Pediatric Brain Tumors - Epigenetic Causes

To demonstrate the use of quantum biology (QB), the following two types of pediatric brain tumors were selected and subjected to the process.

All epigenetic factors addressed in the two examples can be reduced to the elemental constituents (elements/minerals and amino acids) for verification by qualified computational biologists.

Ependymoma Brain Tumors

QB modeling of ependymomas has identified the following factors as several of epigenetic causal paths for these tumors.

Each of the following assertions can be verified using bioinformatic search that links them to ependymomas.

- Copy Error mechanism that result in BRC-Abl mutation
- Nuclear Restorer Factor mutations; e.g. NRF
- The interactions of and imbalances between calnexin - calmodulin and calcineurin; aka YAP1 - YAP2 and HIPPO

A fourth causal factor is histone mutation; e.g. H3K27me3 that can be identified through bioinformatic search. We have set aside histone activity as a task for our TBD DNA Repair partner(s) that seek to address cancers.

https://medicalxpress.com/news/2018-01-approach-tumor-genetic-drivers-unknown.html

Researchers develop approach for identifying tumor targets when genetic drivers are unknown

January 5, 2018, Baylor College of Medicine

Ependymoma is a type of brain tumor that is resistant to chemotherapy. While genomic sequencing has provided molecular targets and resulted in precision oncology therapies for many cancers, **effective targets for ependymomas have remained elusive**. Dr. Stephen Mack, assistant professor of pediatrics – oncology and new faculty member at Baylor College of Medicine and Texas Children's Hospital, **and colleagues have developed a framework for discovering targets in ependymomas, and other cancer that lack known genetic drivers, thereby also providing insights into treatment strategies.**

The study appears in *Nature*.

"Ependymoma is the third most common cancer type in children, and there are no current targeted therapies available. Even with surgery and radiation, the more aggressive tumors will keep coming back," said Mack. "Traditional genomic sequencing revealed that these tumors are relatively silent, meaning mutations in the DNA are few. However, we found changes in the way the DNA is folded and packed and how the genes are regulated."

The research team developed a more in depth approach to find the actively transcribed genes that play a role in tumor formation, as opposed to identifying mutations alone. A specific process in the tumor's epigenome, **called histone acetylation, tells genes to turn on or off, thereby regulating the action of the DNA. The team assayed the markers for this process in the ependymoma tumor type and found that the genes are highly active in tumor development.**

"This is an important strategy to develop because we are looking at gene regulation specifically **as a new approach to targeted therapy for cancers in which there are no known molecular targets**," said Mack. "It can act as a complimentary tool to genomic sequencing to identify potential targets, and could later be useful in developing drug treatment plans."

"As a neurosurgeon, it is very frustrating to operate on babies with ependymoma, and then not have any effective chemotherapy. This new approach to finding effective chemotherapies discovered by Dr. Mack offers a new way forward in this very difficult disease that affects the youngest members of our society," said Dr. Michael Taylor, neurosurgeon and senior scientist in the Program in Stem Cell and Developmental Biology at the Hospital for Sick Children in Toronto.

Explore further: Molecular super enhancers: A new key for targeted therapy of brain cancer in children

More information: Stephen C. Mack et al. Therapeutic targeting of ependymoma as informed by oncogenic enhancer profiling, *Nature* (2017). **DOI: 10.1038/nature25169**

Journal reference: Nature

Pilocytic Astrocytoma

Quantum biology in conjunction with bioinformatic search will verify the following as factors that cause of pilocytic astrocytoma.

- Calmodulin (p21 and Ras signaling) with calcineurin as the enzyme
- Calmodulin (p21 and Ras signaling) with p53 (or other calpains; e.g. p63 or p73) as the enzyme; MDM/HDM signaling

The following is provided for discussion with qualified computational biology professionals.

Alignment of Molecules: For Explanation , Discussion and DIY Exercise

TNF-Alpha: TGF- Alpha: VEGF-A (Calnexin) Density (CD-4)
Calcium – threonine – magnesium (BRCA1) **p16**
Calcium – serine – magnesium (BRCA2) **p18**
Calcium – cysteine - magnesium (BRCA3) **p19**

TNF-Beta: TGF-Beta: VEGF-B (Calmodulin) Motility (CD-8)
Calcium – phenylalanine – magnesium (HRas) **p21**
Calcium – tyrosine – magnesium (KRas) **p27**
Calcium – tryptophan – magnesium (NRas) **p57**

TNF-Gamma: TGF-Gamma: VEGF-C (Calcineurin)
Modulatory Enzyme: IFNγ and Th17 cells (CD-25)
Iron – serine – Manganese
Iron – cysteine – Manganese
Iron – threonine – Manganese

Examples of alternative designations for the IFNγ "enzymes" that have evolved include; AKT, mTOR, PTEN, NF-kB, and MYC.

https://medicalxpress.com/news/2019-02-year-old-brain-tumor-left-paralyzed.html

FEBRUARY 18, 2019

A 9-year-old's brain tumor left her paralyzed. After a Hopkins trial, doctors are using the word 'cure.'

by Sarah Meehan, The Baltimore Sun

Eight years ago, Kaitlyn Dorman was so sick with cancer she was paralyzed and her vision blurred. Dependent on a wheelchair, the little girl was confined to living on the first floor of her family's home.

Now 17, Kaitlyn can walk and see clearly. And she's staring down her final months at Liberty High School, weighing college acceptance letters and composing tunes on her beloved piano.

She came to Dr. Eric Raabe as a 9-year-old with an aggressive brain tumor, and today he doesn't hesitate when he describes her cancer outcome.

"We're using the c-word, for cure," said Raabe, an associate professor of pediatric oncology at the Johns Hopkins Kimmel Cancer Center. "It's not coming back."

In a matter of months, treatment with an experimental drug melted Kaitlyn's debilitating tumor from the size of a walnut to the size of a grain of rice, restoring the mobility and sight she lost as the tumor grew. And eight years later, the mass has not returned.

The kind of treatment Kaitlyn received is what's known as a targeted therapy—using a drug that only works in certain patients, on specific tumors by attacking particular molecules that allow the tumor to grow. It won't work for all kids with the same kind of cancer. Researchers at Hopkins and across the country are conducting another trial of the drug to learn from Kaitlyn's outcome. They want to know how to make the treatment more effective for other pediatric brain tumors.

Such highly tailored treatment is the future of cancer care, doctors say.

While many children survive the cancer Kaitlyn had, a rare few enjoy the quality of life she's achieved—something researchers are striving for in other patients with the same condition.

Low-grade gliomas, the category of brain tumor Kaitlyn developed, are among the most common brain tumors in children. Her specific type of tumor—a pilocytic astrocytoma—is a slow-growing mass that develops in the supporting cells of the brain. It accounts for about one in five brain tumors in children, according to the American Cancer Society.

About 95 percent of children who develop pilocytic astrocytomas survive at least five years from their diagnosis, the American Cancer Society reports. But the tumors can constrict optic nerves and put pressure on other parts of the brain, causing some patients to go blind, have problems with balance or develop other disabilities that can last a lifetime if the tumors don't recede.

"Right now there's still a lot of patients that have lost all their sight ... even though their tumor doesn't grow anymore," Raabe said. "What's exciting in Kaitlyn's case, and in the

case of a few other patients where we've actually seen tumors really shrink down, is that that loss of sight isn't permanent.... .The eye is fine, the nerves are fine, the rest of the brain is fine."

Johns Hopkins researchers say they've unlocked key to cancer metastasis and how to slow it

An onlooker would never know Kaitlyn was once paralyzed in both legs and one arm. She recovered her sight and mobility—down to her toes and, crucially, her fingers.

A piano player from age 5, Kaitlyn continued playing through her cancer treatment, even when she could play only with one hand. Piano lessons later became a form of physical therapy as she regained dexterity in her left hand.

She now plays in a band called Psychosomatic, composes and records songs, and has a mini-album in the works. Colleges have taken notice of Kaitlyn's musical talents—though she also talks of studying Japanese—and her acceptance letters are rolling in, including one from Boston's Berklee College of Music.

Other patients aren't so fortunate. Though their tumors stop growing, they often don't shrink, leaving patients permanently disabled. Many such tumors are inoperable because of their delicate position in the brain—often near the meeting of optic nerves, in the cerebellum or, in Kaitlyn's case, in the brain stem.

After Kaitlyn was diagnosed, doctors placed her on a standard chemotherapy regimen, which typically arrests the cancer's development. But her tumor resisted the first line of drugs, continuing to grow more aggressively.

Due to the high survival rate, there's little research about low-grade glioma in children, Raabe said.

"That has been a problem for patients like Kaitlyn, whose tumor doesn't read the textbook and doesn't respond to the upfront therapy," Raabe said.

More research is being conducted now as families of patients with low-grade gliomas have demanded and funded alternative treatments, said Amy J. Weinstein, director of pediatric low-grade astrocytoma research and advocacy for the North Carolina-based Pediatric Brain Tumor Foundation. Everolimus, the drug Kaitlyn received, was one of the first targeted therapies to be tested in children with low-grade brain tumors, and that trial laid the groundwork for other drug trials, she said.

"Until everolimus came along there really wasn't anybody studying how can we stop these tumors from growing and impacting the kids," Weinstein said.

At the time Kaitlyn was sick, Hopkins was one of a dozen institutions offering a clinical trial using everolimus to treat low-grade gliomas in children.

The oral drug was developed by the Swiss pharmaceutical company Novartis under the brand name Afinitor. Everolimus is already approved for use in adults by the U.S. Food and Drug Administration to prevent rejection of organ transplants and to treat some cancer patients. For cancer, it works by inhibiting proteins that cancer cells need to grow.

"The amazing thing is that there are these drug agents that are already on the shelves at pharmaceutical companies that just haven't been tested in targeted ways," Weinstein said.

The first study, in which Kaitlyn was treated, confirmed the safety of everolimus in pediatric patients with low-grade glioma and found that some patients responded to the medicine. Now in a follow-on trial, researchers in the Pacific Pediatric Neuro-Oncology Consortium are studying brain tissue from patients to establish which are the best candidates for the drug based on the biology of their tumors. Hopkins is one of the 18 institutions in the consortium.

Kaitlyn's caregivers offered the experimental alternative after standard chemotherapy was unsuccessful.

"All we really wanted to know was that our daughter was going to get better," said Mary Dorman, Kaitlyn's mom. "I wasn't apprehensive about the clinical trial or even anything we had to do in terms of collecting additional data or monitoring her. As a parent, I think we would have done anything to give her an opportunity to survive the tumor that she had."

Kaitlyn's outlook remained sunny. Hospital visits didn't seem like a heavy burden, she said, despite having ports placed in her body and shunts surgically inserted to drain spinal fluid.

"It was just a doctor's appointment," Kaitlyn said. "When I got a port ... it didn't really feel like the seriousness of getting treated for cancer. It just kind of felt like I was getting my ears checked or whatever."

But her condition was serious, and she felt worst before she began taking everolimus. Symptoms that began with a mild tremor in her hand deteriorated into the paralysis of her arm and legs. Pressure from the tumor caused her right pupil to dilate, blurring her vision. And she developed a stomach infection during a hospital stay.

She was home-schooled from the February of her fourth-grade year to November of fifth grade.

"I couldn't walk and I couldn't really see," she said. "Hearing that there was, like, something else that could possibly do something, could possibly make everything go away, I was like, 'Awesome. OK, let's try it.' "

When she began taking the drug, she saw benefits almost immediately, she said. And it wasn't long before she regained mobility.

"It was like a snap of the fingers—everything was just working again," she said. "The second it started happening I was like, 'I need more of this.' I need to, like, start moving again, so then I could start walking and start running."

Mary Dorman recalled her daughter summoning the family to her bedside to demonstrate she could lift her left arm above her head again—a trick she later showed Raabe during a hospital visit.

"We didn't even need the MRI picture to know that it was working," Raabe said.

Kaitlyn stopped taking everolimus after experiencing liver damage from the pills—a known side effect. Still, her tumor continued to shrink. And for the five years doctors tracked her recovery after the treatment, it did not return.

Because Kaitlyn had the best response of any patient in the trial, researchers are looking to replicate her results as they continue studying everolimus. Others in the first trial also saw improvements, but some didn't.

"How do we get more patients to have a response to this drug that are like Kaitlyn?" Raabe said. "(We're) figuring out how to make the drug be the right drug for the right patient at the right time."

Raabe expects the current everolimus trial to conclude within the next year. He said future studies could examine how everolimus can make traditional chemotherapy drugs more effective when they're used simultaneously.

Dr. Daphne Haas-Kogan, chair of the radiation oncology department at the Dana-Farber Cancer Institute in Boston, said targeted therapies like everolimus that are tailored to an individual's cancer—down to the molecules—will be transformative for cancer treatment.

Drugs like everolimus are particularly attractive because they're taken orally, require fewer hospital visits and are not toxic like traditional chemotherapy, Haas-Kogan said. She expects a combination of chemotherapy paired with targeted agents like everolimus to dominate cancer care in the future.

Doctors have a "growing armada" of targeted agents that can be used to treat particular tumors, Haas-Kogan said, but their grasp on which drugs will succeed in particular patients remains limited.

Studies like the one at Hopkins provide doctors with a deeper understanding of which patients are more likely to respond, she said.

"Every person's brain tumor is unique—the genetic makeup and the mechanism that led its development and its response to treatment," Haas-Kogan said. "It's personalizing the care—whether it's a child or an adult—that's going to be the most bang for the buck."

Weinstein cautioned that researchers have not yet documented possible long-term side effects of drugs like everolimus because the treatment is so new.

But, she added, "they give (pediatric low-grade astrocytoma) patients the greatest sense of hope for a normal childhood and for a normal future."