Abstracts of papers presented
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NEURODEGENERATIVE DISEASES: BIOLOGY & THERAPEUTICS

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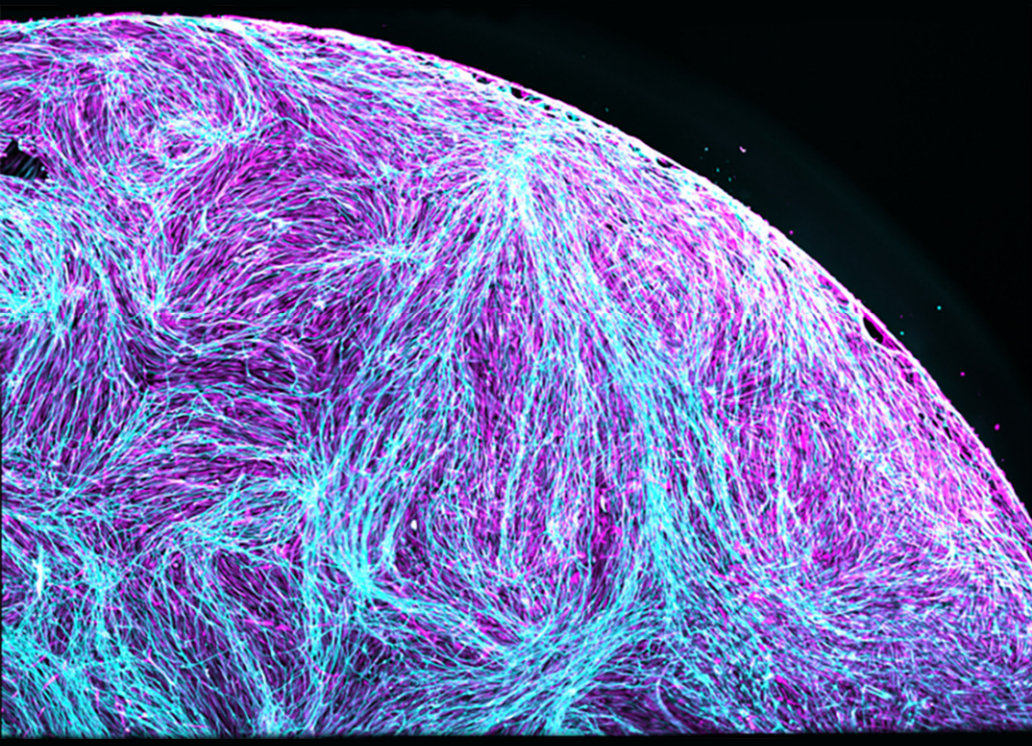

Cold Spring Harbor Laboratory
MEETINGS & COURSES PROGRAM

MICROTUBULE STABILIZATION PROTECTS COGNITIVE FUNCTION AND SLOWS DOWN THE COURSE OF ALZHEIMER`S-LIKE PATHOLOGY IN AN AMYLOIDOGENIC MOUSE MODEL

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Cognitive decline in Alzheimer's disease (AD) is highly related to synaptic dysfunction and neuronal loss. In AD and other tauopathies, the hyperphosphorylation of tau compromises axonal transport and leads to the accumulation of autophagic/vesicular material and the generation of dystrophic neurites, contributing to synaptic impairment. In addition to phospho-tau, AD brains accumulate amyloid-beta (Aβ). The effect of microtubule stabilization has been successfully assessed on tau, but not on Aβ pathology. This study evaluated the effect of the brain-penetrant microtubule-stabilizing agent, Epothilone D (EpoD) in the progression of the disease in a double transgenic mouse model of amyloidosis.
Young APP751SL/PS1M146L mice (3-month-old) were weekly treated with intraperitoneal injections of EpoD (2 mg/kg) or vehicle solution for 3 months. Memory performance was tested using object-recognition tasks, Y-maze and Morris water maze. Levels of Aβ, APP-fragments, AT8 (phospho-tau), ubiquitin, and synaptic markers were analysed by Western/dot-blot, immunostaining and image analysis. Somatostin (SOM)-cell density was calculated by stereology. β- and γ-secretase activities were measured. APPswe-N2a cells were treated with EpoD 100 nM for 12/24 hours.
EpoD-treated mice improved their performance of cognitive tests, while hippocampal phospho-tau and Aβ levels, especially soluble oligomers, decreased significantly. β/γ-secretase activities were not affected by EpoD i*n vitro*. A significant amelioration of synaptic/neuritic pathology was found. Remarkably, EpoD exerted a neuroprotective effect on SOM-interneurons, a highly AD-vulnerable GABAergic subpopulation.
In conclusion, EpoD improved microtubule dynamics and axonal transport in an AD-like context, reducing tau and Aβ accumulation, and promoting neuronal and cognitive protection. These results underline the crosstalk between cytoskeleton pathology and proteinopathy. Therefore, microtubule-stabilizing drugs could be candidates for slowing AD progression at both tau and Aβ pathologies.
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