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Opinions

Protein quality control gone awry in Alzheimer's

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Alzheimer's (AD) is associated with increased accumulation of aggregated β-amyloid hyperphosphorylated tau. These events are closely associated with memory loss and neuronal death [1] and in the case of tau aggregates, with over 20 other dementias and movement disorders, including progressive supranuclear palsy, Pick's disease, and chronic traumatic encephalopathy, collectively known as tauopathies [2].

How and why tau proteins clump as neurofibrillary tangles remains unclear. Most organisms have protein quality control systems that remove defective or misfolded proteins, thus attenuating their accumulation [3].

Tripartite motif (TRIM) proteins play an important role in protein quality control in animal cells [4]. TRIM proteins are E3 ubiquitin ligases involved in recognizing proteins that would be targeted for disposal under healthy conditions [5]. TRIM family proteins have various functions in cellular processes including intracellular signaling, development, apoptosis, protein quality control, innate immunity, autophagy, and carcinogenesis [4–6].

Recently, Zhang et al. [7] found that TRIM proteins play a crucial role in preventing tau aggregation in Alzheimer's disease. Of the 70 human TRIM proteins, they found that TRIM 11 levels were reduced in the postmortem brains of 23 Alzheimer's patients, as compared to age- and sex-matched controls.

The authors demonstrated that TRIM11 possesses three main functions related to tau protein quality control [7]. Firstly, they showed that TRIM11 binds to tau proteins, especially mutant variants or disease-associated hyperphosphorylated tau, subsequently promoting their SUMOylation and proteasomal degradation. Secondly, the found that TRIM11 acts as a "chaperone" for tau, preventing its mis-folding and aggregation. And, lastly, they provided evidence that TRIM11 acts as a "disaggregase" for tau and dissolves pre-existing tau deposits and aggregates (see Fig. 1).

In cell culture models, Zhang et al. [7] demonstrated that down-regulation of endogenous TRIM11 impairs, whereas increased expression of TRIM11 promotes, neuronal viability and the formation of presynaptic and postsynaptic puncta and suggested a neuroprotective role for the molecule.

To determine the potential utility of TRIM11 as a therapeutic agent, the researchers used adeno-associated viral vector (AAV), a tool commonly used in gene therapy, to deliver the TRIM11 gene into the brain of multiple mouse models [7]. They observed mouse models of tauopathy that received *TRIM11* exhibited a marked decrease in the formation of neurofibrally tangles (NFT) that are comprised of abnormally phosphorylated tau. Cognitive and motor abilities of these mice was also improved by *TRIM11* gene therapy.

Overall, the work by Zhang et al. [7] provides a novel mechanism to control tau protein aggregation and tauopathies. The gene therapy tool used in this study - if can be applied to humans – opens a new therapeutic opportunity for treating age-related and other neurodegenerative diseases caused by misfolding and aggregation of proteins.

Declaration of competing interest

Dr. Sadashiva Pai is a founder and CEO of Science Mission LLC.

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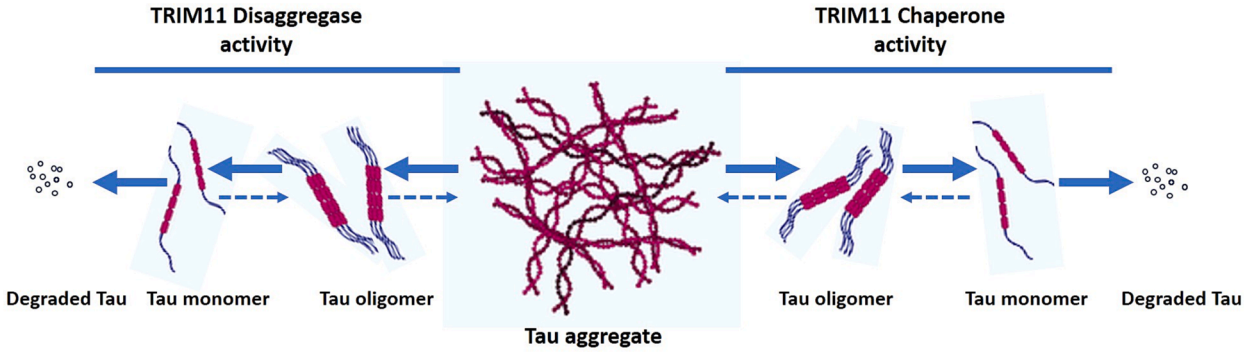

Fig. 1. TRIM11 mediated protein quality control. TRIM11 binds to hyperphosphorylated or mutant tau aggregates and degrades them via its chaperone and disaggregase activity, thus protecting neurons from protein aggregation and cell death.

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