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Investigation of the mechanisms of AnxA11 anchoring in membranes and the impacts of mutations associated with amyotrophic lateral sclerosis

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Annexins, calcium-dependent phospholipid-binding proteins, are essential for organismal health and homeostasis. They are involved in various biological processes, including anticoagulation, cell signaling, cell growth regulation, apoptosis, vesicle fusion, and intracellular transport. Moreover, several annexin family members participate in the repair of plasma membrane injuries, a crucial process for maintaining cellular integrity, especially in mechanically active tissues. (1) This project focuses on Annexin A11 (AnxA11), a vital member of the annexin family. AnxA11, which has an intrinsically disordered and unusually long N-terminal domain, is associated with several medical conditions, including systemic autoimmune diseases and sarcoidosis. (2) Recently, multiple genetic mutations in the D40 residue of the protein have been frequently found in patients with Amyotrophic Lateral Sclerosis (ALS). (3) Although AnxA11 has been observed to relocalize to the plasma membrane in response to increased intracellular calcium ion concentration, its specific role in membrane repair has not yet been explored. This project aims to investigate the underlying mechanisms of AnxA11 anchoring to biological membranes. We will analyze how membrane curvature, phospholipid composition, interactions with protein partners ALG-2 and S100A6, and the formation of condensates through phase separation influence the membrane anchoring process and potentially the repair mechanism. Additionally, we will explore how D40G and D40Y mutations affect the biophysical and interaction properties of AnxA11, contributing to ALS pathogenesis. Preliminary studies indicate a low affinity between AnxA11 and calcium ions, with significant structural modulation of the protein in the presence of these ions. Furthermore, the ability of AnxA11 to form biomolecular condensates, a characteristic not observed in other annexins involved in repair under physiological conditions, is amplified in a calcium-dependent manner.

Palavras-chave: Esclerose lateral amiotrófica; Proteína intrinsicamente desordenada; Reparo de danos em membrana.

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