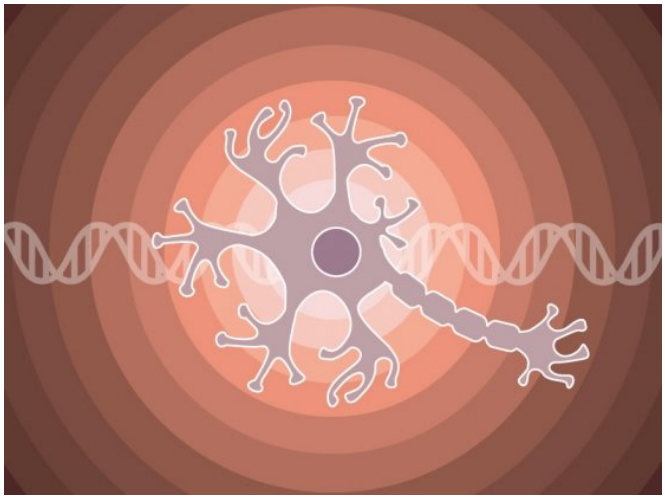
Researchers identify an indirect way of countering a key genetic lesion in neuroblastoma

5 December 2017, by Tom Ulrich



Credit : Susanna M. Hamilton, Broad Communications

Pediatric cancers tend to have relatively "quiet" genomes compared to tumors in adults. They harbor fewer discrete genetic mutations, especially in genes for readily "druggable" targets (such as protein kinases). Instead, these tumors tend to feature other kinds of genetic alterations, such as duplications or translocations.

Such is often the case in high-risk forms of neuroblastoma, a rare childhood tumor of the nerves. The gene MYCN is frequently amplified (duplicated many times) in these cancers, forcing the tumor cells to overproduce a transcription factor—a kind of protein that helps turn genes on and off and is very difficult to target directly.

In a paper in the *Journal of Clinical Investigation*, a team led by postdoctoral researcher Liying Chen and Broad institute member and Dana-Farber Cancer Institute pediatric hematologic malignancies co-director Kimberly Stegmaier (both with the Broad Cancer Program) announced the discovery of a potentially druggable weakness in MCYN-amplified neuroblastomas: a survival dependency on EZH2, a MYCN target gene that helps manage many aspects of a cell's identity and behavior.

The starting point for the team's study was the Cancer Dependency Map, a joint effort bringing together researchers from the Cancer Program's Project Achilles and Cancer Data Science teams, the institute's Genetic Perturbation Platform, and other Broad groups. Chen, Stegmaier, and their colleagues used the Dependency Map team's genome-scale CRISPR screening data to discover their initial list of neuroblastoma targets, a list in which EZH2 and two of its biochemical partners, EED and SUZ12, featured prominently.

Through a combination of informatic, genetic, and pharmacological experiments using cell lines and animal models, the team found that:

1. The MYCN protein directly governs EZH2 expression.
2. The EZH2 protein, in turn, blocks tumor suppressor activity in cancer cells and prevents them from growing into mature neurons (neuroblastoma cells tend to look and act like "immature" nerve cells).
3. Silencing EZH2 using RNA interference or inhibiting it with drug compounds impaired neuroblastoma growth in vitro and in vivo.

Taken together, the team's findings suggest that EZH2 could be a potent and attractive target for developing sorely needed new treatment options against high-risk neuroblastoma.

More information: Liying Chen et al. CRISPR-Cas9 screen reveals a MYCN-amplified

neuroblastoma dependency on EZH2, *Journal of Clinical Investigation* (2017). DOI: 10.1172/JCI90793

Provided by Broad Institute of MIT and Harvard