NEW TARGETS FOR CHILDHOOD BRAIN TUMORS IDENTIFIED

NEURONS, IMMUNE CELLS WORK TOGETHER TO PROMOTE TUMOR GROWTH IN NEUROFIBROMATOSIS TYPE 1

Children with the genetic condition Neurofibromatosis type 1 (NF1) can develop brain and nerve tumors. If a tumor develops within the optic nerve, which connects the eye and the brain, the child may lose his or her vision.

New research at Washington University School of Medicine in St. Louis indicates that the growth of these brain tumors is driven by nearby noncancerous neurons and immune cells, and that targeting immune cells slows tumor growth in mice. The findings, published May 1 in *Nature Communications*, point to new potential treatments for low-grade brain tumors in people with NF1.

“The fact that nerve cells and immune cells interact to support a tumor is a new way of thinking about how tumors develop and thrive,” said senior author David H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor of Neurology and director of the Washington University Neurofibromatosis Center. “These tumors are arising in the nervous system, but until recently, few people had considered that the nerve cells themselves could be playing a role in tumor development and growth. These findings show that we have to consider nerve cells as participants, if not essential drivers, of cancer development.”

NF1 affects about one in every 3,000 people. It is caused by any one of a variety of mutations in the NF1 gene. While people with NF1 usually come to medical attention for birthmarks on their skin, nearly one in five children with NF1 will develop a brain tumor on the optic nerve, called an optic glioma.

To better understand what drives the development and growth of these brain tumors in people with NF1, first author Xiaofan Guo, MD, a graduate student in Gutmann’s research laboratory, and colleagues studied mice with NF1 mutations and optic gliomas. The team previously had discovered that the tumor cells in optic gliomas are interspersed with immune cells that help drive tumor formation and growth. But there is also another cell type in the vicinity of the tumor: neurons.

Suspecting that neurons also might be contributing to tumor growth, the researchers examined human neurons with NF1 mutations that had been grown from stem cells. They discovered that the neurons release a protein that activates immune cells known as T cells, which then produce proteins that promote the growth of tumor cells. The findings jibe with data from people with low-grade gliomas. By analyzing two publicly available datasets, the researchers found that patients whose tumors had more of a kind of T cell, known as CD8+ T, cells had reduced overall survival.

Disrupting the communication between neurons, T cells and tumor cells potentially could slow the growth of tumors, the researchers said. In the new study, they removed T cells from mice with optic gliomas, or prevented T cells from getting into the brains of such mice. In both scenarios, the researchers found that the optic gliomas grew more slowly in the absence of T cells.

“What we have here is a new way of thinking about how neurons and immune cells interact to control tumor growth, adding important new insights to the emerging field of cancer neuroscience,” Gutmann said. “We are excited about harnessing these critical interactions to develop new therapeutic strategies for childhood brain tumors.”

- Written by Tamara Bhandari - Washington University News Hub
PATIENT SPOTLIGHT: DANIEL

At six months of age, Daniel Crum was brought to the Washington University NF Clinical Program at St. Louis Children’s Hospital and received a diagnosis of Neurofibromatosis type 1 (NF1). Although both his father and grandfather had signs of NF1, they had gone without a formal diagnosis, and the news came as a shock. The Crum family immediately rallied around Daniel, and began seeing NF specialist, Dr. David H. Gutmann, every six months.

At two and half, Daniel’s parents noticed that he had a lazy eye – it was then that he was diagnosed with a brain tumor called an optic pathway gliomas (OPG). Through many years of chemotherapy and incredible difficulties, Daniel stayed strong, upbeat, and playful. His parents love that he never stopped playing and loving basketball, even in the midst of his treatments. At nine years old, his tumor stopped growing, reducing Daniel’s NF checkups to once a year. Although this was an indescribably difficult time for Daniel and his family, they made it through with their faith and the support of their community. They now try to help everyone they meet better understand NF1 and those who struggle with it.

In spite of his diagnosis, Daniel thrived in middle and high school. Capitalizing on his love of sports, Daniel became involved in his school’s basketball, football and golf teams. Even though his vision was severely impaired, Daniel played golf for all four years of high school, winning an award for being the first blind student to do so. By the time he graduated, he had won two more awards – he was presented with the Rosemary Zander Award for his ability to go above and beyond what was expected of him, and his class of 2013 began a new award in his name, honoring his dedication and strength, called the Crum Perseverance Award.

After graduation, Daniel brought that love of sportsmanship and athletics to his current job at the Enterprise Center. There, he works in Press Dining to feed the numerous reporters, sports writers, cameramen, and retired athletes who come through the center.

Now 24 years old, Daniel absolutely loves his job and excels at every aspect of it. He gets to know each of his customers on a first name basis, and frequently works in other departments when they need extra help. Recently, Daniel got to see and touch the Stanley Cup at an event for season ticket holders, which was incredibly exciting. His parents are so proud of everything he has accomplished, most importantly, his perseverance and fortitude in pursuing his dreams.

FDA APPROVES FIRST THERAPY FOR CHILDREN WITH NF1

On April 10, 2020, the US Food and Drug Administration (FDA) approved the drug selumetinib (Koselugo) for people with Neurofibromatosis Type 1 (NF1) who are 2 years of age and older. The first of its kind drug will be used to treat symptomatic, inoperable plexiform neurofibromas. These tumors are often detected in young children, and may involve the eye socket, face, arm, leg, back, chest, or abdomen.

The FDA approval came after a clinical trial conducted by the National Cancer Institute showed that nearly two thirds of patients had a positive response to the drug, with at least a 20% reduction in tumor volume. Of these patients, most had responses that lasted 12 months or longer. However, no patients experienced complete disappearance of their tumor.

“These are exciting times for families affected with NF1”, says NF Center Director, David H. Gutmann, MD, PhD. “This success is the result of decades of hard work by scientists, physicians, nurses, and patient advocacy groups.”
NEW STUDY FINDS NF1 MUTATIONS HAVE VARYING EFFECTS IN HUMAN BRAIN CELLS

In the recently published study in *Stem Cell Reports*, Corina Anastasiaki, PhD, Michelle Wegscheid, MD, PhD candidate, and colleagues sought to determine whether different NF1 gene mutations found in patients with NF1 have different effects on human brain cells. To achieve this, the authors used seven human induced pluripotent stem cell lines with different NF1 patient NF1 gene mutations to grow different brain cell types, both as individual cell types, like nerve cells (neurons), but also as three-dimensional (3D) mini-brains (cerebral organoids). They definitely showed that while all mutations increased the production of support cells (astrocytes), mini-brains with different NF1 mutations produced different numbers of neurons. This study opens the door to future investigations into how different NF1 mutations cause different features in people with NF1.

NEW STUDY HOPES TO IMPROVE MANAGEMENT OF BRAIN TUMORS IN YOUNG CHILDREN

Children with Neurofibromatosis type 1 (NF1) are at increased risk of developing low-grade brain tumors. While the majority of these brain tumors arise in the optic pathway (optic pathway gliomas), they can be located in other regions of the brain. In order to better define the MRI features and natural history of non-optic pathway tumors (non-OPTs) in children with NF1, Dr. Jasja Mahdi and her colleagues conducted a retrospective cross-sectional analysis of 64 children with NF1 harboring 100 non-OPTs. Their findings showed that the majority of non-OPTs grew over time and caused medical problems. In addition, she also identified a small subset of children with a particularly aggressive form of brain tumor, which tended to arise in younger children. The researchers hope that these findings will improve the recognition and management of children with NF1. This study was published in *Neurology*.

GUTMANN RECEIVES ADVOCATE OF HOPE AWARD

David H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor and Vice Chair for Research Affairs in the Department of Neurology at Washington University School of Medicine in St. Louis, has received the Advocate of Hope Award from the National Neurofibromatosis (NF) Network. The NF Network is a nonprofit organization dedicated to helping people living with NF.

The Advocate of Hope Award honors Gutmann for his work in the field of NF and his compassion for NF patients. For more than 25 years, he has devoted his academic career to improving the lives of people with NF, through laboratory and clinical research. He established the NF clinical program at St. Louis Children’s Hospital in 1994, which serves as a regional referral center for patients. In addition, he founded and directs the Washington University NF Center, one of the world’s largest centers focused on accelerating the pace of scientific discovery and its application to the care of individuals with NF.
CHECK OUT THE NEW NF CENTER BLOG PAGE: COURTNEY’S CORNER

Courtney Dunn is a physical therapist with over 25 years of experience in providing therapy services for children. She earned her Bachelor of Physical Therapy from the University of Missouri, Columbia in 1995 and her Doctorate of Pediatric Therapy in 2010. Courtney currently works at St. Louis Children’s Hospital, where she is also part of the Washington University Neurofibromatosis (NF) Center multidisciplinary team. As an integral member of our NF care team, she provides essential therapy assessments and recommendations during outpatient clinic visits with Drs. Gutmann and Morris.

Courtney has provided therapy for children in a variety of settings, including inpatient rehabilitation, outpatient therapy, home health, early intervention, school settings, and in multidisciplinary clinics. Since joining the NF Center in 2010, she has spearheaded several clinical research studies relating to motor skills in children with NF1.

Courtney’s approach to PT involves treating the whole child. She addresses sleep patterns, sensory modulation, strength, muscle balance, and coordination to support developing a healthy and active lifestyle. In this regard, Courtney has collaborated with members of the NF Center to create community-based complementary care programs: Beat NF, for preschool-aged children and Club NF, for school-age children, provide motor and social development through community partnerships throughout the St. Louis region.

When not working as a therapist, Courtney adores spending time with her two teenage children and traveling with her husband. Additionally, she enjoys crafts, running, and volunteering in her community.

Through Courtney’s Corner, she will be exploring a variety of topics that support children with NF achieve the best version of themselves.

Visit the blog page at: https://nfcenter.wustl.edu/courtneys-corner/

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