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MicroRNA-218 targets medulloblastoma, most aggressive childhood brain cancer

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Between the blueprint of the genome and the products of its expression lie microRNAs, which can boost or lower the rate at which genes become stuff. In fact, many cancers use microRNA to magnify the expression of faulty genes or shrink the expression of helpful genes that would otherwise suppress tumors. A University of Colorado Cancer Center study published in the December issue of the *Journal of Biological Chemistry* shows that in medulloblastoma, a malignant brain tumor of children, microRNA-218 is especially low. The article also shows that adding microRNA-218 to neural stem cells engineered to develop medulloblastoma decreases the development of the cancer.

"For the past five years, we've been looking at microRNAs in medulloblastoma, asking how they are normally expressed and how this expression differs in the disease. One of the microRNA's most different in the medulloblastoma is microRNA-218," says Rajeev Vibhakar, MD, PhD, MPH, investigator at the CU Cancer Center, assistant professor of pediatrics at the CU School of Medicine, and the paper's senior author.

When Vibhakar and colleagues inquired into the effects of lower microRNA-218 levels, they found its involvement in pathways that signal the metabolism, growth, migration and invasion of tumor tissues. MicroRNA-218 is a tumor suppressor – low miRNA-218 equals low function in a range of tumor suppressor genes, equals high tumor growth.

In fact, the group found 618 genes whose expression was manipulated by microRNA-218.

"One of these genes was CDK6," Vibhakar says. Finding a gene target is especially important because whereas it's difficult to drug microRNA it's fairly simple to drug genes. As it turned out, Pfizer already had a drug that targets CDK6 and in a follow-up study published in the Journal of NeuroOncology, when Vibhakar and colleagues tested the drug in medulloblastoma cells, they found reduced cancer cell survival.

"Especially important is the fact that the drug led to increased radiation sensitivity in cancer cells," Vibhakar says. "Because medulloblastoma is most common in children and because high doses of radiation in children can have adverse long-term side effects, the prospect of a drug that could reduce the intensity of the required radiation is very appealing."

For similar reasons, despite the finding of a druggable target, the group plans to continue its work with microRNA-218. Specifically, the microRNA seems involved in cancer cell migration and invasion – because medulloblastoma is aggressively metastatic along the spinal cord, any advances in stopping the march of the disease from the brain could lead to major patient gains, especially in pediatric patients.

"Also interesting is the fact that studies of microRNA are leading us to genes implicated in cancer that we may not have discovered otherwise," Vibhakar says. In many ways this is the reverse of the traditional workflow in discovering a druggable target. Usually, a researcher would explore for genetic abnormalities and then if needed search inside the gene's signaling chain for a way to turn it on or off. With microRNA, researchers look first for abnormalities in the signaling chain, and then work higher in the system to discover the associated genetic abnormalities and their functions.

Because many of the pathways affected by microRNA-218 are common across many types of cancer, the findings may have implications far

beyond medulloblastoma.

Provided by University of Colorado Denver