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Integrative Biology to tackle mitochondrial respiration in Alzheimer's pathogenesis

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Respiratory complexes located in the internal membranes of our mitochondria are true macromolecular batteries: they couple the flow of electrons through clusters of metals and cofactors with a transfer of protons to create a gradient that provides the energy necessary for the ATP production and therefore to the nourishment of essential life processes. The first complex in the respiratory chain, named Complex I (CI), is one of the largest membrane proteins, made up of 45 subunits. The processes of its assembly and its sophisticated regulation are still poorly understood, although it is known that their disruption leads to neurodegenerative diseases such as Alzheimer's.
While exploring the molecular basis for protein recognition in the Mitochondrial CI Assembly (MCIA) complex, using a combination of biochemical, biophysical and structural techniques, we discovered that the assembly of the MCIA complex juggles between two incompatible activities: fatty acid oxidation and CI assembly. Cryo-EM and crystal structures of the partners in complex and alone allowed us further understanding into how they switch from one function to another. Furthermore, our recent mitochondrial analyses in amyloidogenic cells provide insights into the relationship of CI assembly in neurological dysfunction, suggesting whether MCIA components could detect early AD pre-symptomatic stages.

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Modern Methods in Structural Biology and Dynamics

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