Tau Protein as a Scaffold for Signaling Molecules

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The best-known function of tau protein is as a microtubule-associated protein thought to regulate microtubule dynamics in the neuron, but the tau gene products contain many sequences that are not thought to play a role in microtubule binding. Many of the alternative splice forms involve regions of the molecule outside the microtubule interacting core, raising questions of a functional role for these domains. Several lines of evidence suggest that tau may serve to recruit specific signaling molecules to the microtubule cytoskeleton, perhaps acting as a scaffold to organize signaling pathways. The large number of phosphorylation sites throughout the tau sequence may reflect changes in this scaffold function as well as playing a role in regulation of tau binding to microtubules. The appeal of this idea has grown as the importance of scaffold proteins in organizing kinases and phosphatases in cells has become apparent for many pathways, including PKA, PKC, GSK3, JNK and others (Vondriska et al., 2004).

Phosphatases were among the first phosphotransferases reported to bind tau. Protein phosphatases PP1, PP2A and calcineurin (PP2B) are all reported to interact with microtubules via an interaction with tau protein. Various kinase activities have similarly been reported to interact with microtubules through tau, including cdk5, GSK3β, Fyn and PI3 kinase.

Given the dramatic alterations in kinase activities seen in Alzheimer's disease and other tauopathies (Crews & Masliah, 2010), a consideration of how tau interactions with these various kinases and phosphatases differs in native and pathogenic conformations might illuminate the altered signaling pathways in these diseases. The demonstration that the central proline rich region of tau allows Fyn to dock with tau and modify Y18 (Lee, 2005) provides one example, because the proline-rich region is thought to be buried in the filament. Similarly, a recent study

examined the differential effects of soluble and filamentous tau on fast axonal transport. Soluble, monomeric tau at physiological concentrations had no effect on axonal transport, but tau filaments at the same concentrations selectively inhibited kinesin-based axonal transport. Pharmacological experiments indicated that tau filament effects on FAT were mediated by PP1 and GSK3β (Lapointe et al., 2009). Remarkably, deletion of a conserved 18-amino-acid sequence at the tau N-terminus abolished this effect, suggesting that the tau N-terminus may have a role in regulating PP1/GSK3β in the axon. Studies like these suggest that tau may play an important role in regulating signal pathways associated with microtubules, including ones critical in Alzheimer's and other tauopathies.

References

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