

New pathway identified as a target for precision medicine against a common brain tumor

November 2 2017

St. Jude Children's Research Hospital scientists have discovered a promising target for precision medicines to block a mechanism that drives several cancers, including about 30 percent of cases of the brain tumor called medulloblastoma. The findings appear online today in the scientific journal *Developmental Cell*.

Medulloblastoma develops in the cerebellum at the back of the brain and occurs in about 400 children and adolescents annually in the U.S. That makes it the most common malignant pediatric brain tumor.

Medulloblastoma is less common in adults. In about 30 percent of patients, the signaling pathway called Sonic Hedgehog is inappropriately switched on and drives cell proliferation. The pathway is normally active in the brain during fetal development.

St. Jude researchers have shown that just as manufacturers rely on suppliers to keep assembly lines running, the Sonic Hedgehog pathway depends on another pathway, the mTORC1 pathway, to function.

Investigators reported that inhibiting mTORC1 disrupted the Sonic Hedgehog signaling pathway and significantly extended the lives of mice with the medulloblastoma that is driven by Sonic Hedgehog signaling. Researchers used an investigational drug to inhibit mTORC1. The drug, INK128, is in clinical trials for treatment of another brain tumor, glioblastoma, and other solid tumors.

"The role of mTORC1 in the Hedgehog pathway was unexpected and highlights the mTORC1 pathway as a potentially important molecular target for developing much needed precision medicines for patients with the Sonic Hedgehog medulloblastoma subtype," said corresponding author Young-Goo Han, Ph.D., an assistant member of the St. Jude Department of Developmental Neurobiology. "The results also raise hopes for combination targeted therapies to improve outcomes and ease treatment side effects."

Current treatment of medulloblastoma involves surgery, radiation and chemotherapy and fails to cure 20 to 30 percent of patients. Therapy also often has debilitating life-long consequences for survivors. An investigational drug that blocks Smoothed, a key protein in the Hedgehog signaling pathway, has shown promise for treatment of medulloblastoma. But not all medulloblastoma patients with the Sonic Hedgehog subtype respond to the inhibitor, and those who do eventually become resistant to the drug.

mTORC1 is an enzyme complex that anchors one branch of the MTOR pathway. Like the Sonic Hedgehog pathway, the MTOR pathway helps regulate cell growth and proliferation. Mutations in the MTOR pathway have also been linked to cancer, but the pathway's role in Hedgehog signaling has been unclear.

Using genetic, biochemical and pharmacological tools, Han and his colleagues showed that mTORC1 is part of a previously unrecognized step in the Hedgehog signaling pathway. Loss or inhibition of mTORC1 suppressed Hedgehog signaling in the brains of mice and inhibited medulloblastoma growth even in mice resistant to a Sonic Hedgehog inhibitor in clinical use for treatment of medulloblastoma and basal cell cancer.

Researchers demonstrated that the Hedgehog pathway depended on

mTORC1 to free up cellular machinery to synthesize proteins including the Smoothed protein, a key component of the Hedgehog pathway. Protein synthesis is suppressed by a protein called 4EBP1. mTORC1 tagged (phosphorylated) 4EBP1 with a molecule of phosphate. That released the suppression and promoted synthesis of Smoothed, which plays a pivotal role in the unchecked signaling that is a hallmark of SHH medulloblastoma. But the importance of Smoothed protein synthesis or mTORC1's role in the process had not previously been recognized.

Researchers checked human medulloblastoma tumor samples and found elevated levels of phosphorylated 4EBP1 protein in two medulloblastoma subtypes—SHH and as well as the WNT medulloblastoma subtype. Those and other results suggest that mTORC1 may influence tumor development in other, still unknown ways.

Researchers showed that INK128 inhibited phosphorylation of 4EBP1 via mTORC1 in medulloblastoma, which results of this study suggest should block synthesis of Smoothed. Levels of Smoothed declined in mice treated with INK128. So did levels of another protein, GLI1, whose production is tied to Sonic Hedgehog signaling.

mTORC1 inhibition with INK128 even extended the lives of mice resistant to the [investigational drug](#) that targets Smoothed. "These two targeted therapies act synergistically using different mechanisms to inhibit the Sonic Hedgehog [pathway](#)," Han said. "That suggests combination therapy offers a promising strategy for cancers like [medulloblastoma](#) that are driven by abnormal Sonic Hedgehog signaling."

Provided by St. Jude Children's Research Hospital

Citation: New pathway identified as a target for precision medicine against a common brain

tumor (2017, November 2) retrieved 10 February 2023 from
<https://medicalxpress.com/news/2017-11-pathway-precision-medicine-common-brain.html>

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