MFN2: A Novel Therapeutic Target for Alzheimer's Disease

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Alzheimer’s disease (AD) is the most common neurodegenerative disease and affects memory and learning. Recent data suggest mitochondrial fragmentation in AD likely underlies impaired mitochondrial function in AD. Among the protein regulators of mitochondrial fusion and fission dynamics, MFN2, a fusion protein, is significantly downregulated in the AD brains, which could be the reason for mitochondria fragmentation in AD. In this study, we investigated whether MFN2 overexpression (OE) could rescue mitochondrial deficits and alleviate pathological changes in 5xFAD mice, a widely-used AD mouse model. 5xFAD mice demonstrated fragmented mitochondria which were rescued in 5xFAD&MFN2 mice. MFN2 OE also led to the rescue of memory deficits, neuronal loss, amyloid pathology, and neuroinflammation in 5xFAD mice. Leflunomide, a FDA-approved drug to treat rheumatoid arthritis, has been identified as a MFN2 inducer and promotes mitochondrial fusion. In analyzing medical data, we found a trend toward reduced risk of AD in people who took leflunomide compared to the general population suggesting a preventive effect. Most importantly, leflunomide also reduced the conversion from mild cognitive impairment to AD suggesting a likely treatment effect. Using M17 human neuroblastoma cells, we demonstrated that teriflunomide, the active metabolite of leflunomide, induced MFN2 expression and protected M17 human neuroblastoma cells against Aß-induced mitochondrial deficits and cell death in a cell model of AD. Altogether, this study demonstrates that MFN2 is a promising therapeutic target for AD. Further studies will be pursued to develop teriflunomide or related compounds as potential drugs for AD treatment.

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