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Drug that targets tauopathies in mice reveals sex differences in response

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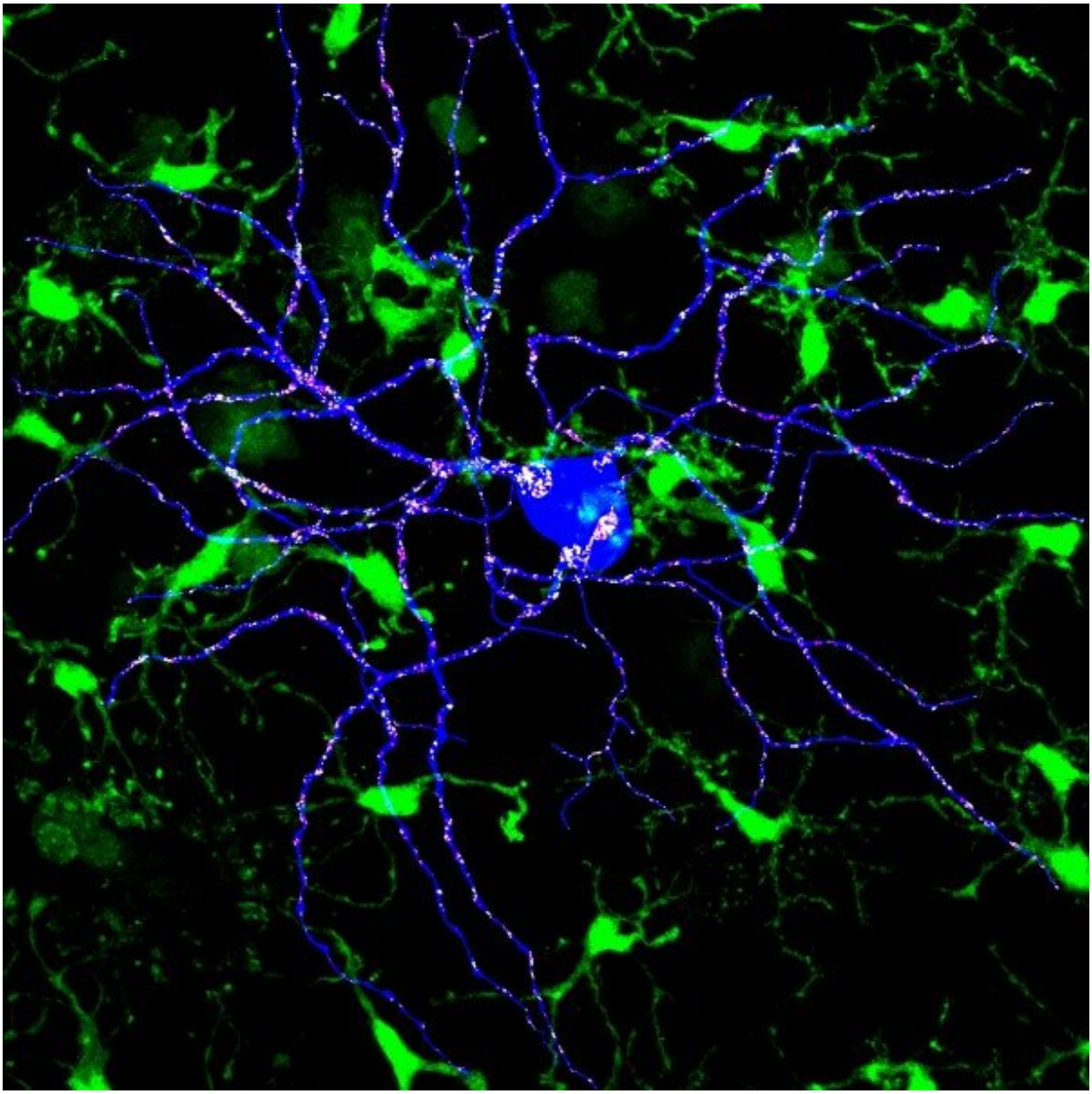

Microglial cells. Credit: University of California, San Francisco (UCSF)

Microglia are cells that are central to both brain health as well as disease progression in many neurological conditions. Normally, microglia stabilize the brain by clearing out damaged neurons and protein plaques often associated with dementia and other brain diseases. But there is growing evidence that microglia also play an early and constant role in tauopathy—a family of neurodegenerative disorders characterized by tau aggregation and neuronal loss.

Despite unequivocal evidence in humans that certain microglial functions are actively involved in the progression of neurodegenerative disease, the precise mechanisms governing microglia function in tauopathy are still not well understood. Genome-wide transcriptomic studies have identified immune pathways that indicate early and strong involvement of microglia in human tauopathy and in related mouse models. Deletion of microglial-specific genes or genetic ablation of microglial cells in mice have been useful approaches to dissect microglial-mediated mechanisms in disease models, but pharmacologic tools used to manipulate microglial function have been limited.

Recently developed small-molecule drugs targeting colony-stimulating factor-1 receptor (CSF1R)—a receptor kinase critical for survival and proliferation of CNS microglia, peripheral tissue macrophages and blood myeloid cells—have been approved for clinical use for oncology purposes.

In a study published January 9, 2023, in *Nature Communications*, senior author Carlo Condello, Ph.D., assistant professor in the UCSF Department of Neurology and the Institute for Neurodegenerative Diseases, systematically tested CSF1R inhibition using multiple drug

analogs at several time points in transgenic mice developing spontaneous tauopathy, and in an inoculation model of induced tauopathy.

The researchers demonstrated a reduction of tau pathology in multiple dosing schemes without complete microglial ablation. Drug exposure levels were correlated with the extent of tau-prion and microglial reduction, and unexpectedly, the researchers observed suppressed plasma biomarkers of neurodegeneration, rescue of aberrant behavior, and extended survival in female mice.

Despite greater drug exposure in male mice, only female mice had functional rescue and extended survival. A dose-dependent upregulation of immediate early genes and neurotransmitter dysregulation were observed in the brains of male mice only, indicating that excitotoxicity (causing cell damage) may preclude functional benefits. Drug-resilient microglia in male mice exhibit morphological and gene expression patterns consistent with increased neuroinflammatory signaling, suggesting a mechanistic basis for sex-specific excitotoxicity.

"To my knowledge, this is the first demonstration of a sex-related difference in efficacy or therapeutic benefit, at least in any neurological indication," said Condello. "The targeted tau deposits were reduced equally in males and females, but CSF1R inhibition extends survival and rescues other functional deficits only in female mice, even though drug exposure is two times higher in males compared to females. We found that drug consumption is same, but the females are much more active so we speculate higher metabolism may play a role in this difference."

CSF1R inhibition appears to preferentially eliminate these microglia in female mice, leaving the brain with a more quiescent and less inflammatory microglial population. In contrast, male mice showed a drug-induced, inflammatory microglial phenotype, which might contribute to neuronal excitotoxicity and diminished therapeutic effect.

In addition, the researchers questioned whether complete or continuous microglial ablation using CSF1R inhibitors was necessary, given the important and diverse roles these cells play in brain health and disease.

"The goal of our study was to define a therapeutic window that not only reduced pathological markers, but also led to functional improvement," said Condello. "Almost all other preclinical models were pushing the drug dose to wipe out all microglia, in effect, treating the cells as this binary thing that all are bad. In contrast, our study really points to the fact that we can ablate a fraction of those, only the tauopathy-activated cells, and still make therapeutic gains. We show that neither continuous dosing nor complete ablation of cells is necessary for efficacy and rescue.

However, Condello notes that therapeutics targeting microglia must consider sex-dependent effects. "While further investigation is needed to determine if similar sex dependent differences exist in humans, our study is perhaps the first to reveal sex-dependent biology caused by pharmacological intervention," said Condello.

More information: Noah R. Johnson et al, CSF1R inhibitors induce a sex-specific resilient microglial phenotype and functional rescue in a tauopathy mouse model, *Nature Communications* (2023). DOI: 10.1038/s41467-022-35753-w

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