Studying resistance to therapy in BRAF-mutated brain tumors

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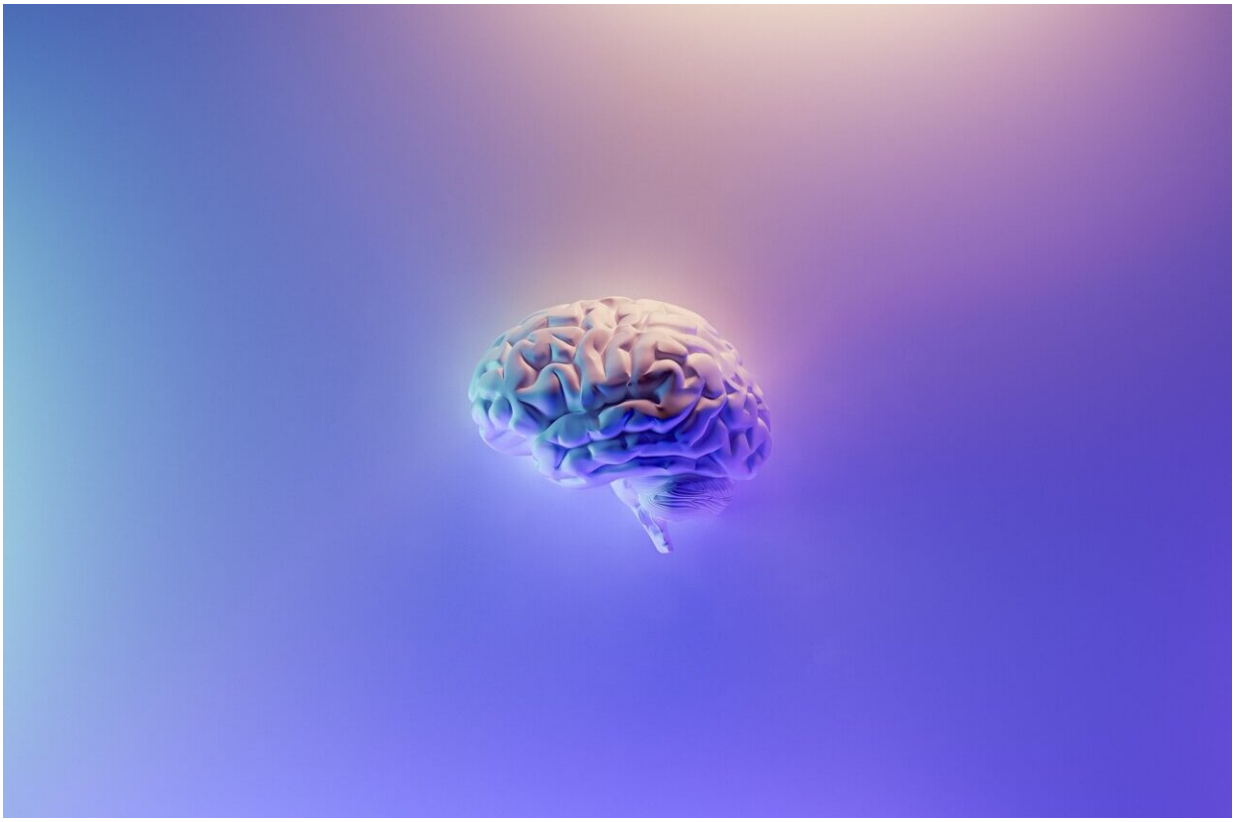

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Looking to understand why some brain tumors with a specific mutation can start to reject drugs commonly used to treat them, CU Cancer Center member Jean Mulcahy Levy, MD, led researchers from

institutions around the country—including several from the University of Colorado School of Medicine—to study samples of brain tumors before and after treatment with the drug.

The study looked specifically at brain tumors called gliomas that had the BRAF mutation, and occur in children and young adults. The same mutation happens in adult melanoma, and several years ago researchers developed a medication to treat the mutation in melanoma that also can be used to treat BRAF-mutated gliomas.

"It's a rare mutation, but it's one of the first mutations that had a targeted medicine we could use," Levy says. "They had a large population and developed the targeted therapies, and that allowed us to use those therapies in our brain tumor patients."

Rise of the resistance

The targeted therapy eliminates the need for chemotherapy in many patients with BRAF-mutated gliomas—not to mention it can help eliminate seizures that can occur in patients with the mutation. However, the new challenge is that some patients develop a resistance to the medicine, eventually causing their tumors to come back. Levy and her team set out to find out what was causing the resistance, and how they could stop it from occurring.

"We collected samples of patient brain tumors before treatment with the targeted medicine and after treatment with the targeted medicine, which is much more difficult in brain tumors," Levy says of the research that was published in August in *Clinical Cancer Research.* "If you think about melanoma, they can do serial biopsies because the lesions are on the skin and easy to get to. But getting the samples from the brain [is] much harder. So, we developed a collaboration that started here at CU School of Medicine, in my lab, and then we incorporated researchers from the

University of California San Francisco, New York University and Johns Hopkins, and that allowed us to create a collaboration and collect 14 patient samples of pre-treatment and post-treatment. We were able to reach out to other institutions, like Valley Children's and Oregon Health Science University, to get their samples as well."

Through deep genetic analysis of the tumors, including RNA sequencing and whole genome sequencing, the researchers found additional mutations that can create resistance to the targeted therapies. Some have been described in other diseases, such as melanoma, but other mutations had never been discovered in either type of tumor before.

"It just goes to show that brain tumors may develop different resistance mechanisms from other kinds of cancers that are treated with these drugs," Levy says. "We can't just rely on, 'Well, melanoma does this, so brain tumors probably do too.' We need to be sure that we're specifically studying brain tumors, because they're a very different kind of disease."

Winning combination

Levy and her fellow researchers are now in the process of following up on their findings, investigating new potential treatments or combination therapies that could help combat drug resistance in BRAF-mutated gliomas. Levy already is conducting a pediatric clinical trial, looking for ways to reverse the resistance.

"The work we're doing now to follow up on our genetic findings will hopefully find other additional medicines or combinations that can be used," she says. "Cancer, at its baseline, is very smart. And it's very rare to have any kind of tumor that you can treat with a single medication. The ultimate goal is to find the right combination of medicines that can treat this cancer and then either prevent resistance or reverse resistance, with the least amount of complications."

Once that combination is found, Levy says, researchers will run more clinical trials—adult and pediatric—to test its effectiveness. Her hope is that eventually, patients with this specific type of glioma won't have to worry about recurrence or resistance.

"If we're not focused on developing the next step in therapy, these patients will develop resistance, and then they'll come back to us and we won't have anything to offer them," she says. "We need to be forward-thinking and be ready for the next therapy that has to happen for these patients."

More information: Karisa C. Schreck et al, Deconvoluting mechanisms of acquired resistance to RAF inhibitors in BRAF V600E mutant human glioma, *Clinical Cancer Research* (2021). DOI: 10.1158/1078-0432.CCR-21-2660

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