy demands of rapid and unchecked cell division that the mutation causes.

"In normal cells that are about to extrude out, large quantities of an important signal called Sphingosine1-Phosphate (S1P) are present. Cells with the K-Ras mutation also produce S1P, but digest it through autophagy, so it cannot do its job and the cells extrude into the tissue," said Gloria Slattum, doctoral candidate in the Rosenblatt Lab and lead author of the article. "When we blocked autophagy using a common anti-malaria drug called Chloroquine, the cells with K-Ras mutations extruded out of the tissue and died, just as normal cells do."

The results were published online Dec. 19 in the journal *Current Biology*.

Future study will investigate whether these cell-culture results hold true in an animal model. Co-authors of the article include Yapeng Gu, research associate in the Rosenblatt Lab, and Roger Sabbadini of LPath, Inc.

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