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Protein prevents DNA damage in the developing brain and might serve as a tumor suppressor

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St. Jude Children's Research Hospital scientists have rewritten the job description of the protein TopBP1 after demonstrating that it guards early brain cells from DNA damage. Such damage might foreshadow later problems, including cancer.

Researchers showed that cells in the developing brain require TopBP1 to prevent DNA strands from breaking as the molecule is copied prior to cell division. Investigators also reported that stem cells and immature cells known as progenitor cells involved at the beginning of brain development are more sensitive to unrepaired DNA damage than progenitor cells later in the process. Although more developmentally advanced than stem cells, progenitor cells retain the ability to become one of a variety of more specialized neurons.

"Such DNA strand breaks have great potential for creating mutations that push a normal cell toward malignancy," said Peter McKinnon, Ph.D., a St. Jude Department of Genetics member and the paper's senior author. "When we selectively knocked out TopBP1 in mice, the amount of DNA damage we saw suggests that TopBP1 is likely to be a tumor suppressor. We are exploring that question now."

The work appeared in the April 22 online edition of the scientific journal *Nature Neuroscience*. The research builds on McKinnon's interest in DNA repair systems, including the enzymes ATM and ATR, which

are associated with a devastating cancer-prone neurodegenerative disease in children called ataxia telangiectasia, and a neurodevelopmental disorder called Seckel syndrome.

TopBP1 was known to activate ATR. Previous laboratory research by other investigators also suggested that activation made TopBP1 indispensable for DNA replication and cell proliferation. This study, however, showed that was not the case. Most progenitor cells in the embryonic mouse brain kept dividing after investigators switched off the TopBP1 gene.

"We showed that rather than being fundamentally important for building the machinery of replication, TopBP1's role is to monitor DNA damage and act when DNA damage occurs during replication," McKinnon said. The results offer insight into normal brain development, DNA damage repair mechanisms and cancer biology.

For this study, researchers tracked the impact of TopBP1 loss in progenitor cells at different stages in the developing mouse brain. The damage was most severe when the protein was knocked out in early progenitor cells. These rapidly dividing cells yield the next generations of progenitor cells that give rise to structures in the cortex involved in memory, vision, movement and sensation. When TopBP1 was silenced in the early progenitor cells, the cortex never developed. When TopBP1 was knocked out a day or two later in progenitor cells responsible for completing brain and nervous system development, the defects were present but less severe.

The progenitor cells that were created following the loss of TopBP1 were equally riddled with broken strands of DNA. In both the early and later progenitor cells, unrepaired DNA damage switched on the p53 gene that activated the cell's suicide pathway.

Researchers used low-dose radiation to show that early progenitor cells were more sensitive to the DNA strand breaks than were progenitor cells created a day or two later. Although the cells suffered comparable damage, the damage was more likely to induce cell suicide in the earliest progenitor cells. "This raises the likelihood that there is a different threshold to DNA damage in the early-born progenitors," researchers noted.

McKinnon added: "These early progenitor cells give rise to the cells that go on to make various brain structures, so it is really important that there are no errors in the blueprint of these starting cells. These findings show that TopBP1 plays a critical role in maintaining the integrity of the genome."

TopBP1 is not the only protein responsible for repairing broken DNA strands, but this study suggests it plays a unique role. When researchers turned off two other key repair factors, the proteins Lig4 and Xrcc1, in the cortex of developing mice, the loss resulted in much less severe defects than when TopBP1 was lost.

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