演講題目: Autophagy and Stem Cell Therapies for Neurodegenerative Disease Treatment

演講摘要:

Neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) remain major therapeutic challenges. Currently, no effective treatments exist to cure or slow the progression of AD and PD. In both diseases, impaired autophagy and mitochondrial function are key pathological features. Small-molecular drugs and stem cell therapy have emerged as promising disease treatment strategies. Our recent research explores small-molecule drugs' therapeutic potential and underlying neuroprotective mechanisms and stem cell-based approaches for AD and PD treatment.

In AD, neurotoxic β-amyloid (Aβ) aggregation and disrupted cholinergic signaling contribute to neurotoxicity and cognitive decline. We demonstrated that galantamine—an FDA-approved first-line treatment for mild-to-moderate AD and a positive allosteric modulator of α7 nicotinic acetylcholine receptors (α7nAChRs) as well as an acetylcholinesterase inhibitor—exerts significant neuroprotective effects. Galantamine activates the JNK signaling pathway to upregulate α7nAChR expression, enhancing autophagy for $A\beta_{1-42}$ intraneuronal degradation. We identified α7nAChR as a novel autophagy cargo receptor containing LC3-interacting regions mediating $A\beta_{1-42}$ sequestration into autophagosomes. This finding represents a new mechanism underlying galantamine's neuroprotective action.

In PD, mitochondrial dysfunction and oxidative stress accumulation lead to dopaminergic neuronal death in the substantia nigra of the midbrain. We tried to fight against these through two distinct strategies. First, we employed intranasal delivery of mesenchymal stem cells overexpressing fibroblast growth factor 21 (MSCs-mCherry-FGF21) in MPTP-induced PD mice. We found that MSCs-mCherry-FGF21 migrated to the substantia nigra, restored dopaminergic neurons and nerve terminals, improved PD motor function, and activated the Akt-BDNF-Bcl-2 neuroprotective signaling pathway. Second, we demonstrated that oleanolic acid—a natural hepatoprotective compound—protected dopaminergic neurons by improving mitochondrial function. It activated the JNK-Sp1-DJ-1 signaling axis in dopaminergic neurons to promote mitophagy to remove damaged mitochondria and reduce oxidative stress, thereby enhancing neuronal survival and improving PD-related motor deficits.

Together, these findings highlight the potential of targeting autophagy and mitochondrial quality control mechanisms—via pharmacological and stem cell-based approaches—as a promising therapeutic strategy for AD and PD.