Cancer-driving signals cause high-risk neuroblastoma

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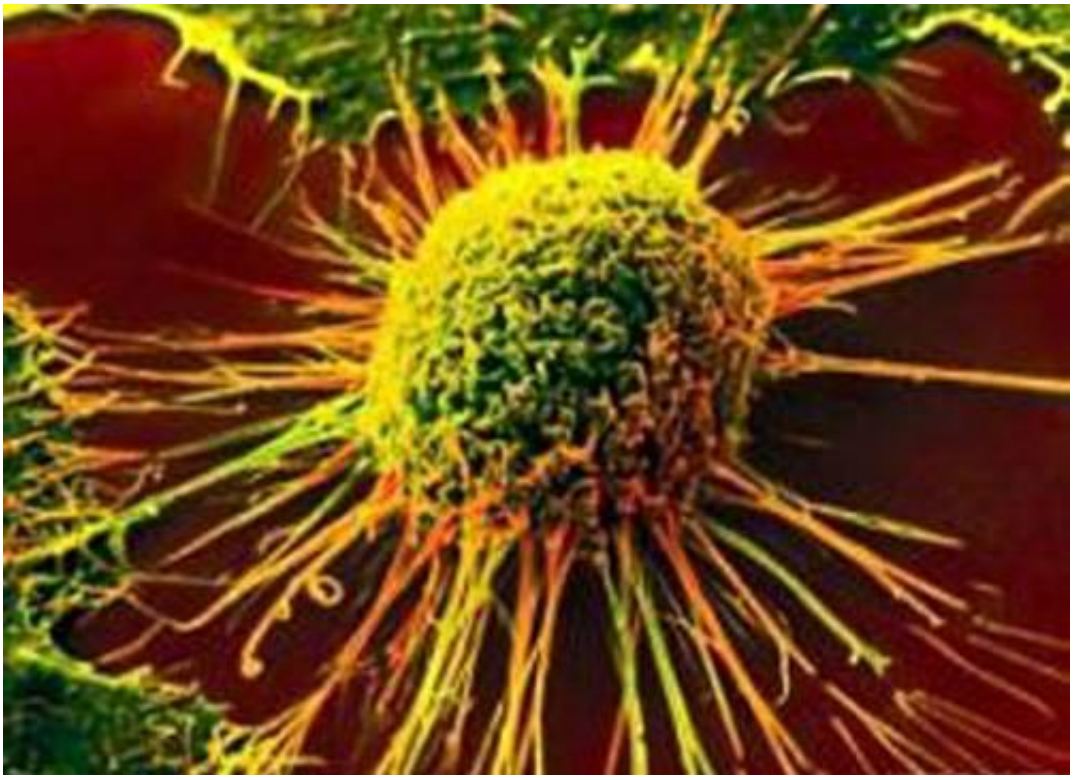

Researchers have discovered details of the abnormal molecular signals and biological events that drive a high-risk form of the childhood cancer neuroblastoma. They aim to use these findings to develop more effective targeted treatments.

"As we improve our knowledge of different biological pathways followed by genes and proteins in this complex disease, we will be better equipped to develop appropriate drug combinations to treat neuroblastoma," said co-senior author Sharon J. Diskin, Ph.D., a pediatric cancer researcher at The Children's Hospital of Philadelphia (CHOP). Diskin and colleagues focused on a signaling network involving three cancer-causing genes: LIN28B, RAN and AURKA.

The study appeared online today in *Cancer Cell*, and will appear in print on Nov. 9.

Diskin's collaborators, both from CHOP, include pediatric oncologists John M. Maris, M.D., her co-senior author, and first author Robert Schnepp, M.D., Ph.D.

A solid tumor of the peripheral nervous system, neuroblastoma usually occurs in the chest or abdomen. It accounts for 7 percent of all childhood cancers, and 10 to 15 percent of all childhood cancer deaths. Although survival rates have improved over the years, more effective treatments are needed for high-risk subsets of neuroblastoma.

Researchers at CHOP and other centers have discovered a variety of genes contributing to this complex disease, and continue to pursue innovative therapies.

The current study builds on a 2012 discovery by Diskin, Maris and colleagues that showed that variants in LIN28B raised the risk of neuroblastoma. The gene was already known to play roles in different cancers, but their study was the first to link it to neuroblastoma.

The new study explored specific mechanisms by which LIN28B drives neuroblastoma. The research team performed cell analyses of 250 tumor samples from neuroblastoma patients, in addition to studies in animal

models.

They showed that variants in the LIN28B gene generate abnormal signals that regulate another gene called RAN. The RAN gene, in turn, becomes overactive and produces higher levels of the RAN protein, causing cells to grow out of control in tumors.

Acting in both direct and indirect ways, LIN28B also blocks tumor suppressor genes that normally put the brakes on cancer. The research suggests that signals originating in LIN28B ultimately promote another gene called AURKA, already known to play key roles in neuroblastoma and other cancers.

All three genes, LIN28B, RAN, and AURKA , function as oncogenes—genes known to drive cancer when affected by genetic changes. In parsing the complex interplay of genes and proteins acting in this signaling network, the researchers say these pathways represent potential targets for future neuroblastoma treatments.

"In preclinical and clinical studies, some existing anticancer drugs show desired effects against components of these pathways," said first author Robert Schnepp, M.D., Ph.D. He added, "Our research offers opportunities to develop possible drug combinations to be tested in future clinical trials."

More information: "A LIN28B-RAN-AURKA Signaling Network Promotes Neuroblastoma Tumorigenesis," *Cancer Cell*, published online Oct. 15, 2015. doi.org/10.1016/j.ccell.2015.09.012

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