

ABSTRACT

Tau is a microtubule-associated protein that is preferentially found in the neuronal axons. In neurodegenerative diseases, collectively termed tauopathies, malfunction of tau and its detachment from axonal microtubules, often associated with abnormal phosphorylation of tau, are correlated with axonal degeneration and loss of microtubule mass (Kneynsberg et al., 2017). Tau can protect microtubules from microtubule-degrading enzymes such as katanin (Qiang et al., 2006) and regulate transport by molecular motors along the microtubule (Vershinin et al., 2007; Dixit et al., 2008). However, how tau carries out these regulatory functions is still unclear. Using in vitro reconstitution and TIRF microscopy, we show that tau molecules can bind to microtubules in two distinct modes: either as (i) single tau molecules independently diffusing on the microtubule surface, or (ii) cooperatively-bound tau that form a cohesive tau "envelope" enclosing the microtubule lattice (Siahaan et al., 2019; Tanetal., 2019; Siahaan et al., 2022). We found that tau envelope formation alters the spacing of tubulin dimers within the microtubule lattice, where envelope formation compacted the underlying lattice, and lattice extension induced tau envelope disassembly (Siahaan et al., 2022). Tau envelopes form a selectively permissible barrier that inhibits kinesin-1 motors while allowing dynein movement, and protects microtubules against the activity of microtubule severing enzymes such as katanin (Siahaan et al., 2019; Tanetal., 2019). Tau envelopes itself are regulated by tau phosphorylation, where phosphorylation of tau leads to destabilization of "healthy" non-phosphorylated tau envelopes and reduced protective functionality of the envelopes (Siahaan et al. (in review)). Combined, our data reveals the microtubule-dependent cooperative binding mode of tau that can constitute an adaptable protective layer on the microtubule surface. The subtle change in the microtubules lattice structure can differentially affect the affinities of other microtubule-binding proteins to the microtubule surface, thus potentially dividing microtubules into functionally distinct segments. Finally, our data suggests that a reduction in microtubule mass linked to tau hyperphosphorylation in neurodegenerative diseases, could be explained by the destabilization and impaired functionality of the tau envelopes upon tau phosphorylation.

Keywords: Cytoskeleton, microtubules, tau, in vitro reconstitution, single molecule imaging, optical trapping, phospho-regulation, microtubule-severing enzymes, neurodegeneration.