NF CENTER RESEARCHERS DISCOVER A NEW TARGET FOR POTENTIAL MPNST TREATMENT

Young adults with Neurofibromatosis type 1 (NF1) are at risk for developing a rare type of sarcoma called a malignant peripheral nerve sheath tumor (MPNST). Unfortunately, even with aggressive surgery, radiation, and chemotherapy, these cancers typically recur or spread to other parts of the body, and most patients die within five years.

In an effort to discover new genetic mutations in these deadly sarcomas, Dr. Angela Hirbe and her colleagues at the Washington University NF Center employed a sequencing platform currently available to most cancer patients. This screening platform was designed to detect mutations in genes that can be targeted by available drug compounds.

Dr. Hirbe found that one-third of these tumors harbored a mutation in the TYK2 gene, such that the protein made by this gene was increased in 60% of MPNSTs examined. The TYK2 protein is important for the growth and survival of cancer cells. In addition, there are drugs in development that can block the function of TYK2.

Ongoing work in Dr. Hirbe’s laboratory is focused on determining whether TYK2 expression identifies a subgroup of MPNSTs most likely to respond to this class of drugs.

This study was published in the journal, Cancer.

FEMALE HORMONES INCREASE RISK OF VISION LOSS IN NF1

Girls with a rare genetic disorder caused by mutations in a gene known as \textit{Nf1} are much more likely to lose their vision than boys with mutations in the same gene. And now, researchers at Washington University School of Medicine in St. Louis believe they know why: Female sex hormones activate immune cells that damage the nerves necessary for vision.

The study was carried out in mice to mimic a common brain tumor arising in a genetic condition called neurofibromatosis type 1 (NF1). The findings, available online in The Journal of Experimental Medicine, suggest that blocking female sex hormones or suppressing the activation of specific immune cells in the brain could save the eyesight of children with NF1-associated brain tumors.

“The take-home message is that a child’s sex matters when it comes to this disease,” said David H. Gutmann, MD, PhD, the David O. Schnuck Family Professor of Neurology and the study’s senior author. “We’ve identified what leads to this difference in vision loss, and that suggests novel potential therapies to treat this serious medical problem in children. Understanding why boys and girls with mutations in the same gene have different outcomes presents unprecedented opportunities to fix the problem.”

NF1 causes children and adults to develop brain and nerve tumors. These tumors are typically benign – meaning they don’t spread to other parts of the body and lead to death – but they still can have serious consequences.

Nearly 20 percent of children with NF1 develop brain tumors that involve the optic pathway, affecting the nerves that carry vision-related signals from the eye to the brain. In some children, these tumors cause vision loss; however, it is not currently possible to predict who will experience vision decline and who will not.

Two years ago, Gutmann and colleagues were the first to report that girls with NF1 were five times more likely to lose their sight than boys, even though there were no clear differences in the size of the tumors between boys and girls.

To discover why girls are more likely to experience vision decline from their tumors, Gutmann, postdoctoral researcher Joseph A. Toonen, PhD, and colleagues studied mice with \textit{Nf1} gene mutations specifically engineered to develop tumors on the optic pathway. Both male and female mice developed tumors that were identical in size and growth rates; however, only the female mice exhibited significant nerve damage and vision loss.

The researchers found that the tumors contain a type of immune cell called microglia. Strikingly, female mice had three times more microglia within these tumors than male mice. When activated, microglia release a range of toxic compounds that can cause collateral damage to nearby nerve cells. When they are activated, they release those compounds and sometimes cause collateral damage to nearby cells. They also found that the microglia within the optic tumors from female mice were activated, and the neurons near the tumors were damaged.

To test whether sex hormones could account for these differences, Dr. Toonen removed the ovaries from female mice and the testes from male mice. The number of damaged and dying cells in the retina – a light-sensitive layer of nervous tissue in the eye – did not change in the castrated males. But in the females without ovaries, fewer cells in the retina died and the number of activated microglia within the tumors was also decreased. These findings suggest that female sex hormones may cause microglial activation and subsequent neuronal damage.

When researchers used a drug to block the action of the female sex hormone in female mice carrying the \textit{Nf1} mutation, they saw a drop in the number of activated microglia and a decrease in retinal damage and nerve cell death. Moreover, their team identified the specific nerve-damaging toxins produced by these activated microglia. Future therapies to attenuate vision loss in children with NF1-optic tumors might target these compounds.

Gutmann stressed that boys with NF1 also experience vision loss, just not as frequently as girls, and that male \textit{Nf1} mice harbor some activated microglia within their tumors. He believes that the process of microglial activation and ensuing neuronal damage is the same in males and females, but that the presence of female sex hormones increases the microglial activation, leading to greater optic nerve damage and vision loss.

This article, written by Tamara Bhandari, originally appeared in the Washington University School of Medicine News Hub on December 13, 2016. Read more of about this article at https://medicine.wustl.edu/news/female-hormones-increase-risk-vision-loss-rare-genetic-disease/
WASHINGTON UNIVERSITY NF CENTER ATTENDS SCIFEST

On April 15, 2017, Washington University NF Center neuroscientists had a great time at the SCIFEST: Brain Matters event, held at the St. Louis Science Center. SCIFEST is a series of weekend expos that allow children to connect with STEM scientists, providing a behind-the-scenes look at real science.

Visitors to the NF Center booth had the opportunity to learn more about Neurofibromatosis Type 1 (NF1) and NF Center research through a variety of interactive games and activities. DNA bracelet-making demonstrated how DNA mutations occur and the many different NF1 gene mutations that are possible. A “spot-the-difference” iPad game enabled visitors to become scientists by identifying images of abnormal brain cells in comparison to normal cells. Additionally, NF1 symptoms, and the different cells causing them, were discussed with visitors through fun, interactive activities.

SCIFEST: Brain Matters was made possible through a partnership between St. Louis Science Center and Washington University in St. Louis.

DR. MATTHEW STROH JOINS THE GUTMANN LABORATORY

After graduating with honors with a PhD in Neuroscience from the University of Kansas Medical Center (KUMC), Dr. Stroh joined the laboratory of Dr. David Gutmann in the Washington University Neurofibromatosis (NF) Center as postdoctoral research fellow.

Matt’s interest in research was first piqued during his undergraduate years when he started working in the laboratory of Dr. Brian Ackley, whose research focuses on the interactions between nerve cells (neurons) and their environment. During his time in the Ackley lab, he worked on axon guidance in the worm. Ultimately, he spearheaded a project that used chimeric/recombinant proteins to investigate neuron development.

After receiving his Bachelor’s of Science in Biochemistry degree from the University of Kansas in 2012, he received a Neurological and Rehabilitation Sciences Fellowship through the Landon Center on Aging, and initiated multiple projects and collaborations under the guidance of Dr. Hao Zhu. Dr. Stroh’s dissertation project aimed to characterize the effects of an important protein called NCB5OR on neural tissue development. He found that NCB5OR deficiency in the mouse brain had dramatic effects on iron and metabolic balance, which are disturbed in disorders like Alzheimer’s and Parkinson's disease. In addition to this research, Dr. Stroh helped design and develop a novel method of detecting methylation in the mitochondrial genome using advanced mass spectrometry.

Dr. Stroh’s work in the Gutmann Laboratory is primarily focused on understanding how growth is controlled in brain cells relative to other tissues. Matt is particularly interested in determining how cells differentially use a limited number of critical signaling molecules to create a high degree of functional diversity.
CHECK OUT SLCH RADIO ROUNDS PODCAST WITH DR. STEPHANIE MORRIS

Listen as Stephanie Morris, MD talks about the management of children with NF1 at the NF Clinical Program at St. Louis Children’s Hospital, and how new clinical research at the Washington University NF Center is providing new ways to care for people with this condition.

To download podcast visit: http://www.stlouischildrens.org/health-care-professionals/radio-rounds

UPCOMING EVENTS

CLUB NF FAMILY PICNIC
JUNE 3, 2017, 11am-1pm

CLUB NF MAGIC & CIRCUS
AUGUST 5, 2017

For more details, or to RSVP, please visit our events website at: https://nfcenter.wustl.edu/events/

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