

# Multivalent cross-linking of actin filaments and microtubules through the microtubule-associated protein Tau

P03-02

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Microtubule-associated proteins regulate microtubule dynamics, bundle actin filaments and cross-link actin filaments with microtubules. In addition, aberrant interaction of the microtubule-associated protein Tau with filamentous actin is connected to synaptic impairment in Alzheimer's disease. Here we provide insight into the nature of interaction between actin filaments and microtubule-associated proteins and the actin/microtubule crosstalk. We show that Tau uses several short helical segments to bind in a dynamic, multivalent process to the

hydrophobic pocket between subdomains 1 and 3 of actin. Although a single Tau helix is sufficient to bind to filamentous actin, at least two, flexibly linked  $\alpha$ -helices are required for actin bundling. In agreement with a structural model of Tau repeat sequences in complex with actin filaments, phosphorylation at serine 262 attenuates binding of Tau to filamentous actin. Taken together the data demonstrate that bundling of filamentous actin and cross-linking of the cellular cytoskeleton depend on the metamorphic and multivalent nature of microtubule-associated proteins.