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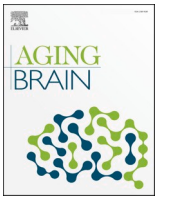

Opinions

New insight into tau immunotherapy

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As more drug trials based on antibodies targeting extracellular amyloid β antibody for Alzheimer's disease are approved and make headlines, it is easy to overlook efforts to develop tau-targeting immunotherapies.

Hyperphosphorylation, misfolding and aggregation of tau are widely considered key pathological players in Alzheimer's disease: tau burden strongly correlates with extent of neurodegeneration and clinical symptoms [1,2]. In a self-amplifying cascade, tau pathology spreads across cells and brain regions as a result of the intracellular uptake of misfolded tau. The transsynaptic spread of abnormally folded tau, referred to as "seeding" eventually results in intraneuronal and glial inclusions.

The rationale behind tau immunotherapy is that antibodies sequester tau in the extracellular space and block neuronal uptake of mis-folded tau species or facilitate their clearance and degradation by microglia. Results of studies in animal models do not however support a role for microglia in tau degradation [3,4]. This prompted the question of how antibodies against tau work.

In a recent publication, Mukadam and colleagues from the UK Dementia Research Institute in Cambridge [5] showed that TRIM21, a cytoplasmic antibody receptor, binds to extracellularly-formed tau-antibody complexes. Demonstration of the key role of TRIM21 came from the observation of a robust reduction in tau seeding (Fig. 1) after treatment of either tau transgenic mice or organotypic hippocampal slice cultures (derived from tau transgenic mice) with a monoclonal antibody against tau. TRIM21 is a ubiquitin ligase which tags proteins for degradation. Importantly, tau seeding was not reduced after tau immunotherapy in TRIM21-deficient mice or in hippocampal slices treated with a polyubiquitin inhibitor.

Although the authors did not complement their investigations with behavioral analyses, their study is important because it proposes a mechanism through which antibodies against tau prevent the intraneuronal accumulation and spread of aggregates of misfolded tau. But this study also raises the question of whether antibody receptors on the surface of neurons mediate the uptake of antibody-bound tau complexes, or whether the complexes enter neurons via endocytosis.

Moving tau immunotherapy a step further must consider that, because extracellular levels of tau are very low, high-affinity

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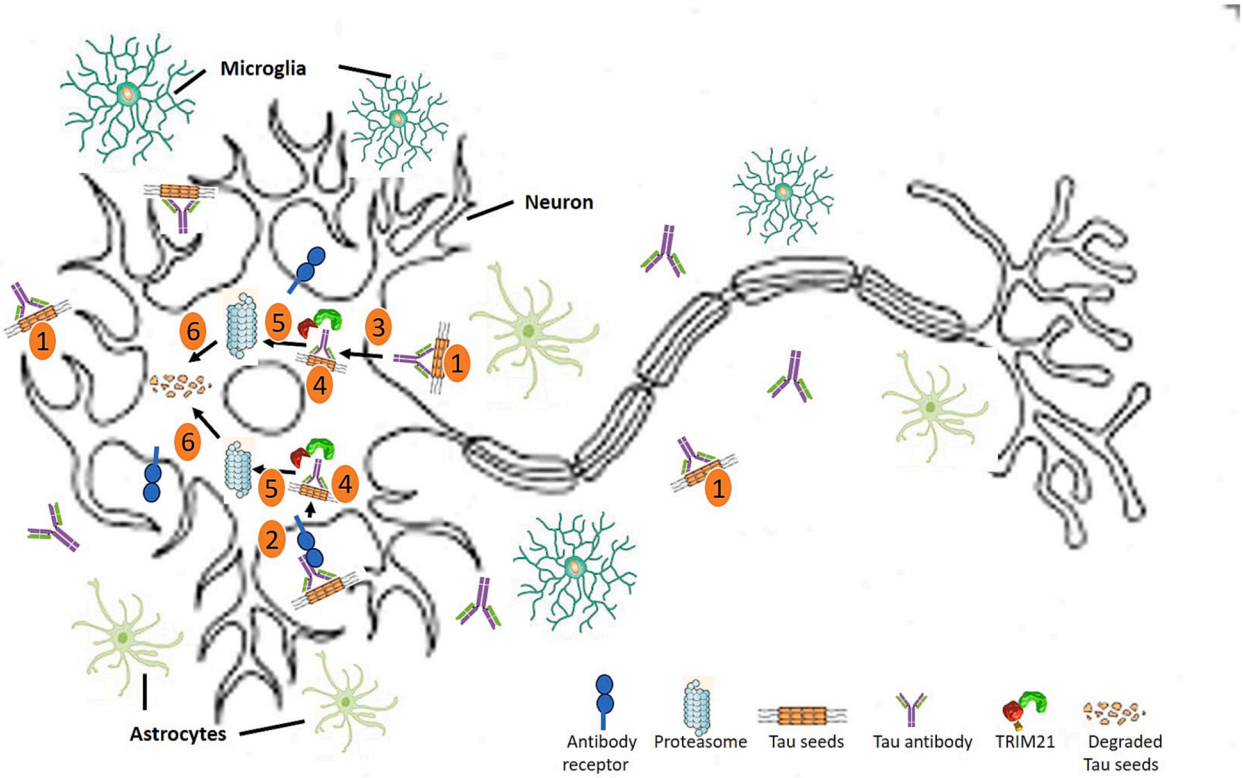

Fig. 1. Postulated mechanism for tau seed clearance in neurons- Tau monoclonal antibody binds to tau seed in the extracellular space (1). The tau-antibody complex is thought to enter neurons either by binding to the neuronal antibody receptor (2) or via endocytosis (3). In the neuronal cytoplasm, the tau-antibody complex binds to TRIM21 (4) which targets the tau seeds to the proteasomal pathway (5) and their degradation (6).

antibodies [6,7] that do not down-regulate the neuronal uptake mechanism will be needed. Lastly of course, the therapeutic potential of anti-tau approaches will be ultimately decided by their efficacy in significantly preventing or ameliorating the cognitive symptoms of Alzheimer's disease.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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