Scientists track impact of DNA damage in the developing brain

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Switching off a key DNA repair system in the developing nervous system is linked to smaller brain size as well as problems in brain structures vital to movement, memory and emotion, according to new research led by St. Jude Children's Research Hospital scientists.

The work, published in the August issue of the journal *Nature Neuroscience,* also provides the first evidence that cells known as cerebellar interneurons are targeted for DNA damage and are a likely source of neurological problems in humans. The cerebellum coordinates movement and balance. The cerebellar interneurons fine tune motor control.

"These data will be important for understanding the role the DNA damage response plays in preventing neurological disease," the investigators wrote.

The study also marks the first time researchers have switched off a pathway for repairing damaged single DNA strands in an organ system, in this case the mouse brain and nervous system. While the results suggest certain brain cells are particularly vulnerable, investigators report that with time DNA damage accumulates throughout the nervous system. Some mice in the study eventually develop seizures and difficulty walking.

Peter J. McKinnon, Ph.D., a member of St. Jude Genetics and Tumor Cell Biology, said the work provides a new model for understanding how

single-strand DNA damage affects the nervous system and offers a new focus for tracking the origins of neurological disease.

The research also reflects growing scientific interest in damage to single strands of DNA. "A variety of human disease syndromes result from problems in the DNA-repair system," explained McKinnon, the paper's senior author.

DNA is the double-stranded molecule found in nearly every cell. In organisms both simple and complex, it serves as the biochemical blueprint for assembling and sustaining life. Diseases like cancer have long been associated with unrepaired damage to both strands of DNA. Single-strand DNA damage is far more common, but was generally considered less catastrophic to the cell.

But the last decade brought evidence linking single-strand DNA damage with human diseases, including ataxia with oculomotor apraxia (AOA1) and spinocerebellar ataxia with axonal neuropathy (SCAN1). Both disorders are inherited and are characterized by progressive difficulty with walking and other movement. AOA1 is among the most common form of certain inherited movement disorders in Japan and Portugal. McKinnon said those reports sparked new interest in single-strand DNA repair.

This study focused on Xrcc1, a protein long recognized as the master regulator of a pathway essential for single-strand DNA repair in the nervous system. The brain is thought to be particularly susceptible to such damage because neurons consume large amounts of oxygen, which can result in excessive production of free radicals and leave them vulnerable to single-strand DNA damage. Because brain cells do not divide, they cannot use the backup repair systems found in other tissues.

Investigators developed a way to switch off Xrcc1 production in the

mouse brain and nervous system as development began. The system meant Xrcc1 still worked normally in the rest of the body.

The strategy used mice developed to make a particular enzyme, known as cre recombinase, in just the nervous system. St. Jude researchers then developed a mouse that carried an Xrcc1 gene outfitted with biochemical tags targeting the gene for inactivation by the enzyme. The result was a mouse whose nervous system lacked Xrcc1 and so was unable to efficiently repair the single-strand DNA damage.

The shutdown triggered a dramatic decline of interneurons throughout the cerebellum. In a subgroup of those cells, the damage triggered apoptosis, or programmed cell death. But the findings suggested the greatest loss occurred as the immature cerebellar interneurons, or progenitor cells, were poised to complete differentiation. In those cells, McKinnon said, loss of Xrcc1 activated the p53 pathway and blocked the cells from completing the cell cycle. "The cells appear to undergo permanent arrest," said McKinnon, noting it is one of the few in vivo examples of the p53 pathway leading to cell cycle arrest rather than apoptosis.

In the hippocampus, which plays a role in memory and emotion, investigators reported abnormal gene expression and neuronal function. Some neurons were eventually replaced by scar tissue in a process known as gliosis. Overall changes in the hippocampus mimicked those found in the brains of adults with the seizure disorder known as temporal lobe epilepsy. In this study, the loss of Xrcc1 also resulted in seizures in mice.

Source: St. Jude Children's Research Hospital