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Pediatric low-grade gliomas with CRAF fusions may require differential and combinatorial targeted therapies

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Unlike pediatric low-grade gliomas (PLGG) that are driven by BRAF fusion proteins, PLGGs that are driven by other forms of RAF fusion proteins, called CRAF fusion proteins, may not respond to single-agent therapy with FDA-approved and investigational RAF inhibitors, suggesting the importance of molecularly stratifying PLGG patients in order to identify appropriate therapies, according to preclinical data presented here at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held Nov. 5–9.

The study also found that preclinical models of PLGG with CRAF fusions responded to a combination of therapies targeting two different signaling pathways, the MAPK pathway and PI3K pathway.

"Despite being the most common brain tumor in children, PLGGs are rather poorly studied and loosely categorized," said Payal Jain, a graduate student at the University of Pennsylvania in the laboratory of Adam Resnick, PhD, assistant professor of neurosurgery, at The Children's Hospital of Philadelphia. "Current treatments for PLGGs can be invasive and toxic to children in the long term. Thus, there is a great need to study the genetic and molecular mechanisms driving PLGGs. This would help define novel precision medicine approaches for affected children," she added.

Jain explained that BRAF and CRAF are related signaling proteins

involved in a cellular growth pathway called the mitogen-associated protein kinase, or MAPK, pathway, which is often affected in human cancers. PLGGs display a combination of mutations driving the MAPK pathway. While BRAF fusions are found in more than 50 percent of patients with PLGG, CRAF fusions have only recently been discovered in some PLGGs, she noted.

"Our goal was to characterize, for the first time, the response of PLGG cell and animal models associated with CRAF fusion to diverse, clinically relevant RAF and MAPK inhibitors," Jain said. "We found that in contrast to PLGGs with BRAF fusions, against which second-generation RAF inhibitors have demonstrated efficacy, PLGGs with CRAF fusions remain largely unresponsive."

To study the CRAF fusions found in PLGGs, Jain, Resnick, and colleagues generated heterologous cell model systems harboring the distinct CRAF fusions found in patients. They found that, like BRAF fusions, CRAF fusions could activate the MAPK pathway in their cell model and also drive tumor formation in mice injected with these cells.

The researchers then tested and compared the effectiveness of PLX4720 (the research version of vemurafenib, a first-generation RAF inhibitor), PLX8394 (a second-generation RAF inhibitor), and GSK1120212/trametinib (a MEK inhibitor, a protein involved in the MAPK pathway) in suppressing cell culture growth and mice tumor formation driven by CRAF fusions. While first-or second-generation RAF inhibitors could not suppress cell growth driven by CRAF fusions, tumors in mice were partially responsive to the MEK inhibitor, which suppresses the MAPK pathway.

The researchers also tested a combination of a MEK inhibitor and an inhibitor of mTOR, a molecule involved in the PI3K signaling pathway, and observed a significant decrease in CRAF fusion-driven tumor

growth in mice, suggesting that dual targeting of the MAPK and PI3K pathways is essential for effective therapeutic response in PLGGs with CRAF fusions.

"Our work shows that children with PLGGs with different RAF fusions may require different treatments and that the fusion setting in solid tumors likely represents a combinatorial array of mechanisms employed by cancers," Jain said. "Pediatric low-grade gliomas exemplify why a precision medicine approach to cancer care can be crucial."

Jain noted that a limitation of the study is the absence of patient-derived PLGG cell lines, despite significant efforts by researchers. This represents a significant hurdle in studying these tumors and related molecular mechanisms, she said. However, model systems like those used in the current study have proven predictive of clinical responses, she added.

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