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Truncated α-synuclein 1-103 fragment promotes Parkinson's Disease-like pathology by inducing mitochondrial impairment

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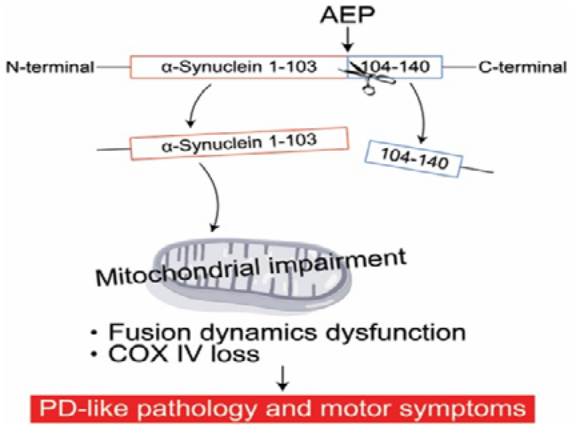
Statement of the Problem: Parkinson's disease (PD) is one of the most common neurodegenerative diseases. However, its pathological mechanisms still wrap in the mist. Previously we reported that the cysteine protease asparagine endopeptidase (AEP) cleaves α-synuclein, generating its 1-103 fragments, and promotes the onset of PD. However, the underlying molecular mechanisms of α-synuclein 1-103-induced PD pathology remain unclear.

Methodology & Theoretical Orientation: We established a transgenic mouse line expressing human α-synuclein 1-103. We investigated the progression of α-synuclein pathology, mitochondrial function, degeneration of the nigrostriatal pathway, and behavioral impairment of the mice. We also tested the effects of a small molecule TrkB agonist 7,8-DHF on rescuing α-synuclein 1-103-induced PD-like pathology.

Findings: α-Synuclein 1-103 overexpressing induces PD-like neurodegeneration, including synaptic degeneration and mitochondrial impairment. The α-synuclein 1-103 mice show age-dependent PD-like motor and non-motor symptoms. α-Synuclein 1-103 induces impairment of the TrkB signaling pathway, inducing mitochondrial impairments both in vitro and in vivo, which was attenuated by 7,8-DHF. Long-term oral administration of 7,8-DHF also ameliorated the pathological alterations and motor dysfunctions in α-synuclein 1-103 mice.

Conclusion & Significance: AEP-derived α-synuclein 1-103 promotes PD-like pathology and motor impairments by disturbing mitochondrial functions, which could be remitted by 7,8-DHF. Our results support a way of ameliorating PD by blocking mitochondrial dysfunction induced by pathological α-synuclein.



Recent publications

1. Yan M, Xiong M, Dai L, et al. Cofilin 1 promotes the pathogenicity and transmission of pathological α-synuclein in mouse models of Parkinson's disease. npj Parkinson's Disease, 2022, 8(1):1.

2. Zhang Z, Kang SS., Liu X, et al. (2017). Asparagine endopeptidase cleaves α-synuclein and mediates pathologic activities in Parkinson's disease. Nat Struct Mol Biol, 24, 632–642.

3. Zhang Z, Li XG, Wang ZH, et al. δ-Secretase-cleaved Tau stimulates Aβ production via upregulating STAT1-BACE1 signaling in Alzheimer's disease. Mol Psychiatry, 2021, 26(2):586-603.

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