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NEURODEGENERATIVE DISEASE

DLK zips across neurodegeneration

> DLK inhibitors might hold promise for the treatment of several neurodegenerative diseases, which could be particularly appealing for drug developers.

Despite recent advances in the understanding of the genetics of chronic neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) and Alzheimer disease, the mechanisms underlying these diseases are still poorly understood, which has hampered the development of drug candidates. Now, the group led by Joseph Lewcock has identified dual leucine zipper kinase (DLK) as a common regulator of neuronal degeneration, suggesting that DLK may be a therapeutic target for the treatment of a number of neurodegenerative diseases.

DLK functions as an injury sensor that initiates the c-Jun N-terminal kinase (JNK)-dependent stress response in neurons, and inhibition of the JNK signalling pathway downstream of DLK can slow neuronal degeneration in mice.

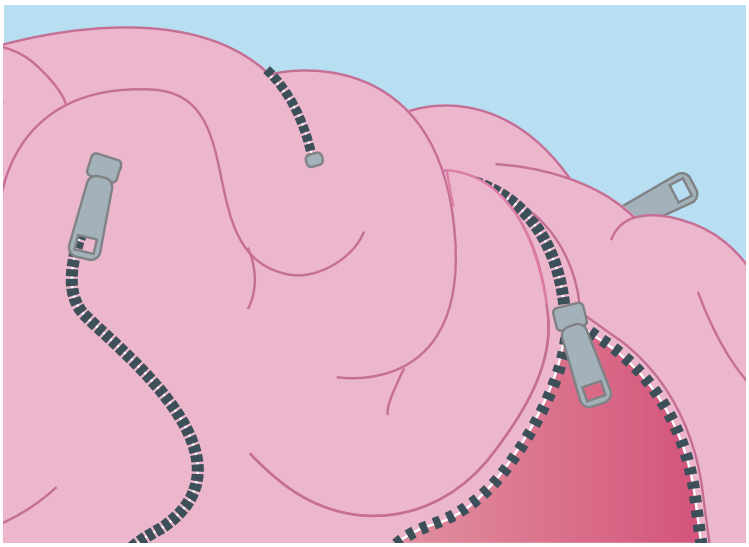
First, the authors assessed the extent to which activation of the DLK–JNK pathway correlates with chronic neurodegenerative disease. They found activation of the JNK pathway in the brains of *SOD1*^{G93A} and *TDP-43*^{A315T} transgenic mouse models of familial ALS as well as in lumbar spinal cord lysates from patients with sporadic ALS. Aberrant activation of JNK was also found in neurons of two transgenic mouse models of Alzheimer disease (*PS2APP* and *Tau*^{P301L}) and in post-mortem central nervous system tissues from patients with either early-stage or established Alzheimer disease.

Next, the authors analysed the effect of inhibiting DLK: *SOD1*^{G93A} mice with normal expression levels of DLK showed a 40% loss of motor neurons, whereas *SOD1*^{G93A} mice lacking DLK (*SOD1*^{G93A};*DLK*cKO) lost only 13% of motor cells. This increase in neuronal survival after *Dlk* deletion provided lasting functional benefit, and loss of DLK increased the median lifespan of these mice by 8 days.

In Alzheimer disease models, the authors observed a 30% reduction in the loss of neuronal spines proximal to plaques and enhanced synaptic integrity in *PS2APP* mice that lacked DLK, which confirmed that Aβ/plaque-associated synaptic loss is partly mediated by DLK signalling. Tamoxifen-induced loss of DLK expression in mice as old as 12 weeks resulted in cognitive improvements.

Finally, the authors tested whether pharmacological inhibition of DLK with two different compounds, GNE-8505 and GNE-351, would also have beneficial effects. Treatment with both inhibitors was well tolerated and reduced the activation of JNK in the spinal cords of SOD1^{G93A} mice compared with vehicle-treated mice. This reduction of DLK–JNK signalling pathway activity was also observed in the brains of *PS2APP* and *Tau*^{P301L} mice with established disease just 6 hours after receiving one dose. Administration of GNE-3511 in food for 5 weeks delayed neuromuscular junction denervation by ~10% compared with vehicle-treated mice.

As DLK expression is specifically enriched in neurons and the DLK–JNK signalling pathway is implicated in multiple disease models, DLK inhibitors might hold promise for the treatment of several neurodegenerative diseases, which could be particularly appealing for drug developers. Indeed, as a result of this study, Genentech has decided to advance a DLK inhibitor (GDC-0134) into a phase I clinical trial in patients with ALS.



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ORIGINAL ARTICLE Le Pichon, C. E. *et al.* Loss of dual leucine zipper kinase signaling is protective in animal models of neurodegenerative disease. *Sci. Transl Med.* **9**, eaag0394 (2017)