

Promising drug target identified in medulloblastoma

March 26 2015

Scientists at Dana-Farber/Boston Children's Cancer and Blood Disorders Center have identified a protein critical to both the normal development of the brain and, in many cases, the development of medulloblastoma, a fast-growing brain tumor that usually strikes children under 10 years of age.

As reported in the journal *Developmental Cell*, when the researchers cut the level of the protein, called Eya1, in half in mice prone to develop [medulloblastoma](#), the animals' risk of dying from the disease dropped dramatically. The findings point to Eya1 as a prime target for new drugs for this type of medulloblastoma, and for other cancers that share the same path of development.

"Medulloblastomas account for about 18 percent of all brain tumors in children," said the study's senior author, Rosalind Segal, MD, PhD, of Dana-Farber/Boston Children's. "Today, 60 to 70 percent of patients can be cured, but the major therapies - surgery, radiation, and chemotherapy - have significant downsides. There is great interest in developing more targeted therapies that can attack the cancer while producing milder side effects."

Medulloblastomas are divided into four molecular subtypes. The current study focused on one in which tumor growth is driven by a cell-signaling pathway initiated by the Sonic Hedgehog (Shh) protein.

"The Sonic Hedgehog subtype accounts for about 30 percent of all

medulloblastomas," Segal remarked. "And, in fact, the Shh pathway is activated in as many as one-third of all human cancers. While Shh signaling clearly plays a key role in many medulloblastomas, the basic mechanism by which it is controlled hasn't been clear."

The new study looked at one of the less-explored aspects of that mechanism. While much research has centered on the role of enzymes known as kinases in cancer, less attention has been given to kinases' biological counterparts - enzymes known as phosphatases. Kinases attach compounds known as phosphate groups to proteins; phosphatases remove phosphate groups. Together, kinases and phosphatases act as a red light/green light mechanism for protein activity: kinases generally switching a protein on, phosphatases switching it off.

To learn which phosphatases are most important for the Sonic Hedgehog pathway to function, first author Adriana Eisner, PhD, of Segal's lab measured the amounts of all 380 types of phosphatases in medulloblastoma cells driven by Shh signaling. Eya1 stood out because it was very highly expressed - produced in large amounts - in the cells.

Follow-up experiments in mice confirmed Eya1's key role in the Shh pathway, both in normal brain development and in medulloblastoma. In embryonic mice, the development of the rear portion of the brain - a process dependent on Shh signaling - faltered in the absence of Eya1. In young mice genetically predisposed to develop medulloblastoma, reducing the levels of Eya1 by half (by canceling one of the two copies of the gene responsible for the protein) caused death rates from the disease to plunge. Normally, 35 percent of such at-risk animals die of medulloblastoma. By contrast, only 10 percent of those with lowered Eya1 levels succumbed to the disease.

One of the potential advantages of Eya1 as a drug target in medulloblastoma is that it belongs to a subfamily of phosphatases with

only four members in it. As a result, drugs that target Eya1 are likely to interfere with only a few other phosphatases, potentially reducing the severity of side effects, the researchers say.

Provided by Dana-Farber Cancer Institute

Citation: Promising drug target identified in medulloblastoma (2015, March 26) retrieved 24 April 2024 from <https://medicalxpress.com/news/2015-03-drug-medulloblastoma.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.