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Details of gene pathways suggest fine-tuning drugs for child brain tumors

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Pediatric researchers, investigating the biology of brain tumors in children, are finding that crucial differences in how the same gene is mutated may call for different treatments. A new study offers glimpses into how scientists will be using the ongoing flood of gene-sequencing data to customize treatments based on very specific mutations in a child's tumor.

"By better understanding the basic biology of these tumors, such as how particular mutations in the same gene may respond differently to targeted drugs, we are moving closer to personalized medicine for children with cancer," said the study's first author, Angela J. Sievert, M.D., M.P.H., an oncologist in the Cancer Center at The Children's Hospital of Philadelphia.

Sievert, working with co-first author Shih-Shan Lang, M.D., in the translational laboratory of neurosurgeon Phillip Storm, M.D., and Adam Resnick, Ph.D., published a study ahead of print today in the *Proceedings of the National Academy of Sciences*.

The study, performed in cell cultures and animals, focused on a type of astrocytoma, the most common type of brain tumor in children. When surgeons can fully remove an astrocytoma (also called a low-grade glioma), a child can be cured. However, many astrocytomas are too widespread or in too delicate a site to be safely removed. Others may recur. So pediatric oncologists have been seeking better options—-ideally, a drug that can selectively and definitively kill the

tumor with low toxicity to healthy tissue.

The current study focuses on mutations in the BRAF gene, one of the most commonly mutated genes in human cancers. Because the same gene is also mutated in certain adult cancers, such as melanoma, the pediatric researchers were able to make use of recently developed drugs, BRAF inhibitors, which were already being tested with some success against melanoma in adults.

The current study provides another example of the complexity of cancer: in the same gene, different mutations behave differently. Sievert and her colleagues at Children's Hospital were among several research groups who reported almost simultaneously in 2008 and 2009 that mutations in the BRAF gene were highly prevalent in astrocytomas in children. "These were landmark discoveries, because they suggested that if we could block the action of that mutation, we could develop a new, more effective treatment for these tumors," said Sievert.

However, follow-up studies in animal models were initially disappointing. BRAF inhibitors that were effective in BRAF-driven adult melanomas made brain tumors worse—via an effect called paradoxical activation.

Further investigation revealed how tumor behavior depended on which type of BRAF mutation was involved. The first-generation drug that was effective in adult melanoma acted against point mutations in BRAF called V600E alterations. However, in most astrocytomas the mutation in the BRAF gene was different; it produced a fusion gene, designated KIAA1549-BRAF. When used against the fusion gene, the first-generation drug activated a cancer-driving biological pathway, the MAPK signaling cascade, and accelerated tumor growth.

By examining the molecular mechanisms behind drug resistance and

working with the pharmaceutical industry, the current study's investigators identified a new, experimental second-generation BRAF inhibitor that disrupted the cancer-promoting signals from the fusion gene, and did not cause the paradoxical activation in the cell cultures and animal models.

This preclinical work result lays a foundation for multicenter clinical trials to test the mutation-specific targeting of tumors by this class of drugs in children with astrocytomas, said Sievert. As this effort progresses, it will benefit from CHOP's commitment to resources and collaborations that support data-intense research efforts.

The direction of brain tumor research over the past several years reflects some of those data-driven advances, says Adam C. Resnick, Ph.D., the senior author of the current paper and principal investigator of the astrocytoma research team in the Division of Neurosurgery at Children's Hospital. "For years, astrocytomas have been lumped together based on similar appearance to pathologists studying their structure, cell shape and other factors," said Resnick. "But our current discoveries show that the genetic and molecular structure of tumors provides more specific information in guiding oncologists toward customized treatments."

Earlier this year, Children's Hospital announced its collaboration with the gene-sequencing organization BGI-Shenzhen in performing next-generation sequencing of pediatric brain tumors at the Joint Genome Center, BGI@CHOP. The center's sophisticated, high-throughput sequencing technology will greatly speed the discovery of specific gene alterations involved in childhood brain cancers.

This genomic discovery program dovetails with the work of the Childhood Brain Tumor Tissue Consortium, a multi-institutional collaboration recently launched by CHOP, with support from the Children's Brain Tissue Foundation. Because even large research centers

may not hold enough tumor tissue specimens to power certain research, the consortium pools samples from a group of institutions, providing an important scientific resource for cooperative studies.

"The better we understand the mutational landscape of tumors, the closer we'll be to defining therapies tailored to a patient's specific subtype of cancer," added Resnick.

More information: "Paradoxical activation and RAF inhibitor resistance of BRAF protein kinase fusions characterizing pediatric astrocytomas," *Proceedings of the National Academy of Sciences*, Online Early Edition, March 26, 2013. www.pnas.org/cgi/doi/10.1073/pnas.1219232110

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