Microtubule affinity regulating kinase (MARK/Par1) isoforms differentially regulate Alzheimer-like TAU missorting and Aβ-mediated synapse pathology

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Importance of TAU protein for dementia syndromes: Dementia currently affects about 55 million people worldwide, with Alzheimer’s disease (AD) being the most prevalent form. The one crucial pathological hallmark of AD that correlates best with loss of synapses and cognitive decline are the so-called intracellular neurofibrillary tangles composed of mislocalized/missorted and hyperphosphorylated TAU protein (Naseri et al., 2019). Many other neurodegenerative diseases, both genetic and non- genetic, demonstrate similar pathological features or pathological accumulation of the protein TAU and are thus termed “tauopathies”. Tauopathies include AD and related aging-associated dementia syndromes like frontotemporal dementia and variants thereof (progressive supranuclear palsy, Pick’s disease, corticobasal degeneration), but also childhood-onset genetic diseases (Zimmer-Bench and Zempel, 2021).

Importance of TAU missorting in disease: The protein TAU, encoded by the microtubule-associated tau (MAF)-gene, is a neuronal protein phosphatase (dephosphorylated in the axon, regulating microtubule (MT) dynamics, and microtubule transport, synaptic function, and more (Morris et al., 2011). In AD and related tauopathies, TAUopathies are thus termed “tauopathies”. Tauopathies include AD and related aging-associated dementia syndromes like frontotemporal dementia and variants thereof (progressive supranuclear palsy, Pick’s disease, corticobasal degeneration), but also childhood-onset genetic diseases (Zimmer-Bench and Zempel, 2021).

Perspective evidence pointing to differential effects of the different MARKs on TAU: We recently found that amyloid-beta (Aβ) toxicity is mediated by TAU, but only when TAU is phosphorylated or phosphoratable at MARK-type phosphorylation sites, the KxGS-motifs in the repeat domains of TAU (Zempel et al., 2013). Whether they have different physiological functions and roles in AD/taupathy pathophysiology is unknown. Despite the likely importance of MARK in TAU-related AD pathology, the individual physiological roles of the MARK isoforms and their impact on TAU toxicity are understudied.

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untreated cells in general (Figure 1A, F, G and data not shown). Aside from MARK-mediated Aβ induced TAU phosphorylation, these data could also point towards MARK-mediated TAU phosphorylation potentially requiring additional triggers. A potential mechanism underlying MARK-mediated TAU phosphorylation may be MARK activation and inactivation by various kinases (named above) at different sites. Aβ however, usually being targeted to dendritic spines, might induce spine-signaling that directly or indirectly alters the kinases affecting the activity of MARK. Another possibility might be MARKs being activated in response to Aβ-mediated changes in MT dynamics with TAU phosphorylation as a bystander effect. This might be either due to pathological changes of microtubules induced by Aβ (directly via changed calcium or SPASTIN activity, or indirectly via the loss of mitochondrial function physiologically providing energy for MT stability (Zempel et al., 2013; Tjiang and Zempel, 2022), or due to increased amounts of TAU present, as Aβ exposure induces TAU missorting into the somatodendritic compartment, where MARKs may be more active. The exact underlying mechanisms of these effects need further elucidation in future studies, in order to determine key players resulting in MARK activation in response to Aβ. This might reveal novel signaling pathways relevant for pathomechanisms of neurodegeneration.

Need for isoform specific studies and therapeutic strategies: In conclusion, all members of the MARK family have the potential to disrupt the microtubule binding of TAU, priming TAU for disease-associated and pathology-mediating TAU missorting. However, previously shown that MARK activity may be essential for neuronal regeneration and re-establishment of TAU sorting. Here, we demonstrate that the different MARKs, while in principle highly homologous, show different subcellular localizations, effects on dendritic morphology, and the mediation of oAβ toxicity. Future studies aiming at therapeutic inhibition of MARK must pay careful attention to the MARK isoforms and disruption of MARK physiological functions.

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Figure 1  Preliminary data show differential subcellular distribution and induction of spine formation, phosphorylation of TAU, and effects on dendrite outgrowth of the different isoforms of microtubule affinity regulating kinase (MARK).

Methodology as described in detail before (Zempel et al., 2017). (A–C, E, G) EYFP-tagged versions of MARK were expressed in primary rat neurons aged 21 days in vitro for 6 days. (A) Inserts show magnifications of boxed areas. Note the increased presence of MARK2 and MARK4 in spines, axonal exclusion of MARK2 but axonal enrichment of MARK4, short and dense dendritic processes of the cell transfected with MARK2, changed axodendritic morphology and absence of spine of the cells transfected with MARK3, and no apparent influence and ubiquitous distribution of MARK1. (B) Cells transfected with a control plasmid (EYFP) show no somatodendritic presence of TAU or phosphorylated TAU (KxGS motifs, 12E8 antibody). (C) Cells transfected with MARK1 show no increase in TAU missorting, and a marginal increase in 12E8 staining (upper panels), while cells transfected with MARK3 show increased somatodendritic TAU presence and slightly elevated 12E8 signals compared to control cells (B). (D) Different MARKs (and cotransfected tdTomato as a volume marker, shown here) were expressed in primary neurons aged 11 days in vitro for 5 days from wild-type or murine TAU/Mapt-knockout mice, the longest dendrite is marked by an arrow. Quantification reveals a TAU-dependent decrease of the longest dendrite in MARK2 expressing cells and an increase in MARK3 expressing cells. (E) Cells transfected with MARK2 show somatodendritic and dendrite-protrusion-localized presence of marked 12E8 signals. Confocal and stimulated emission depletion (STED) superresolution (inserts) microscopy of MARK2 transfected cells show strong enrichment of MARK2 in spines and structures resembling post-synaptic densities. Circled areas are magnified in inserts. (F) Overview of the differential effects of MARKs, as observed in preliminary experiments in mouse and rat neurons transfected with the different isoforms of MARK and imaged for phosho-TAU (pTAU), TAU, and the MARKs as above (not all shown here). (G) Primary rat neurons aged 21 days in vitro expressing MARKs for 6 days and treated with 1 µM of oligomeric amyloid-beta (oAβ) show increased phosphorylation of TAU at the KxGS motifs (by 12E8 staining) compared to control cells only transfected with EYFP (B) and treated with oAβ (not shown) or MARK1 transfected cells without oAβ treatment (C, upper panels). Unpublished data.

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