Biomarker may identify neuroblastomas with sensitivity to BET bromodomain inhibitors

21 February 2013

Neuroblastoma, the most common malignant tumor of early childhood, is frequently associated with the presence of MYCN amplification, a genetic biomarker associated with poor prognosis. Researchers have determined that tumors containing MYCN amplification are sensitive to a new class of drugs, BET bromodomain inhibitors.

The researchers made this discovery in a preclinical study, which was funded in part by a Stand Up To Cancer Innovative Research Grant and was published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"BET bromodomain inhibitors are a class of drugs that many researchers are hopeful may offer a new therapeutic option for treating patients with certain cancers," said Kimberly Stegmaier, M.D., assistant professor of pediatrics in the Department of Hematology/Oncology at Dana-Farber/Children's Hospital Cancer Center in Boston, Mass. "The challenge has been identifying biomarkers that can help direct clinical translation of these drugs by pinpointing those patients with the highest likelihood of response."

To identify genetic biomarkers of responsiveness to BET bromodomain inhibitors, Stegmaier and colleagues screened more than 600 cancer cell lines with known genetic characteristics for sensitivity to a prototypical BET bromodomain inhibitor.

Using this high-throughput, cell-based screening process, the researchers found that neuroblastoma cells in which the MYCN gene was amplified were sensitive to BET bromodomain inhibitors.

"Neuroblastoma is a devastating childhood cancer, and only a minority of children with high-risk disease will be cured with currently available treatments," Stegmaier said. "Prior research has shown that MYCN amplification is common in neuroblastoma, but it has been an elusive drug target."

To further validate their findings, the researchers tested a BET bromodomain inhibitor, from the laboratory of James E. Bradner, M.D., at the Dana-Farber Cancer Institute, using cultured MYCN-amplified neuroblastoma cell lines and three animal models of MYCN-amplified neuroblastoma. Together, they found that the drug decreased levels of MYCN protein in cultured cells, and that this led to impaired cell growth and cell death. In each animal model, including a mouse model of neuroblastoma that is known to be resistant to many standard therapies, the drug was shown to have anti-tumor effects and to prolong survival.

"My Stand Up To Cancer grant, which focused on modulating difficult drug targets in childhood cancers, was instrumental to us being able to do this exciting work," Stegmaier said. "These types of studies are generally considered high-risk, particularly because they start with unbiased screening, and they are generally less likely to be supported by traditional sources of funding."

Provided by American Association for Cancer Research