Caution needed for drugs in development for most common malignant pediatric brain tumor

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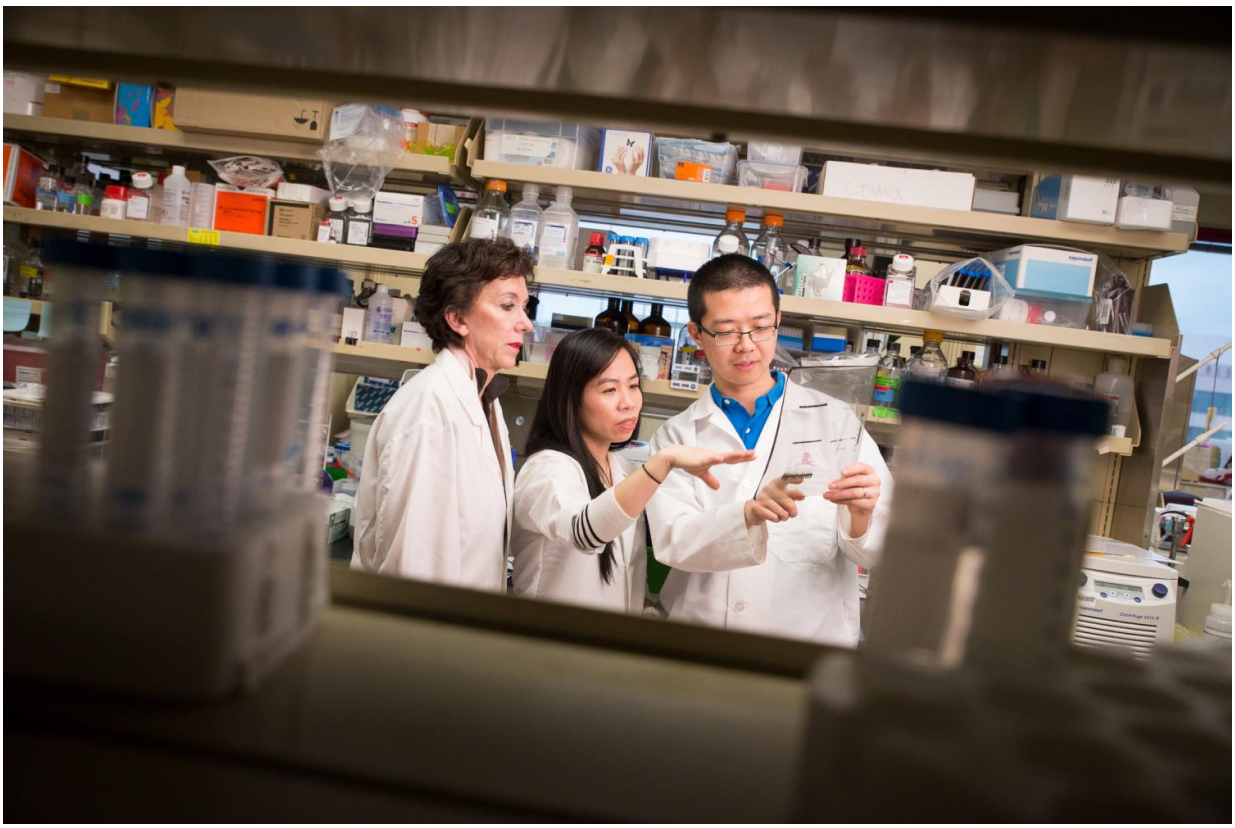

St. Jude Children's Research Hospital scientists Martine Roussel, Ph.D., BaoHan Vo, Ph.D., and Chunliang Li, Ph.D., used CRISPR gene editing to reveal how a histone writer enzyme plays a role in suppressing as well as driving the most aggressive form of medulloblastoma. Credit: St. Jude Children's Research Hospital

Researchers led by St. Jude Children's Research Hospital scientists have worked out how a crucial cancer-related protein, a "histone writer" called Ezh2, plays a role in suppressing as well as driving the most aggressive form of the brain tumor medulloblastoma.

Ezh2 is a histone writer, an enzyme that can tag or label other proteins in a way that turns off genes. The new findings, which appear online today in *Cell Reports*, show that unlike in some earlier studies where the protein helped to advance disease, Ezh2 can also suppress cancer. This dichotomy has implications for the potential use of drugs intended to inhibit this enzyme, some of which are being tested in clinical trials.

The enzyme looked at in this study is the histone H3K27 mono-, di- and trimethylase of polycomb repressive complex 2, or Ezh2 for short. This histone writer adds methyl groups to specific histone proteins leading to epigenetic modifications that affect gene expression. The team used CRISPR gene editing to knock out the activity of the protein in a mouse model. Loss of function of this protein due to gene editing resulted in acceleration of the development of medulloblastoma tumors.

Medulloblastoma, which starts in the cerebellum of the brain at the base of the skull, is the most common malignant brain tumor of childhood, accounting for about 20 percent of all childhood brain tumors. Grade 3 medulloblastoma is one of the most aggressive forms of the tumor and accounts for almost a third of cases. The researchers used a mouse model that allowed them to study similar tumors in an experimental system.

"We expected Ezh2 to be an oncogene in this aggressive tumor, but our gene-editing work revealed it to be a tumor suppressor," said corresponding author Martine Roussel, Ph.D., a member of the Department of Tumor Cell Biology at St. Jude Children's Research Hospital. "Clearly this poses questions about the use of inhibitors to

target this protein in a way that stops the progress of this aggressive form of medulloblastoma."

The new work revealed that several proteins are involved in the development of medulloblastoma tumors—the well-known oncogene Myc, the histone writer Ezh2 and another protein known as Gfi1.

"It appears that a conspiracy among three proteins is required to drive this most aggressive form of medulloblastoma, but the precise details of interaction still need to be worked out," said co-author Charles J. Sherr, M.D., Ph.D., chair of the St. Jude Department of Tumor Cell Biology and a Howard Hughes Medical Institute (HHMI) investigator.

By inactivating Ezh2 in Group 3 medulloblastoma, the researchers were able to implicate Gfi1. Cancer was enhanced when Ezh2 declined and Gfi1 increased.

"Earlier work revealed that two genes, Gfi1 and Gfi1b, cooperate with Myc to promote the development of Group 3 medulloblastoma," said Paul Northcott, Ph.D., a study author and assistant member of the St. Jude Department of Developmental Neurobiology. "The new study further substantiates the tumorigenic role of Gfi1 in medulloblastoma, and reveals that this oncogene is normally repressed by Ezh2. The loss of this regulation by Ezh2 'releases the brakes' on Gfi1 and leads to uncontrolled cell growth. The findings in the current study help refine our knowledge of some of the important molecular mechanisms involved in Group 3 medulloblastoma and will be useful for probing therapeutic potential."

Other studies have revealed that Ezh2 is linked to a wide range of aggressive and advanced forms of cancer. Proteins that act as molecular switches for cancer are emerging as attractive targets for new drugs. Ezh2, which acts as an epigenetic switch, is no exception. Scientists have

succeeded in developing potent inhibitors of this protein that put the brakes on cancer in early preclinical and phase I/II studies. The new findings suggest that inhibiting Ezh2 could be counterproductive for cancer treatment in certain situations.

Scientists have known that Ezh2 behaves in different ways depending on the specific type of cancer. The new system will be able to tease out the details of how the different proteins drive medulloblastoma development.

"The model system we have developed will be extremely useful to reveal the mechanisms that cause this cancer to progress and to study the different options for potential therapeutic interventions before proceeding to more advanced preclinical studies," Roussel said.

Provided by St. Jude Children's Research Hospital