The brain's immune system may be key to new Alzheimer's treatments

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Huaxi Xu, Ph.D., professor and director of SBP's Neuroscience Initiative. Credit: Sanford Burnham Prebys Medical Discovery Institute

Sanford Burnham Prebys Medical Research Institute (SBP) researchers have published two new studies in *Neuron* that describe how TREM2, a

receptor found on immune cells in the brain, interacts with toxic amyloid beta proteins to restore neurological function. The research, performed on mouse models of Alzheimer's disease, suggests boosting TREM2 levels in the brain may prevent or reduce the severity of neurodegenerative disorders including Alzheimer's disease.

"Our first paper identifies how amyloid beta binds to TREM2, which activates neural immune cells called microglia to degrade amyloid beta, possibly slowing Alzheimer's disease pathogenesis," says Huaxi Xu, Ph.D., professor and director of SBP's Neuroscience Initiative, Jeanne and Gary Herberger Leadership Chair in Neuroscience Research and senior author of the study. "The second study shows that increasing TREM2 levels renders microglia more responsive and reduces Alzheimer's disease symptoms."

Alzheimer's disease affects more than 47 million people worldwide, a number expected to grow as the population ages. One of the hallmarks of the disease is the accumulation of amyloid plaques that form between neurons and interfere with brain function. Many drug companies have been working for years to reduce amyloid beta production to thwart Alzheimer's—but with minimal success.

"TREM2 offers a potential new strategy," says Xu."Researchers have known that mutations in TREM2 significantly increase Alzheimer's risk, indicating a fundamental role for this particular receptor in protecting the brain. This new research reveals specific details about how TREM2 works, and supports future therapeutic strategies to strengthen the link between amyloid beta and TREM2, as well as increasing TREM2 levels in the brain to protect against pathological features of the disease.

Xu led the first study (TREM2 is a receptor for β-amyloid which mediates microglial function), showing that TREM2 binds quite specifically to amyloid beta. In particular, it connects with amyloid beta

oligomers (proteins that bind together to form a polymer), which are the protein's most toxic configuration. Without TREM2, microglia were much less successful at binding to, and clearing out, amyloid beta.

Further investigation showed that removing TREM2 downregulated microglial potassium ion channels, impairing the electrical currents associated with the activation of these immune cells. In addition, TREM2 turned on a number of mechanisms associated with the amyloid beta response in microglia.

The second study (TREM2 Gene Dosage Increase Reprograms Microglia Responsivity and Ameliorates Pathological Phenotypes in Alzheimer's Disease Models), a collaboration led by with X. William Yang, M.D., Ph.D., professor in Jane and Terry Semel Institute for Neuroscience and Human Behavior, and Department of Psychiatry & Biobehavioral Sciences at David Geffen School of Medicine at UCLA, added TREM2 to a mouse model with aggressive Alzheimer's disease. They found that the added TREM2 signaling stopped disease progression and even restored cognitive function.

"These studies are important because they show that in addition to rescuing the pathology associated with Alzheimer's disease, we are able to reduce the behavioral deficits with TREM2," says Xu. "To our knowledge this provides convincing evidence that minimizing amyloid beta levels alleviates Alzheimer's disease symptoms." As they learn more about how TREM2 modulates the amyloid signals that put microglia to work, the Xu lab and other researchers have their work cut out for them.

"It could be beneficial in early stages to activate microglia to eat up amyloid beta," says Xu, "but if you over-activate them, they may release an overabundance of cytokines (causing extensive inflammation) damaging healthy synaptic junctions as a side-effect from overactivation."

Still, the ability to use the brain's existing immune mechanisms to clear amyloid offers intriguing possibilities.

"Going after microglia, rather than amyloid beta generation, may be a new research avenue for Alzheimer's disease," says Xu. "We could use brain immune cells to solve what's becoming a public health crisis."

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