Nature Reviews Neurology | Published online 29 Sep 2017; doi:10.1038/nrneurol.2017.141

STROKE

Tau — a new target in acute brain ischaemia

> "accumulated iron in aged (12-month-old) tau$^{-/-}$ mice exacerbated the stroke lesion"

The microtubule-associated protein tau has been the subject of considerable research interest for several decades, largely owing to its involvement in the pathogenesis of neurodegenerative diseases such as Alzheimer disease (AD). Now, the findings of two preclinical studies involving mouse models of ischaemic stroke and excitotoxicity indicate a role for this protein in acute excitotoxic brain damage, suggesting that agents targeting tau and related proteins have the potential to reduce the severity of acute brain damage following stroke.

"Our new study is a continuation of our previous work on the postsynaptic role of tau and the role of this protein in excitotoxicity in AD," explains Lars Ittner, the lead author on one of the studies. "Given the central role of excitotoxicity in brain damage after stroke, we decided to explore whether tau also contributes to this acute brain condition."

Photo-Dave/iStock/Getty

Both research teams used a tau-knockout (tau$^{-/-}$) mouse model, which has no apparent phenotypic differences from wild-type mice of a similar age under standard living conditions. In both studies, middle cerebral artery occlusion (MCAO) of varying durations produced significantly lower levels of neurological impairment in 3–6-month-old tau$^{-/-}$ mice than in their wild-type counterparts. These differences emerged as early as 6 h after reperfusion.

Ittner and colleagues found that MCAO promoted the upregulation of the immediate-early genes *Arc*, *Fos* and *Junb*, signifying an excitotoxic gene response. These effects were not observed in tau$^{-/-}$ mice.

Bioinformatic investigations demonstrated differential activation of several signalling pathways in tau$^{-/-}$ mice relative to their wild-type counterparts, the most notable differences being observed in the activation of mitogen-activated protein kinase (MAPK) pathway components. Further investigations of the MAPK pathway revealed the presence of significantly elevated postsynaptic levels of SynGAP1 — an inhibitory regulator of excitotoxic RAS–ERK signalling — in tau$^{-/-}$ mice. Targeted short hairpin RNA-mediated knockdown of SynGAP1 in tau$^{-/-}$ mice restored sensitivity to MCAO.

In the other study, Peng Lei and co-workers investigated the role of tau-mediated iron export in MCAO-induced ischaemic stroke. "We previously reported that loss of tau causes age-dependent iron accumulation in the brain," says Lei. "In the new study, we showed that accumulated iron in aged (12-month-old) tau$^{-/-}$ mice exacerbated the stroke lesion."

Consistent with a role for iron in MCAO-induced ischaemic stroke, parenteral administration of ceruloplasmin, a copper-binding protein with ferroxidase activity, reduced both the severity of neurological impairment and hippocampal iron levels in wild-type mice. Crucially, substitution of ceruloplasmin with a deactivated form of this protein reversed this effect.

The researchers then explored the activity of inhibitors of ferroptosis, an iron-dependent form of non-apoptotic cell death. Both liproxstatin-1 and ferrostatin-1, administered immediately after reperfusion, were found to ameliorate the effects of MCAO in wild-type mice. Infusion of either agent 6 h after reperfusion partially rescued MCAO-induced neurodegeneration.

Taken together, the findings of these studies reveal a central role for tau protein in the response to stroke, in addition to the better-established role of this protein in AD.

"We tested multiple doses of the new ferroptosis inhibitor liproxstatin-1 in multiple stages of the stroke lesion," says Lei. "These conditions are highly relevant to the real-world scenario." Ittner adds "we are testing the possibility of targeting tau therapeutically in stroke models after the ischaemic infarct."

Peter Sidaway

ORIGINAL ARTICLES Bi, M. *et al.* Tau exacerbates excitotoxic brain damage in an animal model of stroke. *Nat. Commun.* http://dx.doi.org/10.1038/s41467-017-00618-0 (2017) | Tuo, Q. Z. *et al.* Tau-mediated iron export prevents ferroptotic damage after ischemic stroke. *Mol. Psychiatry* http://dx.doi.org/10.1038/mp.2017.171 (2017)