TOMM40-mediated mitochondrial dysfunction and Alzheimers disease

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Research Abstract
Summary Mitochondrial dysfunction and synaptic damage are early pathological features of the Alzheimer’s disease (AD) affected brain. A? has deleterious effects on mitochondrial and synaptic dysfunction. The underlying mechanisms and strategies to rescue such injury remain unclear. Recent studies have highlighted the role of mitochondrial A? in AD pathogenesis.

Accumulation of mitochondrial A? may be an initiating pathological event leading to mitochondrial and neuronal perturbation. TOMM40 (Translocase of the Outer Mitochondrial Membrane-40kD) is the key subunit of the TOM complex, the main entry channel for the vast majority of imported proteins must pass to enter the mitochondrial interior. A polymorphism inTOMM40 is associated with an increased risk of late-onset AD and decreased cognitive performance48. This polymorphism is the only nuclear-encoded gene identified in genetic studies to date that presumably contributes to LOAD-related mitochondrial dysfunction. A? and APP can be imported into the mitochondria through the TOMM40 channel in an in vitro cell culture, however, the TOMM40-mediated A? import mechanism remains unclear and the impact of TOMM40 on amyloid pathology, mitochondrial and synaptic degeneration, and neuroinflammation in A? milieu have not yet been elucidated. In our pilot studies, we observed that TOMM40 knockdown mice displayed significantly reduced mitochondrial A? levels, along with improvement in mitochondrial and synaptic function in Tg mAPP mice overexpressing A?. Furthermore, reduced TOMM40 levels in Tg mAPP mice attenuate the innate immune and proinflammatory response. These data suggest that TOMM40 may potentially be of importance in mitochondrial amyloid pathology of AD. We hypothesize that impaired function of TOMM40 contributes to chronic mitochondrial A? accumulation relevant to developing amyloid pathology of AD, leading to mitochondrial and synaptic degeneration. The goal of this proposal is to gain new insight into the role of TOMM40 in AD pathogenesis, focusing on mitochondrial A? accumulation/clearance, amyloid pathology, synaptic mitochondrial properties, oxidative stress, inflammation, and synaptic function, utilizing a novel genetically manipulated transgenic TOMM40/AD mouse models and neuronal culture with altered TOMM40 levels (gaining/losing) in an A?-rich environment (genetic deficiency of global and neuronal TOMM40 and increased neuronal TOMM40 in AD-type transgenic mice overexpressing A?). The outcomes of the project could present that TOMM40 might be a potential new therapeutic target for limiting mitochondrial amyloid pathology thereby halting AD progression.

Further information available at:

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