MedicalXpress

Study finds missing piece of pediatric cancer puzzle

July 19 2013

Most of the time, it takes decades of accumulating genetic errors for a tumor to develop. While this explains the general occurrence of cancer in adults, it leaves a gap in understanding of the cause of pediatric tumors.

In a study published in the July issue of the *Proceedings of the National Academy of Sciences*, researchers found a missing piece of the pediatric cancer puzzle. Changxian Shen, PhD, senior research associate at the Center for Childhood Cancer and Blood Diseases at The Research Institute at Nationwide Children's Hospital, and Peter Houghton, PhD, director of the center, may have identified one mechanism behind the early development of some pediatric solid tumors – as well as a target for future pediatric cancer therapies.

In healthy cells, a checkpoint prompts the cell to repair damaged DNA before it replicates. Many researchers believe that cancer cells flourish when these checkpoints are skipped or inhibited, as the mutated cells can survive and rapidly reproduce. A growing collection of damaged cells can lead to the solid tumors of many childhood cancers, such as those of rhabdomyosarcoma, neuroblastoma and osteosarcoma.

In their study, Drs. Shen and Houghton found that dampening a particular feedback loop between a repair checkpoint and its controlling pathways may promote the growth of tumors.

"Our prior studies had shown that the DNA damage checkpoint protein,

ATM, was very low in most pediatric solid tumors," Dr. Houghton, also a faculty member at The Ohio State University College of Medicine, said. "The question was why?"

The study revealed that a number of problems may be at play in the development of pediatric solid tumors. First, a pathway called mTOR regulates the production of a cancer-causing gene that tells the cell to produce too much of two kinds of microRNAs. These microRNAs, in turn, suppress the synthesis of ATM, which makes it hard for cells to initiate the damage checkpoint. Low levels of ATM allow the mTOR pathway to keep producing the microRNAs that further reduce the ATM-mediated checkpoint activity. When the microRNAs weaken the cell's damage checkpoint, the checkpoint cannot effectively prevent mutated cells from proliferating.

By making this connection, Drs. Shen and Houghton have identified a potential explanation for the early development of pediatric tumors as well as a potential target for new cancer therapies. Early tumor growth seems to be caused by cells' rapid bypass of the damage checkpoints instead of the gradual accumulation of damage at play in adult tumor growth. Future treatments that can help cells increase ATM checkpoint activity or fight the overproduction of microRNAs may slow or stop the growth of cancerous pediatric tumors.

"These results help us to not only understand the early genesis of some tumors in children, but also why many solid tumors are highly sensitive to drugs and ionizing radiation that damage DNA," Dr. Houghton said. "They also help explain why, in children not cured by these treatments, resistance to therapy arises – the rapid rate of mutation due to suppression of ATM. Potentially, the rate of mutations that lead to drug or radiation resistance could be slowed by targeting mTOR."

Provided by Nationwide Children's Hospital