

Decrease in specific gene 'silencing' molecules linked with pediatric brain tumors

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A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

Experimenting with lab-grown brain cancer cells, Johns Hopkins Medicine researchers have added to evidence that a shortage of specific tiny molecules that silence certain genes is linked to the development and growth of pediatric brain tumors known as low-grade gliomas.

A [report](#) of the findings was published this fall 2018 in *Scientific Reports*, and supports the idea of increasing levels of microRNAs as a potential means of treating these tumors.

An estimated 1,600 cases of pediatric low-grade gliomas (PLGGs) are diagnosed annually in the United States, and the vast majority of these slow-growing tumors are treatable and curable mainly by surgical removal, although in some cases surgery has the potential to damage critical nearby brain tissue, depending on [tumor](#) location. Unlike high-grade glioblastomas such as the one that took the life of Arizona Senator John McCain, PLGGs mostly affect school-age children and young adults.

"It has long been known that microRNAs play a role in controlling various tumor properties such as growth," says Fausto Rodriguez, M.D., associate professor of pathology at the Johns Hopkins University School of Medicine and the study's senior author.

"Our findings identified a subset of microRNAs that, in sufficient quantity, seem to decrease the growth and invasion of cancerous [cells](#) in pediatric low-grade gliomas."

MicroRNAs are tiny molecules that, in ways similar to how an orchestra conductor controls the flow of each instrument group, command the expression of entire gene networks that make proteins by essentially silencing them, and are responsible for regulating biological processes such as nutrient intake, cell growth and [cell death](#). Altered levels of specific microRNAs can disrupt entire biological pathways just as a

misguided section of an orchestra can unsettle an entire score.

"One microRNA can target multiple genes and have a profound effect on cell processes, and the alterations are dynamic," notes Rodriguez, who says PLGGs are good candidates for analyzing microRNA types and levels because genetically PLGGs are stable compared with other tumors. That makes it relatively easier, he says, to identify any relevant genetic abnormalities and potential targets for therapy.

For the new study, the researchers first analyzed previously gathered microRNA subtype data in two studies. They examined tumors from 125 patients with low-grade gliomas for levels of a specific microRNA, known as miR-125b, using chromogenic in situ hybridization (CISH), a technique that is applicable to routinely processed tissue in pathology and allows for identification of specific microRNAs in the cells of interest. Levels of this microRNA were lower in 43 pilocytic astrocytomas (the most common subtype of PLGG) when compared with 24 diffuse astrocytomas and normal brain tissues.

Rodriguez and the research team next looked at eight cancerous cell lines derived from brain (glial) tumors in children for levels of microRNA 125b-p using a method that can rapidly make thousands to millions of copies of a genetic sequence for easier analysis of how much of a gene is expressed. Although levels of microRNA 125b-p varied across the lab-grown cell lines, they were significantly and uniformly lower in cancerous cell lines than noncancerous cell lines, Rodriguez reports.

In further experiments designed to identify the role of these microRNAs in cell growth, the investigators increased levels of miR-125b in cancerous cell lines by introducing a DNA segment in the tumor cells using specific viruses, and saw a decrease in cell division and growth. To check whether cell death contributed to this decrease in [cell growth](#), Rodriguez stained cells containing high levels of microRNA 125b and

noted cell death in all cell lines, suggesting that increasing levels of microRNA 125b can stop the growth of PLGG.

"These findings are an example of where advances in precision medicine might take us, and show how, someday, increasing levels of specific genes and microRNAs might be a targeted treatment for PLGGs," says Rodriguez.

Provided by Johns Hopkins University School of Medicine

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