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Single-molecule Imaging Reveals Tau Membrane Dynamics Modulated by Microtubule-binding Domain Composition

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The microtubule-associated protein Tau is essential for neuronal stability and its pathological aggregation is a hallmark of Alzheimer's disease and related tauopathies. Although Tau is primarily recognized for its interaction with microtubules, accumulating evidence suggests that it also localizes near the plasma membrane, raising the possibility that it may perform membrane-associated functions beyond canonical roles. However, the mechanisms underlying its membrane interaction and how they differ between isoforms remain poorly understood. In this study, we used TIRF microscopy to visualize Tau molecules near the plasma membrane in differentiated PC12 cells, and analyzed their trajectories using single-molecule tracking. Diffusion analysis revealed that Tau diffusion includes two distinct mobility states, likely corresponding to freely diffusing and membrane-associated populations. Comparative analysis of all six human Tau isoforms showed that the presence of the R2 repeat domain had a greater impact on membrane-proximal diffusion than the number of N-terminal inserts. These findings suggest that the microtubule-binding region, particularly the inclusion of R2, plays a key role in modulating Tau's interaction with the membrane environment, offering insight into isoform-specific behaviors that may underlie Tau's physiological and pathological functions.