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Electron Transport Chain Acts as Potential Regulator of ER-Mitochondria Interactions

Mitochondria are highly dynamic organelles that interact with various cellular components, including the endoplasmic reticulum (ER). This essential interaction occurs through mitochondria-associated membranes (MAMs) to carry out key processes such as phospholipid trafficking. However, the effects of mitochondrial dysfunction, specifically within the electron transport chain (ETC), on mitochondria-ER interactions are not fully understood. To investigate how perturbed bioenergetics impact MAM activity, phospholipid trafficking and synthesis were assessed, in which the conversion of phosphatidylserine (PS) to phosphatidylethanolamine (PE) was analyzed after inhibiting ETC complexes. Using two human cell models—fibroblasts with a mutation on the nuclear gene NDUFS4, interrupting complex I of the ETC, and a human osteosarcoma cell line (143B cells) treated with ETC inhibitors and uncouplers—it was found that inhibition of ETC complexes I, III, IV, and V results in a significant lack of conversion between PS and PE ($p < .0001$), demonstrating altered MAM activity due to mitochondrial dysfunction, and indicating that the ETC is a regulator of such interactions. However, inhibition of complex II, which has no effect on mitochondrial membrane potential (MtMP), was observed to have no impact on MAM connections, suggesting that MtMP may also regulate ER-mitochondria contact sites. The findings of this research contribute to the understanding of how ETC dysfunction impacts inter-organelle crosstalk, providing new insights into the pathophysiology of mitochondrial disorders and a greater understanding of the dynamic role of mitochondria in cells.