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Study sheds light on why brain cancers become aggressive and treatment-resistant

HUTCH NEWS

Study shows how glioblastomas get a leg up

New computational method sheds light on how cancer-contributing genes make brain tumors more aggressive and radiation-resistant

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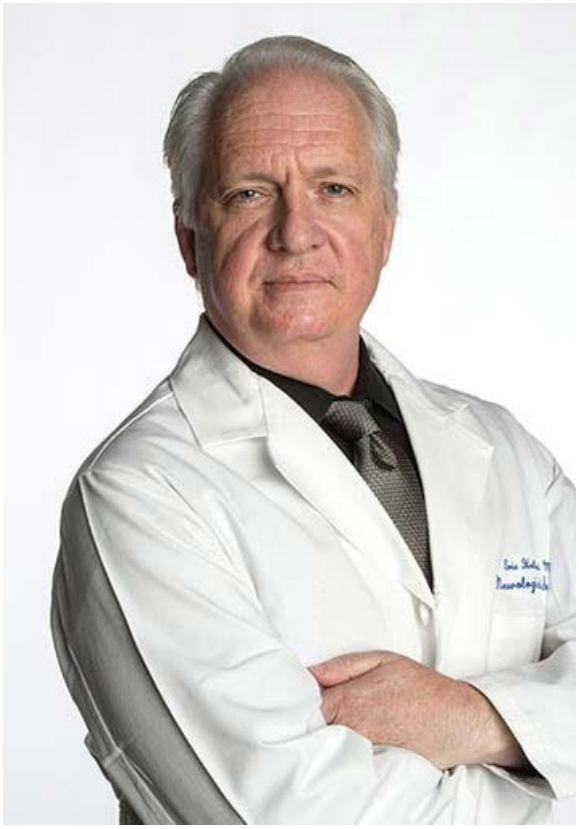

Study co-leader Dr. Eric Holland
Photo by Robert Hood / Fred Hutch News Service

As cancers develop, they accumulate a host of genetic alterations. Sometimes, this includes gain or loss of whole chromosomes. But when tumor cells gain a whole chromosome, they carry extra copies of hundreds or thousands of genes, making it difficult to pinpoint which are key players in cancer development, progression and treatment response.

Researchers at Fred Hutchinson Cancer Research Center and the Dana-Farber Cancer Institute have developed a computational method to sift the important cancer-promoting genes from thousands of irrelevant genes.
The team used the approach to figure out why gaining all of chromosome 7 increases aggression of a certain type of brain cancer called glioblastoma and recently reported their findings in Genes & Development.

“When you have a big chunk of DNA that is gained or lost, lots of genes are affected. But only some provide a selective advantage to the tumor, said Dr. Eric Holland, who directs the Human Biology Division and led the study with Dana-Farber computational biologist Dr. Franiska Michor. Now we have a way to quantify across a big chunk of DNA what s driving the tumor .

The gain of whole chromosome 7 is an early event in the development of one of the more aggressive types of glioblastoma. Platelet-derived growth factor A, or PDGFA, is located on the tip of chromosome 7 and actively promotes glioblastoma development.. But when glioblastoma cells could acquire extra copies of PDGFA by simply amplifying the tip of chromosome 7, why do they instead replicate the whole thing?

Holland and Michor set out to solve the mystery. Michor's group developed theoped the mathematical models that allowed the collaborators to scan across all the genes coded on chromosome 7 that, when increased in copy number, might give glioblastoma cells a leg up. One gene, homeobox A5, or HOXA5, stood out. Homeobox genes encodecode transcription factors that control whether other genes are turned on and are usuallyy expressed early in development. Holland's team examined what cancer cells migh gainn from having more copies of HOXA5.

Extra HOXA5 by itself doesn't cause brain tumors. But the researchers found that extra HOXA5 made PDGFA-driven glioblastomas more aggressive and resistant to radiation therapy. They saw that glioblastoma patients whose tumors had increased levels of HOXA5 had decreased survival, and they confirmed this association in a preclinical model of the highly malignant disease.

Holland's group also found that HOXA5 levels are increased in glioblastoma tumors that have recurred after treatment. Mouse glioblastoma cells with elevated HOXA5 levels multiplied more than those with normal amounts of the gene. HOXA5 also appears to protect glioblastoma from the damaging effects of radiation. By gaining an extra chromosome 7, glioblastoma cells gain both PDGFA's cancer-promoting power and HOXA5's ability to both promote cell growth and protect against damage.

Holland and Michor plan to apply their method to gaining a deeper understanding of cancer-contributing genes in other tumors characterized by the gain or loss of large pieces of DNA.

"It gives us a window of understanding we didn't have before," Holland said.

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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.

TAGS: brain cancer, Eric Holland, glioblastoma, Good News, Human Biology, Tumor specific translational research