Molecular characterization of the mitochondrial complex I assembly (MCIA) complex: insights into Alzheimer's disease pathogenesis

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Alzheimer's disease (AD) is a fatal neurodegenerative disorder featured by amyloid-β (Aβ) plaques and whose causality remains unclear. There is evidence that Aβ accumulates into the mitochondria in brains of AD patients and impairs the mitochondrial respiratory supercomplex, leading to defective neurotransmission, synaptic damage and cognitive impairments associated with AD. Complex I (CI or NADH:ubiquinone oxidoreductase) is the largest enzyme of the system and defects in its assembly are often observed. Recently, several chaperones have been suggested to form the Mitochondrial CI Assembly (MCIA) complex, with a key role in the assembly and stability of the mature CI (Figure 1) [1]. Previously, we identified the MCIA factor ECSIT (Evolutionarily Conserved Signaling Intermediate in Toll pathway) as an interacting node between Aβ producing enzymes and mitochondrial energetics [2-3]. Our current work focuses on the structural and functional analyses of the human MCIA core complex composed of NDUFAF1, ECSIT and ACAD9 proteins and their interplay with Aβ burden regulation. Here, we present the preliminary biochemical and structural characterization of the complex by small angle X-ray scattering (SAXS) and electron microscopy (EM) negative staining. Deciphering the mechanistic details underlying MCIA function will advance our understanding of AD etiology by (i) elucidating how mitochondrial respiration is coupled to Aβ dynamics and (ii) unveiling the causal link between mitochondrial dysfunction and amyloid pathology in the early stages of AD. It will also establish whether MCIA factors are potential biomarkers that may contribute to mitochondria-targeted therapeutics.

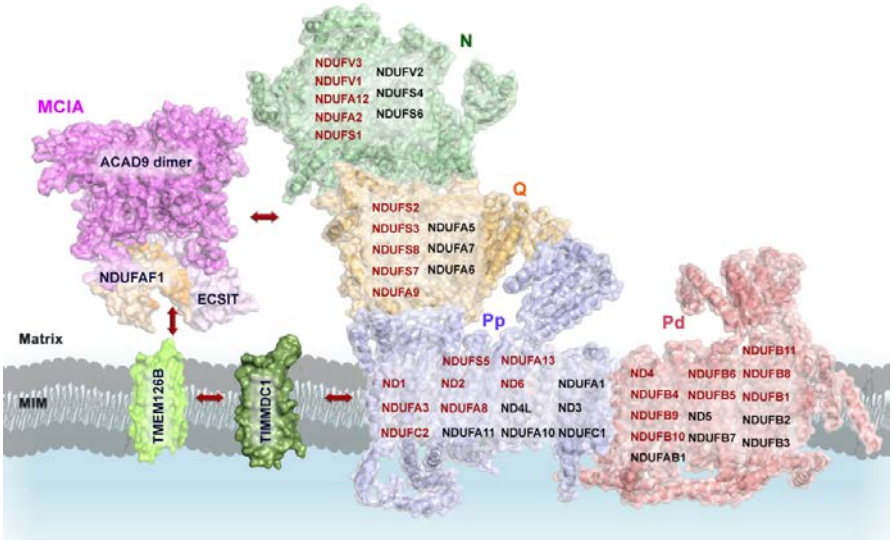

Figure 1: Proposed model of the molecular assembly of the MCIA complex and its role in the assembly of the CI.

References

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