New potential treatment for aggressive brain cancer in children

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Chicago...Using state-of-the-art gene editing technology, scientists from Ann & Robert H. Lurie Children's Hospital of Chicago have discovered a promising target to treat atypical teratoid/rhabdoid tumor (AT/RT) - a highly aggressive and therapy resistant brain tumor that mostly occurs in infants.

They found that these tumors' growth and tendency to metastasize are regulated by a protein kinase called Polo-like kinase 4 (PLK4), which is increased in AT/RT. They also have demonstrated that an experimental drug, a PLK4 inhibitor, stopped tumor growth. Findings were published in *Pediatric Blood & Cancer*.

"This is the first time that PLK4 has been described as a therapeutic target for brain tumors or in pediatric cancer," said lead author Simone T. Sredni, MD, PhD, Associate Professor of Pediatric Neurosurgery at Northwestern University Feinberg School of Medicine and cancer researcher at the Stanley Manne Children's Research Institute at Lurie Children's.

Sredni and team were able to identify PLK4 as a potential target for treatment by using a novel gene editing technology called CRISPR/Cas9. It allowed them to mutate individual kinase genes - key regulators of cell function - in order to reveal the kinase that most significantly affected tumor cell growth. Then they targeted that kinase with an available kinase inhibitor, currently being tested for breast cancer.

Sredni and colleagues also found that the PLK4 inhibitor (CFI-400945) was safe for normal tissue, while attacking the cancer cells. "The drug we used to inhibit PLK4 significantly impaired tumor proliferation, survival, invasion and migration, while sparing normal cells," said Sredni. "This may be a paradigm shift for the treatment of AT/RT and possibly other pediatric brain tumors".

The scientists tested the safety of the drug by exposing zebrafish larvae to extremely high doses of the drug for extended periods of time. They observed that the drug did not affect the fish development, implying that it may be safe to be used in the pediatric population.

"This could also be an opportunity for a precision medicine approach as we can stratify patients who are eligible for treatment with the drug by investigating the level of PLK4 expressed in their tumors," said Sredni.

The group is currently testing the drug in animal models of AT/RT, as well as other types of brain tumors. Sredni envisions a Phase I clinical trial soon.

Provided by Ann & Robert H. Lurie Children's Hospital of Chicago