LSU Health Sciences Center NEW ORLEANS

School of Medicine

Neuroscience Center of Excellence

Chancellor's Award Lecture

in Neuroscience

Strategies to Reverse Neural Network Dysfunction in Alzheimer's Disease

Amyloid-β (Aβ) peptides are widely thought to cause Alzheimer's disease (AD), but the underlying mechanisms remain to be determined. The microtubule-associated protein tau and tyrosine kinases may play critical roles in Aβ-induced neuronal impairments. Even partial reduction of tau effectively prevents Aβ-induced neuronal and cognitive dysfunction in mouse models of AD, possibly by preventing aberrant neuronal activity and Aβ-induced changes in the intracellular transport of factors that regulate synaptic functions. Modulation of the src family kinase Fyn modulates Aβ-induced neuronal deficits in ways suggesting synergism among Aβ, tau and Fyn. Aβ oligomers bind directly to the receptor tyrosine kinase EphB2, promoting EphB2 degradation in the proteasome. Because EphB2 regulates the function of synaptic NMDA-type glutamate receptors, EphB2 depletion may contribute to Aβ-induced synaptic deficits. Knockdown of EphB2 in neurons of nontransgenic mice caused synaptic deficits similar to those seen in untreated AD model mice. More importantly, normalization of neuronal EphB2 levels in AD models reversed their deficits in synaptic plasticity and in spatial learning and memory. Ongoing studies aim to unravel the intriguing relationships among Fyn, tau, Aβ, EphB2 and related molecules with the ultimate goals of blocking copathogenic interactions and improving cognitive functions in the context of AD.

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8th Floor

Neuroscience Center of Excellence Conference Room

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