

## ALZHEIMER'S DISEASE

## JNK3 as new target in AD?



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A hallmark of Alzheimer's disease (AD) is the accumulation of amyloid- $\beta$  ( $A\beta$ ) peptides, which are released from neurons after cleavage of amyloid precursor protein (APP). Soluble oligomeric  $A\beta$  peptides, particularly  $A\beta_{42}$ , have neurotoxic functions; however, the molecular mechanisms underlying their generation and toxicity are poorly understood. Reporting in *Neuron*, Yoon and colleagues have dissected the steps of  $A\beta_{42}$  generation and toxicity, and demonstrate that AD is a metabolic disease in which  $A\beta_{42}$  peptides induce a translational block that leads to neurotoxicity and cleavage of APP in a complex feed-forward loop that is tightly controlled

by JUN N-terminal kinase 3 (JNK3). Deletion of JNK3 in a mouse model of AD was shown to alleviate symptoms.

The idea that  $A\beta_{42}$  oligomers might induce a block of protein translation was based on the fact that treatment of mice with  $A\beta_{42}$  causes similar long-term potentiation (LTP) and memory impairments as treatment with compounds that induce a translational block. Using cultures of rat hippocampal neurons, the authors discovered that  $A\beta_{42}$  induces the phosphorylation of AMP-activated protein kinase (AMPK), a kinase that responds to energy imbalance in the cell. AMPK, in turn, inhibits the mammalian target of rapamycin (mTOR) pathway, inducing endoplasmic reticulum (ER) stress and a rapid translational block that initiates the unfolded protein response (UPR). The UPR had previously been shown to induce the activation of the JNK pathway. In the nervous system, JNK3 is the predominant JNK isoform, and further *in vitro* experiments revealed that activated JNK3 can phosphorylate APP at position T668P. This, in turn, was shown to lead to the internalization of APP and its cleavage into pathogenic  $A\beta_{42}$  — thereby forming a positive feedback loop.

The authors then set out to explore where and how this vicious cycle can be interrupted. Further *in vitro* experiments showed that the increase in  $A\beta_{42}$  production in

response to a translational block is dependent on JNK3 — thus implying that JNK3 can control this process.

Increased JNK3 activation had previously been reported in brains of patients with AD and in the mouse model of familial AD (FAD), but its role was not well understood. To gain insight into the role of JNK3 in AD pathogenicity *in vivo*, the authors introduced a JNK3 deletion into FAD mice. Brain samples of *FAD;JNK3<sup>-/-</sup>* mice showed dramatically reduced levels of insoluble  $A\beta_{42}$ ; at 6 months of age, the mice had an 87% reduction in  $A\beta_{42}$  plaque load compared to *FAD;JNK3<sup>+/+</sup>* mice. Moreover, the number of neurons in the frontal cortex was higher in *FAD;JNK3<sup>-/-</sup>* mice compared to their *FAD;JNK3<sup>+/+</sup>* counterparts (although it did not reach the levels seen in non-FAD mice), and they performed significantly better in memory tasks.

Taken together, these results indicate that AD is a metabolic disease that is under tight control by JNK3, and that JNK3 perpetuates the cycle of an  $A\beta_{42}$ -induced translational block via ER stress, JNK3 activation and further production of  $A\beta_{42}$ . JNK3 could therefore be a promising new target for the treatment of AD.

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