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News & views

Neurodegeneration

Neuronal gatekeeper for dementia protein

Katrin Deinhardt

In many neurodegenerative disorders, the spread of protein aggregates underlies disease progression in the brain. A receptor molecule has now been found that mediates the neuronal uptake of one such harmful protein.

A key characteristic of many neurodegenerative diseases is the slow accumulation of misfolded protein deposits in the neurons of the brain. In particular, the accumulation and spread of a protein known as tau is a feature of several forms of dementia, ranging from the most common form, Alzheimer's disease, to chronic traumatic encephalopathy, a dementia associated with repetitive head injuries. Writing in *Nature*, Rauch *et al.*[1] provide a clue to how this harmful protein spreads: they identify a cell-surface receptor that enables tau to move between neurons.

In tau-associated forms of dementia, or tauopathies, disease progression correlates with the spread of tau deposits throughout the brain. This is thought to occur because of misfolded, disease-associated (pathological) tau entering healthy neurons. Pathological tau interacts with normal (physiological) tau already present in the neuron and acts as a template for the misfolding of the normal protein, thus propagating tau pathology across neuronal networks. There is therefore great interest in elucidating the mechanisms that allow pathogenic tau to exit one neuron and enter the next.

The spread of pathogenic proteins throughout the brain is an active process, rather than simply the result of affected neurons dying, disintegrating and passively dispersing their contents[2]. The outer membranes of both the originating and the target cell need to be actively crossed, so that the misfolded tau can interact with physiological tau in the cytoplasm of the receiving neuron (Fig. 1a). Rauch and colleagues wondered whether a member of the low-density-lipoprotein receptor (LDLR) protein family — present at the neuronal surface — could hold the key to entry.

The authors eliminated all LDLR-family members individually from neurons grown in culture. They showed that the loss of LRP1 specifically reduced tau internalization into neurons. Interestingly, this loss interfered with the internalization of all forms of soluble, physiological tau and of small aggregating clumps (oligomers) of pathological tau. This suggests that LRP1 could mediate the transfer of both physiological and pathological tau. (The transmission of physiological tau across neuronal networks has been described previously[3], although its role is unclear.) Rauch *et al.* also found that the loss of LRP1 only partially blocked the uptake of larger 'fibril fragments' of tau. However, these fragments might also be taken up through less specific engulfing mechanisms that are known to occur in neurons[4].

Furthermore, the authors showed that tau competes with known LRP1 partners, including the lipid transporter ApoE, for binding to LRP1. They went on to map the areas of tau and LRP1 that interact, pinpointing two domains in the portion of LRP1 located outside the cell (its ectodomain), as well as a series of lysine amino-acid residues in tau that are exposed on the pathogenic protein. Targeting these residues using chemical inactivation prevented neuronal tau uptake, highlighting their importance.

Findings from cell culture do not always translate to complex *in vivo* settings. To test the relevance of LRP1 in tau transmission across networks in the intact brain, the researchers went on to downregulate the expression of LRP1 in mouse brains and then to express mutant human tau in a defined brain region. This mutant tau readily spreads through the brains of wild-type mice. But the authors found that it remained highly

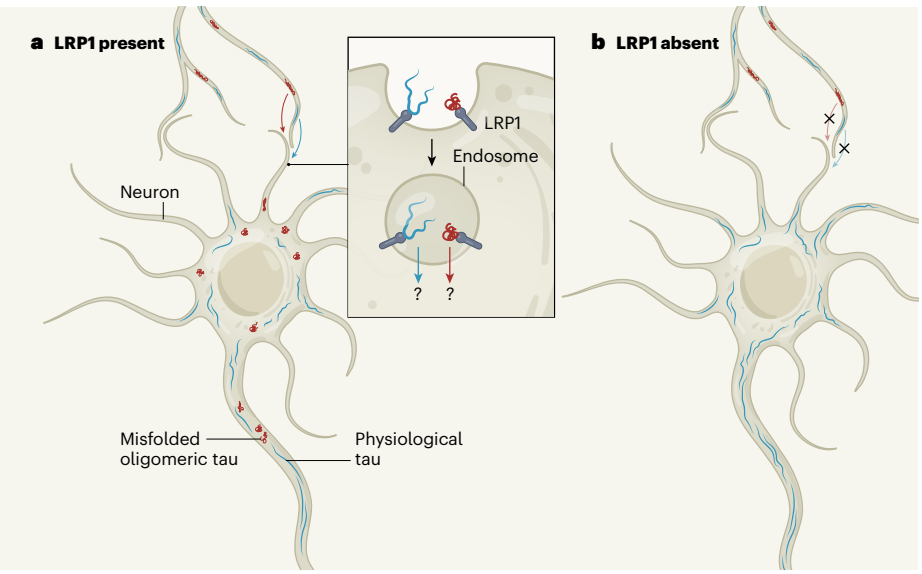

Figure 1 | A surface receptor for tau uptake. Misfolded forms of the protein tau can propagate through neurons in neurodegenerative disease. **a**, Rauch and colleagues[1] have discovered that the membrane-spanning protein LRP1 acts as a receptor for both normal (physiological) tau and for short strings (oligomers) of misfolded tau. Binding between LRP1 and tau leads to the uptake of tau into neurons and its spread through connected neuronal networks. Once internalized, tau resides in membrane-bound compartments called endosomes. How it escapes across the endosomal membrane into the cytoplasm is unknown. **b**, Rauch *et al.* show that an absence of LRP1 prevents tau transmission through the brain in live mice, potentially inhibiting the spread of pathology. (Physiological tau is generated in all neurons, and so is present throughout neural networks in spite of the lack of transmission.)

restricted to the expression site in mice lacking LRP1 (Fig. 1b).

These exciting findings suggest that LRP1 indeed holds a key to tau transmission across intact brains. Of note, the authors limit their analysis to the detection of misfolded human tau in brain areas far away from the site at which the group had induced the protein's expression, and analysed the mice at early stages of tau spread. In addition, there is no indication that the transmitted mutant tau in control brains is rich in β-sheets — a feature of tau deposits in degenerating brains. Indeed, there is also no evidence that neuronal health is adversely affected in these control brains. So the findings stop short of conclusively demonstrating a role for LRP1 in the spread of tau pathology, or, conversely, of demonstrating that downregulation of LRP1 can prevent the progression of pathology.

Nevertheless, the identification of a receptor that allows tau access to neurons constitutes a major advance in our understanding of tau biology and its spread in the brain. It opens the door to detailed analysis of the intracellular trafficking and signalling events that are activated following the internalization of tau, under both normal and pathological conditions. This might help to unpick the poorly understood role for transmission of physiological tau across neuronal networks. This is directly relevant to efforts aimed at stopping tau spread using antibody therapies, because most of these approaches do not discriminate between physiological and pathological tau.

The identification of LRP1 as a neuronal entry gate for tau will also enable direct investigation of the potentially different signalling pathways downstream of LRP1 that are activated by distinct tau species, giving insight into the earliest changes that occur in healthy neurons receiving pathogenic tau. Understanding these early events is crucial to finding strategies to combat devastating tau-related diseases before they cause irreversible damage in the brain.

LRP1 is widely expressed in the brain. In mice, loss of this receptor from neurons causes deficits in excitatory neuronal transmission[5] and in motor function[6]. In addition, LRP1 has been suggested to have a role in clearing build-ups of the amyloid-β peptide[7] (accumulation of which is associated with Alzheimer's disease) and in repairing the myelin coat that insulates neurons[8]. So, although the current results might point to the potential of blocking LRP1 function, this intervention might not necessarily be therapeutically beneficial: the possible positive effect of stopping the spread of tau in the brain might be offset by defects in network function and increased amyloid deposition.

Knowing the cell-surface receptor for tau, however, does allow for a mechanistic investigation of tau trafficking in the neuron. Following receptor-mediated internalization, tau resides in intracellular compartments known as endosomes, from which cargo normally gets degraded (in another compartment, the lysosome) or recycled back to the cell surface. It remains an open question how tau escapes the endosome to interact with and act as a template for the misfolding of native tau in the cytoplasm. A better understanding of this pathway might highlight options for rerouting internalized tau to be degraded or exported.

Finally, Rauch and colleagues' mapping of amino-acid residues in tau that allow it to interact with LRP1, in combination with emerging structures of different conformations of pathogenic tau[9–11], could enable the design of molecules that target tau to combat its spread. Perhaps this work marks a first step towards preventing the progression of tau-related disease.

Katrin Deinhardt is in the Faculty of Environmental and Life Sciences, University of Southampton, Southampton SO17 1BJ, UK.
e-mail: k.deinhardt@soton.ac.uk

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