Tau-Mediated Cytoskeletal Stabilization Modulates Cell Mechanics and Vulnerability to Mechanical Strain

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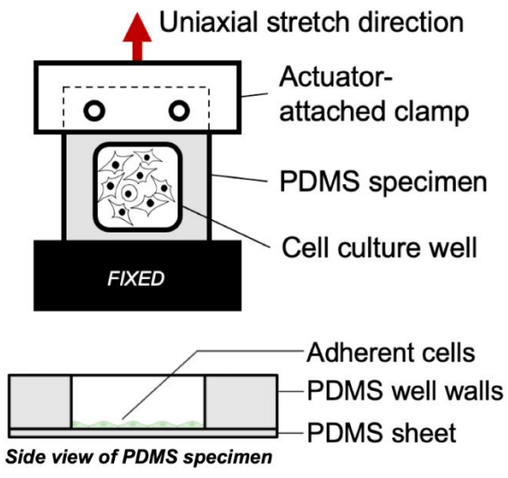
Cells experience mechanical loading across a broad range of loading rates, from low strain rates that are generated during morphogenesis and tissue remodelling, to high and injurious strain rates that are sustained during ventilation-induced lung injury, blast-induced injury, and impact-induced traumatic brain injury. Cell survival under high strain rate loading conditions depends on the ability of the cytoskeleton and plasma membrane to sustain mechanical load without permanent damage, but the underlying mechanisms of injury at high strain rate are poorly understood. Here, we investigated how Tau expression, phosphorylation, and microtubule binding modulates cell viscoelastic behaviour and membrane integrity during high strain-rate uniaxial stretch.

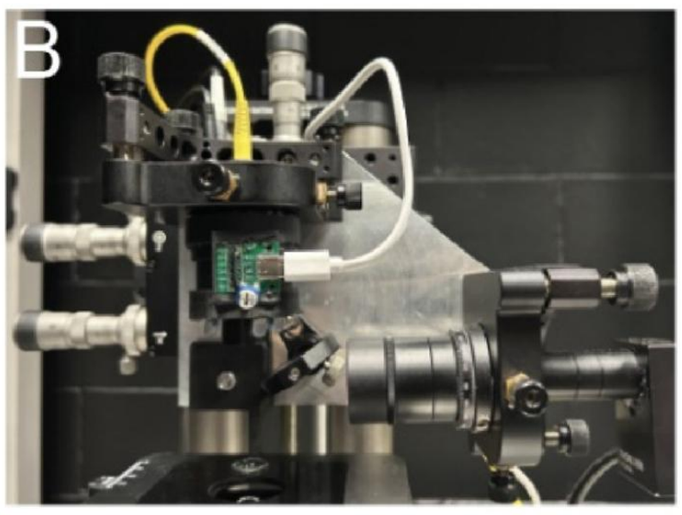
Methods

1. Cell Stretching



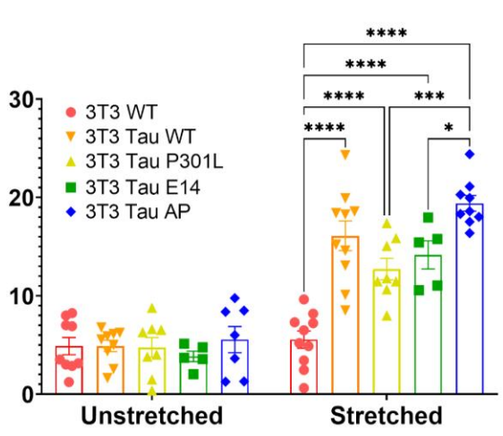
2. Microscopy + FRAP

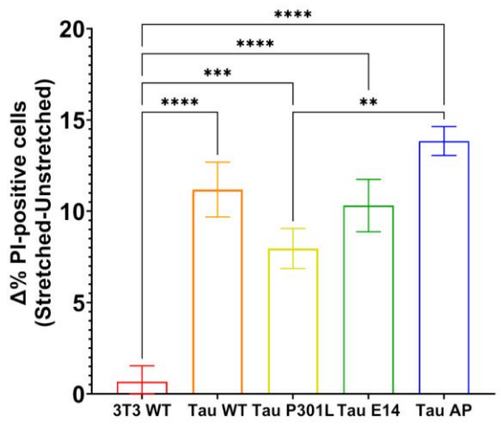
3. AFM

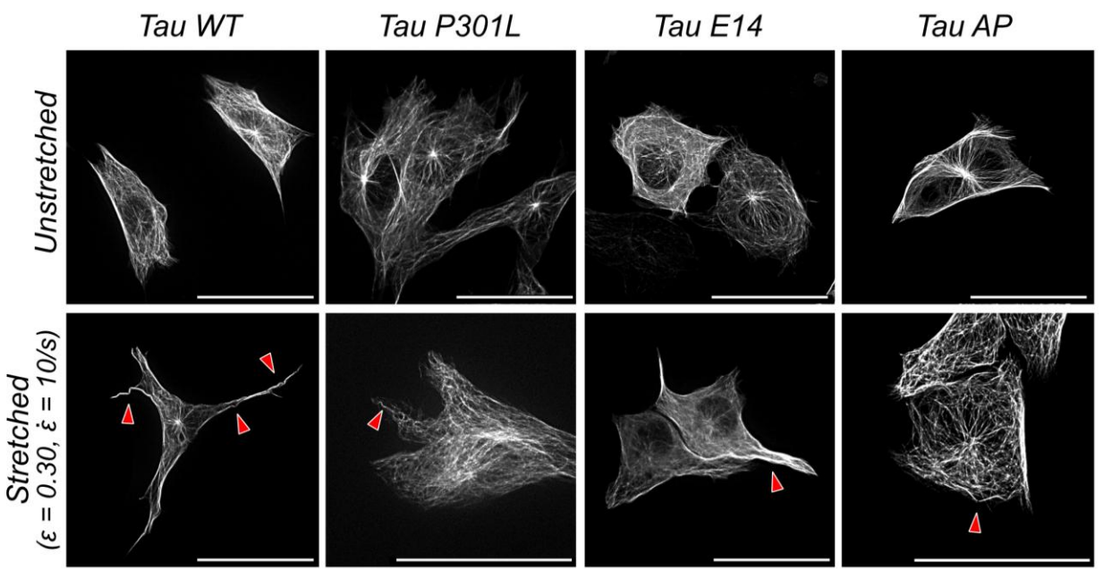


Results

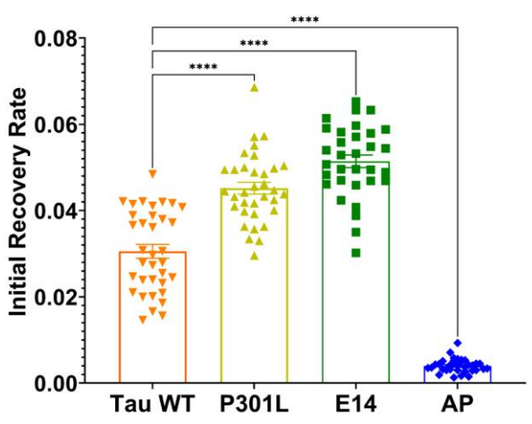
Expression of Tau increases cell vulnerability to mechanical strain

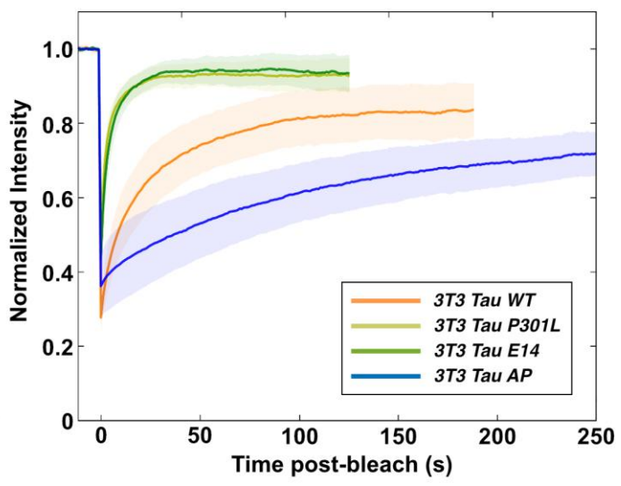




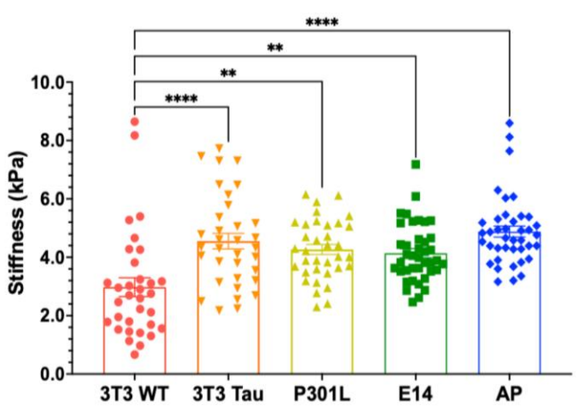


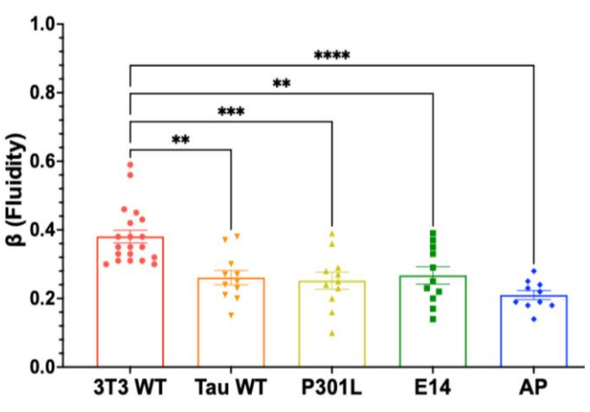
Tau phosphorylation state and disease causing mutants have different binding dynamics…



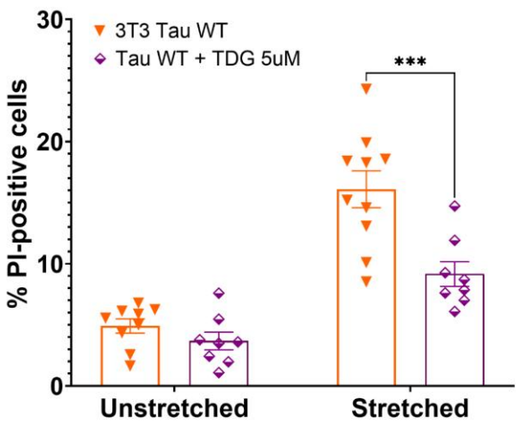


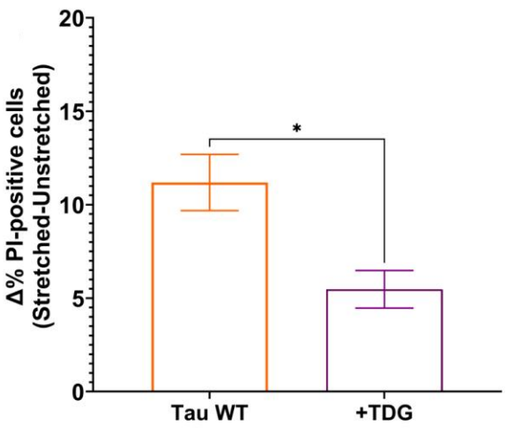
…and alter cell stiffness and fluidity

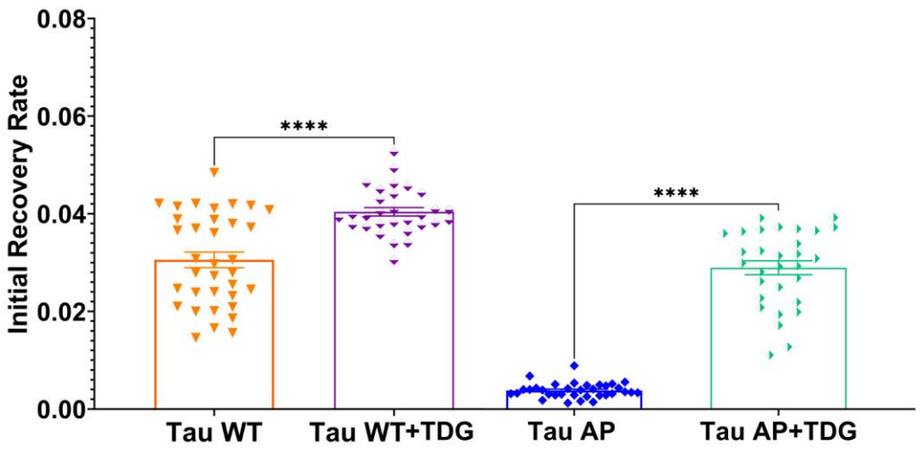




Targeting Tau de-phosphorylation with the drug Tideglusib protects against injury?







Conclusion

Stabilization of microtubules through the expression of the binding protein Tau causes increases in cell stiffening and plasticity that increase vulnerability to strain injury. Targeting Tau binding (de-phosphorylation) with the drug Tideglusib has an off-target effect on actin polymerization, which confers a protective effect against injury.

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REFERENCES

Kang, Gia, Vineeth Aljapur, Oren E. Petel, and Andrew R. Harris. "Tau-Mediated Cytoskeletal Stabilization Modulates Cell Mechanics and Vulnerability to Mechanical Strain." *bioRxiv* (2026): 2026-04