Inhibiting a protein found to reduce progression of Alzheimer's and ALS in mice

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(Medical Xpress)—A team of researchers with Genetech Inc. and universities in Hamburg and San Francisco has found that inhibiting the

creation of a protein leads to a reduction in the progression of Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS) in mice models. In their paper published in the journal *Science Translational Medicine*, the team describes the protein, how it works and their hopes for a clinical trial they have begun.

AD and ALS are very different brain disorders, of course, but they do have one thing in common—both are the result of losing brain cells. Scientists have been hard at work looking for ways to prevent and cure these ailments, but to date, there is no cure. Scientists also seek ways to delay the progression of both disorders to give patients more healthy years. In this new effort, the researchers report that inhibiting the production of a protein called dual leucine zipper kinase (DLK) in mice genetically altered to have AD or ALS slowed the progression of both diseases.

Prior research has shown that DLK is one of the regulators of neurodegeneration in both ALS and AD, and that it also activates another protein called c-Jun N-terminal kinase (JNK). That is a problem, because JNK is one of the agents involved in causing brain cells to die. The researchers with this new effort first conducted experiments showing elevated levels of both DLK and JNK in humans and mice with AD or ALS. They then genetically altered mice to remove the gene responsible for creating DLK and found that those mice with induced ALS experienced less neuron loss. The team next developed two drugs that inhibit DLK production, both of which were found to reduce JLK levels in mouse models. One of them was also found to reduce the progression of ALS in mice.

Pleased with their results thus far, Genetech has already launched a phase 1 clinical trial to test the drugs on human patients. They were able to move so quickly because DLK is a kinase, which means it belongs to a group of targets that have been deemed "very druggable."

More information: Claire E. Le Pichon et al. Loss of dual leucine zipper kinase signaling is protective in animal models of neurodegenerative disease, *Science Translational Medicine* (2017). DOI: 10.1126/scitranslmed.aag0394

Abstract

Hallmarks of chronic neurodegenerative disease include progressive synaptic loss and neuronal cell death, yet the cellular pathways that underlie these processes remain largely undefined. We provide evidence that dual leucine zipper kinase (DLK) is an essential regulator of the progressive neurodegeneration that occurs in amyotrophic lateral sclerosis and Alzheimer's disease. We demonstrate that DLK/c-Jun N-terminal kinase signaling was increased in mouse models and human patients with these disorders and that genetic deletion of DLK protected against axon degeneration, neuronal loss, and functional decline in vivo. Furthermore, pharmacological inhibition of DLK activity was sufficient to attenuate the neuronal stress response and to provide functional benefit even in the presence of ongoing disease. These findings demonstrate that pathological activation of DLK is a conserved mechanism that regulates neurodegeneration and suggest that DLK inhibition may be a potential approach to treat multiple neurodegenerative diseases.