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How mutations in a single gene alter the course of a deadly brain cancer

New laboratory study of glioma links more aggressive immune response to poorer prognosis

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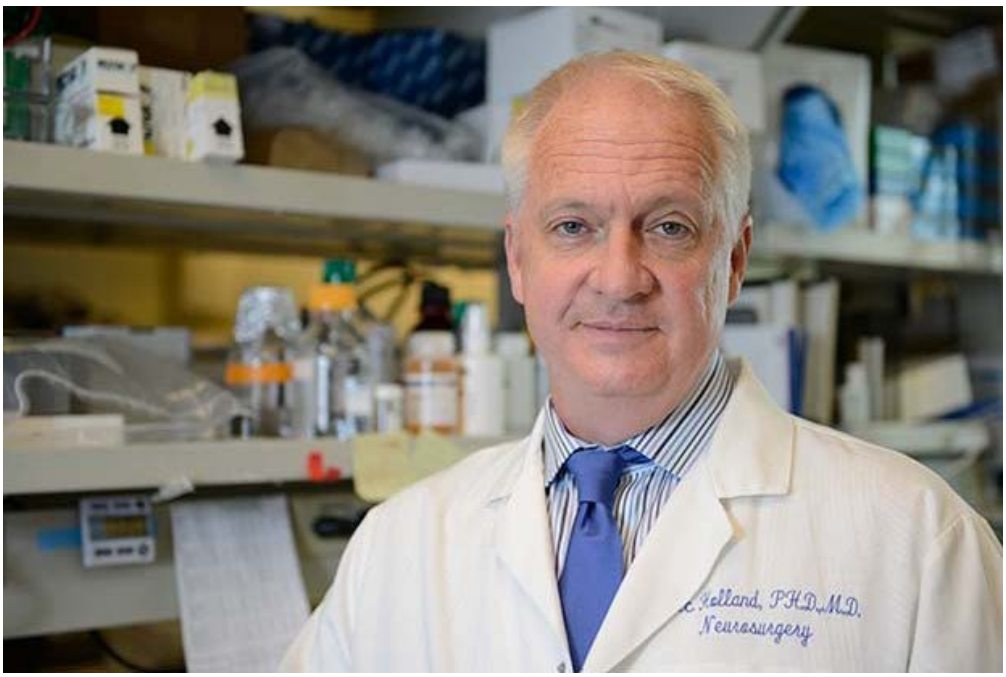

Brain cancer researcher Dr. Eric Holland led a new study linking aggressive immune response to poorer survival in patients with glioma.
Fred Hutch file

A diagnosis of glioma, a particularly aggressive form of brain cancer, is never one that oncologists want to deliver. But not all gliomas are created equal.

Those with mutations in a gene known as IDH, for example, are linked to much longer survival, regardless of the cancer's stage at diagnosis. In fact, clinicians often look for

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this molecular detail when patients are first diagnosed. The presence or absence of IDH mutations in a biopsy can help predict that patient's prognosis.

New results published earlier this month in the journal Genes and Development show that part of this difference is directly due to the IDH mutation leading to a tempered immune response against glioma, in turn reducing the aggressiveness of tumors and prolonging patient survival. Gliomas with unmutated IDH, in contrast, prompt stronger immune responses that increase tumor aggressiveness and reduce survival. Scientists at Fred Hutchinson Cancer Research Center made their discovery by creating the first mouse models of gliomas with the IDH mutation and using them to study the tumors in detail.

"We tested two questions," said Dr. Eric Holland, the study's senior author and a brain cancer researcher and neurosurgeon who directs Fred Hutch's Human Biology Division, Seattle Translational Tumor Research and the Nancy and Buster Alvord Brain Tumor Center at the University of Washington. First, his team looked at whether mutations in IDH cause a drop in the number of immune cells entering tumors. Second, they asked whether this drop affects survival.

The team found that "if you reduce certain cell types [in gliomas with normal IDH], you can affect survival," said Holland. Their findings point to potential new therapeutic avenues for glioma, he said, adding that the new preclinical model will also make deeper investigations into this type of glioma possible.

A key gene

Brain tumors are not uniform. Many characteristics influence how quickly each tumor will progress, how well it will respond to treatment, and how long a patient diagnosed with glioma may live. For decades, pathologists estimated all of these factors by examining the shapes and arrangement of brain tumor cells under the microscope. Based on these assessments, they would give the tumor a grade from 1 to 4, with 1 being least aggressive and 4 the most aggressive.

With the advent of in-depth tumor gene sequencing studies came a new appreciation of genetic changes that could influence patient prognosis. One of the major insights was that gliomas with mutations in a gene known as isocitrate dehydrogenase, or IDH, are usually significantly less aggressive than gliomas with a normal IDH gene.

Patients whose gliomas carry a normal IDH gene have a median survival of about 18 months, meaning that half of patients will live longer than one-and-a-half years after their diagnosis. In contrast, median survival for patients with IDH-mutant gliomas can be five or even 10 years, depending on the specific tumor type. It turns out, said Holland, that the presence or absence of mutations in the IDH gene is a better predictor of survival than tumor grade.

But research is still needed to better understand gliomas with IDH mutations. Though less aggressive, they are "still deadly," said Holland. "If you have a glioma, even if it's mutant for IDH, it is likely to eventually kill you."

IDH linked to immune response

A notable difference between IDH-mutant and normal gliomas is that IDH-mutant gliomas have fewer immune cells. The interplay between cancer and our immune system is complex. Immunotherapies, which are designed to harness or amplify certain components of the immune system, are showing promise in the targeted treatment of some cancers. But an immune response against cancer is not always a good one. In

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many tumor types, including gliomas, the inflammation triggered by an immune response is linked with increased tumor growth and spread — and worse prognosis.

“You think of the immune system as good, but it’s not always good” when it comes to cancer, said Holland.

T cells are a type of immune cell whose presence in tumors is often correlated with better survival and which are the focus of some experimental immunotherapies. But the immune cells that find their way inside gliomas are mostly macrophages, which are able to engulf pathogens, stimulate cell growth and enhance cell spread.

This “is part of a normal inflammatory response, which is a wounding response,” said Holland. “That’s not a cell-killing response, that’s a promoting cell proliferation, and fixing tissue, and roll up your sleeves and make more cells” type of response — but the problem is that the cells being fixed and stimulated to grow are tumor cells, he said.

Holland and Dr. Nduka Amankulor, the study’s first author and a brain cancer physician-scientist (formerly in Holland’s lab and now at the University of Pittsburgh) assessed this response in more detail. Their team examined the immune cells in tumor samples from 16 patients; six gliomas carried mutations in IDH and 10 did not. They found that in human IDH-mutant gliomas, far fewer immune cells, particularly macrophages, had shouldered their way in when compared to gliomas with normal IDH. This suggested that the vigor of the immune response against gliomas was linked to tumor aggressiveness.

But “If that’s all you knew [about human gliomas], then that would be just correlation,” said Holland. “So you need a system to test that, to figure out whether IDH mutation messes with the immune system, whether the immune system messes with survival. … You need to do an experiment.”

A new model

Doing an experiment requires a preclinical model of IDH-mutant gliomas — which, up until this point, didn’t exist. Though IDH mutations can have big implications for patients, gliomas carrying these changes have resisted scientists’ attempts to study them. For still-unknown reasons, IDH-mutant glioma cells taken from patients won’t grow in laboratory cultures — although glioma cells with normal IDH do just fine. Mutating the IDH gene alone isn’t enough to trigger cancer development either, making it difficult for researchers to create laboratory models they could use to gain a better understanding of how IDH mutations affect gliomas.

Holland, Amankulor and their team made three types of glioma mouse models with varying levels of glioma aggressiveness. For every model, they made another complementary one that was the same in every way, except for the addition of a mutated IDH gene, making this the only initial difference between each pair. The IDH-mutant tumors from their models shared many characteristics with human IDH-mutant tumors.

And when the researchers examined the immune cells within gliomas from the most aggressive pair of models, they found that the tumors continued to mimic their human counterparts: IDH-mutant gliomas harbored significantly fewer immune cells than did those with normal IDH.

Immune cells track sites of injury and disease by detecting molecules released by nearby tissue. Like bloodhounds, they follow the trail to its strongest point. When the scientists looked at the levels of these molecules, they found that IDH-mutant gliomas produced lower levels than gliomas with normal IDH, suggesting that IDH somehow

dampened the immune cell–attracting, red-alert signals cancer cells usually give off.

And when Amankulor and the team experimentally depleted tumors of these immune cells, they found that mice with normal IDH survived longer. Trying to similarly modify the immune response to IDH-mutant gliomas, already low in immune cells, didn't affect survival.

Holland expects that, with the new model he and his team developed, research into the fundamental nature of IDH-mutant glioma cells is just beginning. He is already teaming up with several Hutch colleagues to look more deeply at the interplay between IDH-mutant glioma cells and the immune system, and there is much more to be learned.

The complementary models give researchers the opportunity to study "the whole landscape" of IDH-mutant and normal gliomas, said Holland. And, he hopes, find "an Achilles' heel to be exposed."

Sabrina Richards, a staff writer at Fred Hutchinson Cancer Research Center, has written about scientific research and the environment for The Scientist and OnEarth Magazine. She has a Ph.D. in immunology from the University of Washington, an M.A. in journalism and an advanced certificate from the Science, Health and Environmental Reporting Program at New York University. Reach her at srichar2@fredhutch.org.

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