When Mitochondria Lose Their “Wiggle”: Cholesterol-Induced Membrane Rigidity Stalls Drp1-Driven Fission in Metabolic Syndrome and Alzheimer’s Disease -- A Multi-omics and Biophysical Modeling Study

Zhang, Lin (School: Shanghai Foreign Language School Affiliated to SISU)

Yin, David (School: Shanghai Foreign Language School Affiliated to SISU)

Metabolic dysfunction in Alzheimer’s and fatty liver disease is characterized by a paradoxical progression from mitochondrial hyperfission to pathological elongation. While lipid remodeling is a known hallmark of these conditions, the physical mechanism governing this transition remains poorly defined. This study employs a multi-omics approach—integrating 100GB of coarse-grained molecular dynamics (MD) simulations, Mendelian Randomization (MR) using genomic data from 500,000 individuals, and transcriptomic analysis of patient RNA-seq profiles—to quantify the mechanical barriers to mitochondrial division. MD simulations reveal that pathological cholesterol enrichment (10%+) induces a ~105% increase in membrane bending rigidity ~93% rise in area compressibility(KA). We propose a novel “Motor Stall Theory,” wherein this increased stiffness raises the fission energy barrier beyond the ~80 kBT work capacity of the Drp1 motor. This creates a "kinetic bottleneck" where the membrane enters a jammed state at constriction diameters of 30–40 nm, preventing the final scission cliff. To validate this causal link, MR analysis confirms that genetic variants predisposed to high membrane cholesterol are significantly associated with earlier Alzheimer’s onset. Furthermore, transcriptomic data show a compensatory upregulation of fission machinery (DNM1L/MFF) in stressed cells, indicating a failed genetic attempt to overcome the physical stall. By establishing the first quantitative bridge between nanoscale membrane physics and systemic disease progression, this work identifies "Mechanomedicine" as a vital therapeutic horizon for restoring mitochondrial "wiggle" and preventing metabolic cellular failure.

Awards Won: