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NEURODEGENERATIVE DISEASE

First, tau causes NO problem

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Pathological tau disrupts the association between nitric oxide (NO) synthase and PSD95, impairing NO signalling and neurovascular coupling before causing neurodegeneration. Stopping production of pathological tau rescues NO signalling, neurovascular coupling and neuronal function, but doesn't remove tangles, suggesting that (like amyloid-β) soluble tau is an important driver of early neurovascular dysfunction and subsequent neuronal damage.

Reducing the incidence of dementia and its impact on quality of life will require targeting interventions to the very early stages of the disease process, before substantial neuronal damage has occurred. We therefore need to know what goes wrong in the brain preclinically to cause the later cognitive decline. One early change is the dysregulation of cerebral blood flow, which may promote accumulation of the classic hallmarks of Alzheimer's disease (AD), amyloid-β (Aβ) and tau, and subsequent neurodegeneration[1]. Park and colleagues[2] now demonstrate a novel mechanism by which this may occur, whereby pathological tau reduces formation of the vasodilator nitric oxide (NO), and that suppressing pathological tau preserves NO production and improves cerebrovascular and cognitive function.

Neuronal activity is energetically expensive, and disruption to the brain's blood supply produces neurodegeneration-like changes[1]. Furthermore, cardiovascular disease and dementia share risk factors -- vascular pathology is often seen post mortem in the brains of patients with dementias, and decreased cerebral blood flow is observed in dementia patients[1]. Therefore, a decrease in the brain's blood flow is thought to play a key role in the development of AD and other dementias such as frontotemporal dementia (FTD) [3,4]. Indeed, changes in vascular function may even trigger neurodegenerative processes as they occur before accumulation of beta amyloid or cognitive decline in people who go on to develop AD[5]. One mechanism linking vascular function with neurodegeneration in AD is the interaction between blood vessels and Aβ, where Aβ is cleared from the brain across blood vessels[1], but itself also constricts blood vessels, potentially slowing its own clearance[6]. This suggests a vicious cycle of impaired vascular function and Aβ accumulation that could lead to a neuronal energy crisis and neurodegeneration. But what about the other classic feature of AD, pathological tau? Tau is also involved in other dementias such as FTD, is better correlated with cognitive function than Aβ, and can also accumulate around blood vessels[7,8]. Here Park et al [2] show that tau, too, may play a critical role in dementia by impairing vascular function in early stages of the disease, before irreversible neuronal damage has occurred.

To test how pathological tau affects neurovascular function, Park et al used mice that express a mutated version of tau (pathological tau) that causes familial FTD in humans and, in mice, aggregates to form tangles, neurodegeneration and cognitive deficits by 7-8 months of age [9]. One important aspect of the study is that Park et al initially studied the effects of tau well before that stage, at 2-3 months, when such neuronal deficits were not yet present. They measured neurovascular coupling -- the increase in blood flow that occurs when neurons are activated -- by stimulating the whiskers and measuring blood flow and blood vessel diameter in the whisker barrel cortex. Small blood vessels (< 14 μm diameter) within

the cortex dilated less and blood flow increased less in mice that expressed pathological tau. Application of recombinant pathological tau to the brains of wild-type mice produced the same deficits, confirming that the impairment in neurovascular coupling was due to mutated tau.

Demonstrating a potential treatment window, this neurovascular coupling deficit was reversible and correlated with cognitive function. Using a different mouse model where tau expression was controlled by doxycycline, the authors showed that suppressing mutant tau expression from 3-4 months of age rescued the neurovascular coupling deficits observed 4 months later in mice that continually expressed mutant tau. This recovery of neurovascular function was associated with a prevention, as previously reported [9], of the memory deficits and loss of brain tissue seen in 7-8 month old mice when pathological tau is not suppressed. Crucially, the recovery of neurovascular and neuronal function occurred in the continued presence of neurofibrillary tangles, suggesting that soluble but not aggregated tau is the species driving both neurovascular and neuronal dysfunction[9].

So, these decreases in blood flow could be important for driving later neuronal and cognitive changes, but how does tau interfere with normal neurovascular coupling processes? A smaller blood flow response to whisker stimulation could be due to vascular cells being less able to dilate, neurons being less active during whisker stimulation, or a decrease in the signalling between neurons and the vasculature. Pathological tau did not reduce the ability of blood vessels to dilate, as acetylcholine (which directly stimulates vasodilation) produced the same increase in cerebral blood flow in mutant tau as wildtype mice. Neuronal activity was also unaffected by pathological tau at this age, as field potentials recorded in vivo during whisker stimulation, or increases in calcium in dissociated neurons in response to activation with N-methyl-D-aspartate (NMDA) were no different between WT and mice expressing mutant tau.

Instead, Park et al found that signalling between neurons and blood vessels was reduced by pathological tau expression. In the healthy brain, one of the main signalling pathways that links neuronal activity to blood vessel dilation involves NMDA receptor-dependent activation of NO production. Neuronal NO synthase (nNOS) is co-localised with NMDA receptors at the post-synaptic density as both proteins bind to the key anchoring protein, post-synaptic density protein 95 (PSD95). Calcium influx through NMDA receptors activates NO synthesis, and NO then diffuses to blood vessels where it causes them to dilate (see Figure) via production of cyclic guanosine monophosphate (cGMP), or in some cases by inhibition of the synthesis of the contractile molecule 20-hydroxyeicosatetraenoic acid (20-HETE)[10]. In mutant tau mice, however, the NMDA receptor/NO-dependent component of neurovascular coupling was absent. Blocking NMDA receptors or NO synthesis reduced the increase in blood flow in response to whisker stimulation but did not affect the residual blood flow response in mutant tau mice. Levels of NO produced by activating NMDA receptors were also reduced in these mice.

These experiments suggest that pathological tau interferes with NMDA receptor-induced production of NO. How could this occur? Using immunoprecipitation to detect proteins bound to the scaffolding protein PSD95, Park et al found that pathological tau expression reduced nNOS binding to PSD95, while the association of PSD95 with the NMDA receptor subunit, GluN2B, was unchanged. Binding of nNOS to PSD95 was also blocked by tau in HEK cells which exogenously expressed mutated tau and nNOS. Thus, it is likely that pathological tau impedes NMDA receptor-mediated activation of NO synthesis by blocking binding of nNOS to the post-synaptic density.

This study by Park et al therefore reveals a novel and potentially important mechanism whereby pathological tau can interfere with neurovascular function before

neurodegeneration and cognitive impairments, via disruption of the association between PSD95 and nNOS, and post-synaptic production of NO (see Figure). It raises several new key questions about how tau pathology causes neurodegeneration.

Physiologically, NO signals not only to blood vessels but to neurons, where it can be critical for synaptic plasticity and regulation of membrane excitability[11,12]. What, therefore, are the consequences for neuronal function of tau-mediated impairments in NO signaling? Are the interactions between PSD95 and any other proteins disrupted by soluble pathological tau, and therefore are there any NO-independent consequences of tau binding to PSD95? Do the observed neurovascular deficits cause neurodegeneration, or are they an epiphenomenon that might nonetheless serve as a useful marker for early tau-mediated changes in brain function? Finally, does pathological tau have the same effect in humans? Studies showing a lack of early cerebrovascular deficits in FTD patients carrying tau mutations suggest it may not, (unlike some other forms of FTD with non-mutated tau [4]), though blood flow decreases are observed in these patients after cognitive changes have developed [13].

Answering these questions will be vital for understanding the neurodegenerative process in FTD produced by tau mutations. It will also be important to discover if disruption of PSD95 binding and NO signalling occur in other tauopathies, such as Alzheimer's disease, where tau is not mutated, so levels and binding properties of the soluble protein may be different. Because tau phosphorylation is increased by hypoxia [14] such tau-mediated reductions in NO signalling could then form another strand in the web of factors linking early cerebrovascular dysfunction with progressive synaptic dysfunction and formation of classic Alzheimer's disease plaques and tangles. For both AD and FTD, restoration of NO signalling could therefore also be considered a novel target for therapeutic intervention.

By revealing this novel interaction between pathological tau and PSD95, and the consequent disruption of NO signalling to blood vessels (and presumably neurons), this study by Park et al reveals a new spoke in the wheel of factors linking pathological tau to neurodegeneration, providing new potential targets for intervention and opening a door to a wealth of new research directions.

Figure: Neurovascular coupling under physiologic conditions and with tauopathy

A: In normal physiologic conditions, glutamate release activates NMDA receptors in the post-synaptic density. Neuronal nitric oxide synthase (nNOS) is associated with NMDA receptors via the scaffolding protein PSD95, so that calcium entering through NMDA receptors can activate NO synthesis from L-arginine. NO diffuses to local microvessels and dilates pericytes (the predominant vascular mural cell on vessels of this size[15]), increasing blood flow. White box with arrow indicates dilation from baseline vessel diameter.

B: In mice that express a mutated form of tau, pathological tau reduces NO-mediated blood vessel dilation by binding to PSD95 and blocking its association with nNOS. NMDA receptor activation can no longer activate NO synthesis, reducing dilation of blood vessels, though neuronal activity can lead to residual vasodilation via other pathways. White box indicates baseline vessel diameter.

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