Interfering with antiviral pathway may deter Alzheimer's disease and frontotemporal dementia

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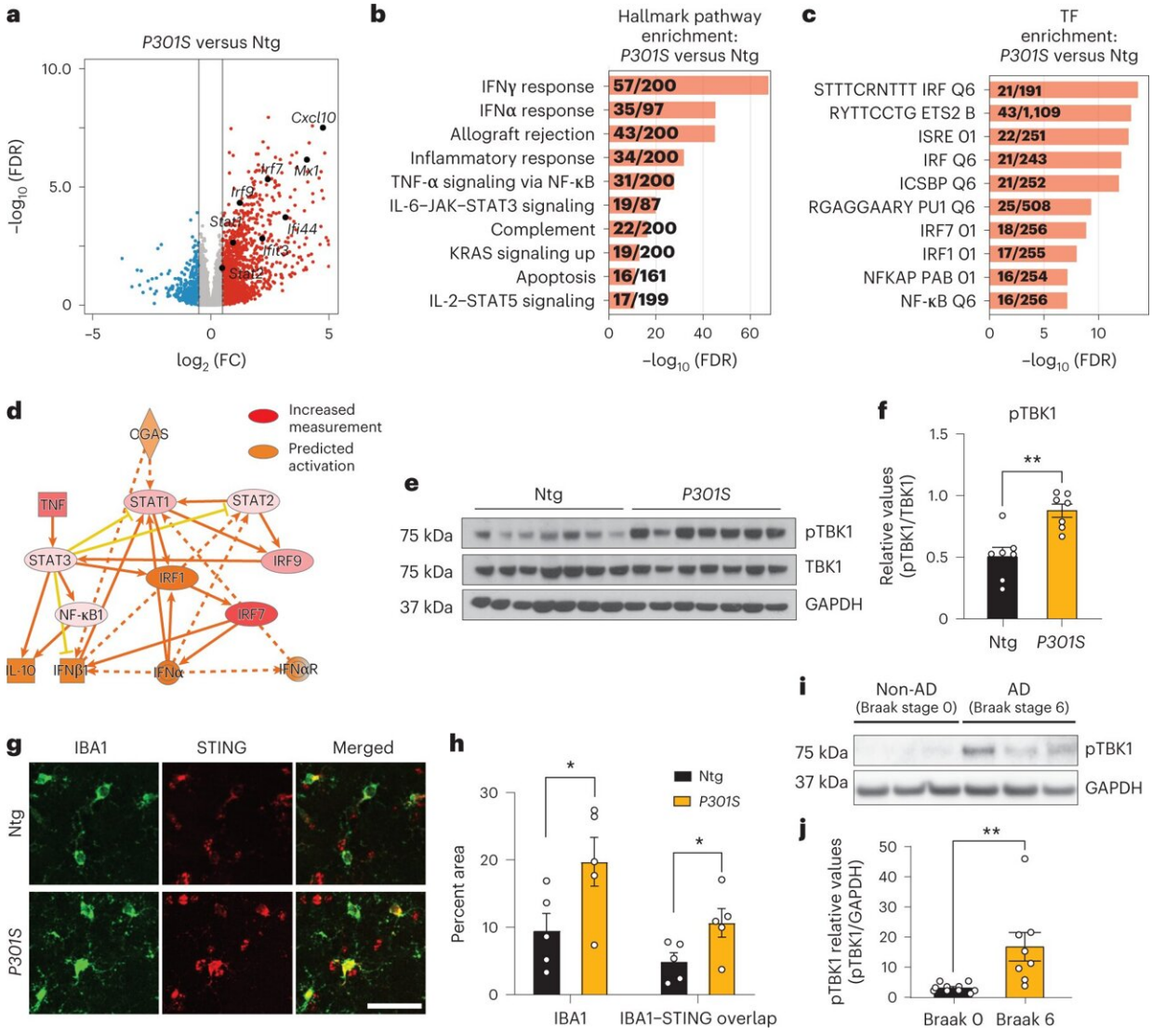

The cGAS–STING pathway is activated in the hippocampi of mice with

tauopathy and in human AD brains. Credit: *Nature Neuroscience* (2023). DOI: 10.1038/s41593-023-01315-6

Targeting part of an antiviral pathway triggered by the accumulation of a key pathogen shared in Alzheimer's disease and frontotemporal dementia may one day offer a new therapeutic approach to deterring or delaying cognitive decline, according to preclinical research led by Weill Cornell Medicine scientists.

The study, published April 24 in *Nature Neuroscience*, demonstrates that inhibiting an innate immune system enzyme called cyclic GMP-AMP synthase (cGAS) helps neurons become resilient to the build-up of the protein tau into bundles known as fibrils, a hallmark of Alzheimer's and some forms of frontotemporal dementia, the two most common dementias in the elderly population.

"We are interested in this antiviral pathway because of its importance in modulating innate immunity—the body's first line of defense against pathogens—which emerges as a major driver in neurodegenerative dementia," said the study's senior author, Dr. Li Gan, director of the Helen and Robert Appel Alzheimer's Disease Research Institute and the Burton P. and the Judith B. Resnick Distinguished Professor in Neurodegenerative Diseases at Weill Cornell Medicine.

Dr. Gan and her colleagues studied immune cells of the nervous system called microglia. When microglia were exposed to abnormal tau, the mitochondria—or organelles that produce a cell's energy—leaked DNA into the cell fluid. This mitochondrial DNA leakage was perceived by the immune system as a viral invasion, activating cGAS. This enzyme then triggered the sustained release of the immune system protein type I interferon (IFN-I).

"When loaded with tau protein bundles, brains get tricked into launching an antiviral response when there is actually no infection," Dr. Gan said. The sustained IFN-I signaling from microglia decreased the activity of a protein called myocyte enhancer factor 2c (MEF2C), which is a molecular switch that provides neurons with the blueprint to function normally and resist cognitive decline. "By inhibiting the antiviral response both genetically and pharmacologically, we were able to turn the switch on to instruct normal neuronal function, even in brains loaded with tau bundles."

The researchers investigated the antiviral pathway by conducting laboratory studies in an Alzheimer's disease mouse model. "These mice have abnormal tau accumulation in their brain and cognitive dysfunction that exacerbates with age," said one of the first co-authors of the paper Dr. Sadaf Amin, a postdoctoral associate in neuroscience in Gan lab at the Appel Alzheimer's Disease Research Institute at Weill Cornell Medicine. "Tau activates innate immune system and interferon signaling, which is switched off if we inhibit cGAS enzyme."

The researchers used single-nuclei RNA sequencing to study gene expression in individual cells genome-wide. "We were able to evaluate changes at the single-cell level across the whole genome and pinpoint cross-talks between different cell types, meaning we could identify changes that occurred through genetic deletion of the antiviral pathway or with pharmacological inhibition," Dr. Gan said.

Notably, removing the cGAS gene in these mice dampened the immune response of microglia and IFN-I. This preserved the function of synapses, or the communication junction between neurons and other cells, and protected against cognitive decline function regardless of the accumulation of abnormal tau protein.

"Deleting the cGAS gene preserves the function of Mef2c that renders

the neurons resilient to tau pathology by limiting the interferon signaling from microglia," said Yige Huang, another first co-author of the paper and a doctoral candidate in the Weill Cornell Graduate School of Medical Sciences in the Gan lab. The researchers were able to verify that these physiological mechanisms occur in humans using postmortem human tissue samples from Alzheimer's patients.

In addition, the researchers discovered that a small molecule cGAS inhibitor could restore MEF2C activity and improve memory function in mice with abnormal tau proteins. The inhibitor also modulated the antiviral pathway in human microglia derived from induced pluripotent stem cells.

"While further studies are needed, by suppressing the hyperactive antiviral response, we may be able to harness the brain's resilience program, postpone the disease onset, and extend normal cognition and quality of life in dementia patients," Dr. Gan said.

More information: Joe C. Udeochu et al, Tau activation of microglial cGAS–IFN reduces MEF2C-mediated cognitive resilience, *Nature Neuroscience* (2023). DOI: 10.1038/s41593-023-01315-6

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