New step in DNA damage response in neurons discovered

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Researchers have identified a biochemical switch required for nerve cells to respond to DNA damage. The finding, scheduled for advance online publication in *Nature Cell Biology*, illuminates a connection between proteins involved in neurodegenerative disease and in cells' response to DNA damage.

Most children with the inherited disease ataxia telangiectasia are wheelchair-bound by age 10 because of neurological problems. Patients also have weakened immune systems and more frequent leukemias, and are more sensitive to radiation.

The underlying problem comes from mutations in the ATM (ataxia telangiectasia mutated) gene, which encodes an enzyme that controls cells' response to and repair of DNA damage.

ATM can be turned on experimentally by treating cells with chemicals that damage DNA. After other proteins in the cell detected broken DNA needing repair, scientists had thought that the ATM protein could activate itself directly. Emory researchers have shown that an additional step is necessary first.

"In neurons that are not dividing anymore, we now know that another regulator is involved: Cdk5," says Zixu Mao, MD, PhD, associate professor of pharmacology and neurology at Emory University School of Medicine.

Working with postdoctoral fellows Bo Tian, PhD and Qian Yang, PhD, Mao found that the Cdk5 protein must activate ATM before ATM can do its job in neurons.

The results support the idea that Cdk5 may be a potential drug target. Cdk5 contributes to normal brain development, and aberrant Cdk5 activity is known to be involved in the death of neurons in several neurodegenerative diseases, including Alzheimer's, Parkinson's and amyotrophic lateral sclerosis.

"Cdk5 has a complex character," Mao says. "It can be bad for neurons if its activity is either too high or too low."

Mao says he and his colleagues were intrigued by reports that in these diseases, neurons that had stopped dividing appear to restart that process, copying their DNA, before dying.

"That's what really kicked us into high gear," he says.

The same process, called "mitotic catastrophe," occurs when neurons suffer DNA damage. Inhibiting either Cdk5 or ATM can reduce the number of neurons that suffer mitotic catastrophe after DNA damage, the authors found.

Reference:

Tian, B., Yang, Q. and Mao, Z. Phosphorylation of ATM by CDk5 mediates DNA damage signaling and regulates neuronal death. *Nature Cell Biology*, advance online publication.

Source: Emory University