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Previously unconnected molecular networks conspire to promote cancer

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An inflammation-promoting protein triggers deactivation of a tumor-suppressor that usually blocks cancer formation via the NOTCH signaling pathway, a team of researchers led by scientists at The University of Texas MD Anderson Cancer Center reports today in Molecular Cell.

Working in liver cancer cell lines, the team discovered a mechanism by which tumor necrosis factor alpha (TNFα) stimulates tumor formation, said senior author Mien-Chie Hung, Ph.D., professor and chair of MD Anderson's Department of Molecular and Cellular Oncology. Hung also is MD Anderson's vice president for basic research.

"We've discovered cross-talk between the TNFα inflammation and NOTCH signaling pathways, which had been known to separately promote cancer development and growth," Hung said. Liver cancer is one of several cancers, including pancreatic and breast, associated with inflammation.

Their findings have potential implications for a new class of anti-cancer drugs currently in clinical trials. "Pharmaceutical companies are developing NOTCH inhibitors," Hung said. "TNFα now presents a potential resistance mechanism that activates NOTCH signaling in a non-traditional way."

Pathways also unite in colon, lung, prostate cancers

"In addition, co-activation of these two pathways was also observed in colon, lung and prostate cancers, suggesting that the cross-talk between these two pathways may be more generally relevant," Hung said.

However, TNFα also presents an opportunity to personalize therapy, Hung said. The presence of TNFα or a separate protein that it activates called IKK alpha may serve as useful biomarkers to guide treatment.

"If a patient has only NOTCH activated, then the NOTCH inhibitor alone might work. But if TNFα or IKKα are also activated, then the NOTCH inhibitor alone might not work very well and combination therapy would be warranted," Hung said.

"We'll try this in an animal model and then go to clinical trial if it holds up," Hung said.

A path from inflammation to liver cancer

In a series of experiments, Hung and colleagues connected the following molecular cascade:

- TNFα, a proinflammatory cytokine, signals through a cell's membrane, activating IKKα, a protein kinase that regulates other proteins by attaching phosphate groups (one phosphate atom, four oxygen atoms) to them.
- IKKα moves into the cell nucleus, where it phosphorylatesFOXA2, a transcription factor that normally fires up the tumor suppressor NUMB.
- NUMB usually blocks a protein called NICD, the activated portion of NOTCH1 that slips into the cell nucleus to activate genes that convert the normal cell to a malignant one.
- But when FOXA2 is phosphorylated, it does not activate NUMB.

With NUMB disabled, NOTCH1 is activated. New understanding, new targets for cancer therapy

In liver cancer (hepatocellular carcinoma) tumors, IKKα, the phosphorylated version of FOXA2 and NOTCH1 are expressed more heavily than in normal liver tissue. Expression of all three is correlated in liver cancer tumors, the team found.

The authors conclude that identifying the link between TNFα and NOTCH1 pathways provides a new starting point for understanding the molecular basis for TNFα-related tumor growth and for identifying new targets for cancer therapy.

Finding ways to inhibit FOXA2 phosphorylation or to activate NUMB would provide new options for treating and perhaps preventing cancer, Hung said.

Provided by University of Texas M. D. Anderson Cancer Center