RNA-based therapy shows promise against aggressive childhood brain tumors in mice

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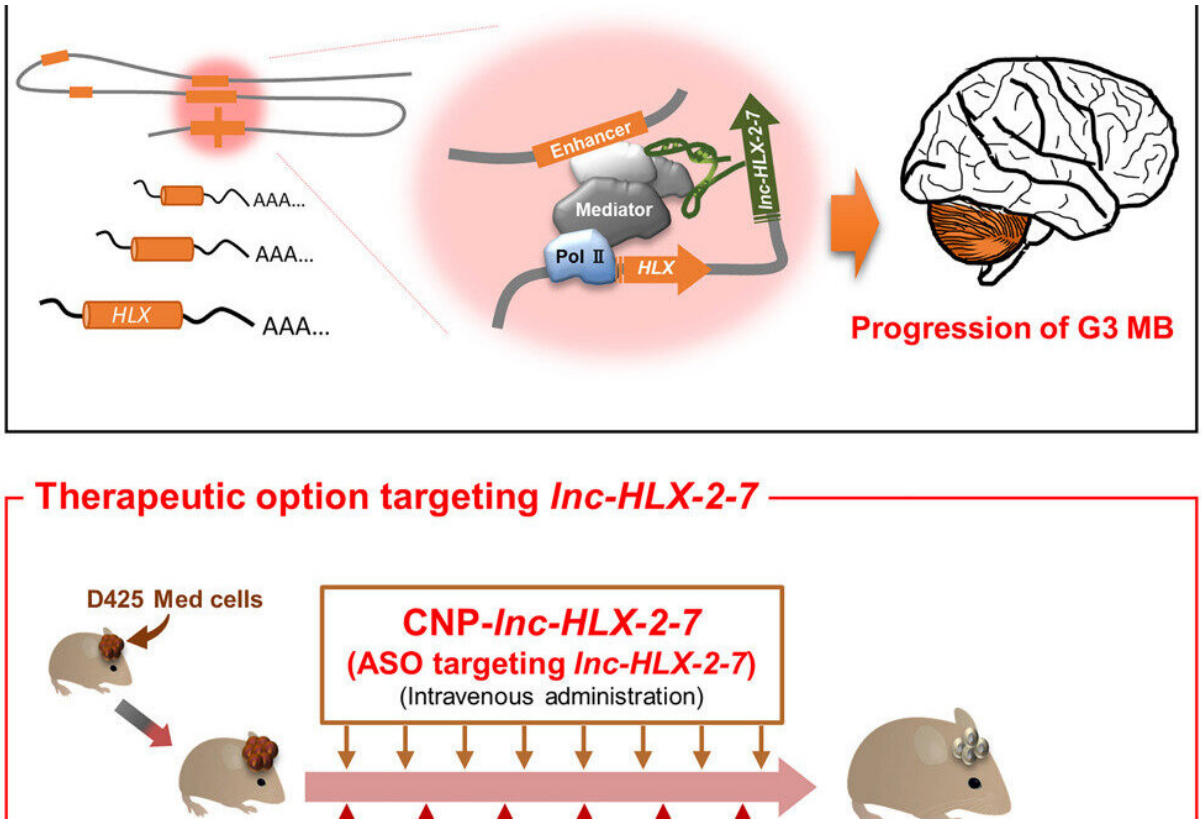

Credit: *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.113938

Targeting a non-encoding stretch of RNA may help shrink tumors caused by an aggressive type of brain cancer in children, according to new research in mice reported March 8 in *Cell Reports* by Johns Hopkins Kimmel Cancer Center investigators.

Medulloblastoma are the most common type of malignant brain cancer in children. The most aggressive and difficult-to-treat form of the disease is group 3 medulloblastoma, which is often fatal.

By targeting long, noncoding genetic material called lnc-RNAs that drive the expression of cancer-causing genes, the study's senior author, Ranjan Perera, Ph.D., director of the Center for RNA Biology at Johns Hopkins All Children's Hospital in St. Petersburg, Florida, and his colleagues have demonstrated an innovative new approach that shrinks group 3 medulloblastoma tumors in mice.

"Group 3 medulloblastoma is very aggressive, and there are currently no targeted therapies," says Perera, who has a primary affiliation in the Department of Neurosurgery, is a member of the Johns Hopkins Kimmel Cancer Center and is an associate professor of oncology at the Johns Hopkins University School of Medicine. He is also a senior scientist at the Johns Hopkins All Children's Hospital Cancer and Blood Disorders Institute, and has a secondary affiliation with the hospital's Institute for Fundamental Biomedical Research.

"Our novel therapeutic approach based on noncoding RNA could fill an urgent need for new therapies for this devastating disease in children," says Perera.

RNA acts as a template for building proteins based on instructions encoded in the DNA. Until recently, scientists thought 97% of RNA was

"junk" because only 3% is used to build proteins. However, scientists have realized that RNA's nonprotein encoding stretches control gene expression.

A previous study by Perera and colleagues showed that a long noncoding stretch of RNA called lnc-HLX-2-7 contributes to the growth of group 3 medulloblastoma tumors by attaching to a DNA promoter that increases expression of cancer-causing genes. Promoters are nongene coding stretches of DNA adjacent to genes that act like switches turning them on.

The new study provides additional details showing that lnc-HLX-2-7 specifically binds to the HLX promoter region of DNA, increasing HLX gene expression and causing the tumor to grow. HLX triggers tumor growth by binding to promoter regions for several other cancer-causing genes, increasing their expression.

One gene that HLX increases expression of is MYC, which also increases the expression of several other cancer-causing genes, causing a cascade of activity that accelerates the growth of group 3 medulloblastoma tumors.

Perera and his team developed an intravenous treatment to block lnc-HLX-2-7 from binding to the HLX promoter to stop this cascade of cancer-gene expression. They assembled a sequence of nucleotides (called antisense oligo nucleotides), the building blocks of RNA, that can bind to the corresponding nucleotides that make up lnc-HLX-2-7, preventing it from binding to the HLX promoter in the DNA and leading to its destruction. They coated the sequence with microscopic particles called cerium oxide nanoparticles to protect the lnc-HLX-2-7 until it reaches its target.

When the team treated a mouse model of group 3 medulloblastoma with

the experimental intravenous therapy, it reduced tumor growth by 40%–50%. Adding cisplatin, a chemotherapy drug currently used to treat medulloblastomas, alongside the new therapy caused the tumors to shrink even more and prolonged the animals' survival. The combination therapy extended the animals' lives by about 84 days compared with a 44-day increase in survival on lnc-HLX-2-7 alone.

"When you combine the two treatments, you see dramatic effects," Perera says.

Perera and his colleagues will collaborate with Johns Hopkins neurosurgeons to plan studies of the therapy in humans to further test its safety and efficacy.

"Understanding why MYC is elevated in these tumors is extremely important, and this new link to HLX provides insights that open new therapeutic possibilities," says study co-author and Kimmel Cancer Center researcher Charles Eberhart, M.D., Ph.D., director of neuropathology and ophthalmic pathology and a professor of oncology and pathology at the Johns Hopkins University School of Medicine.

More information: Keisuke Katsushima et al, A therapeutically targetable positive feedback loop between lnc-HLX-2-7, HLX, and MYC that promotes group 3 medulloblastoma, *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.113938

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