Quantifying Organellar Ultrastructure in Cryo-Electron Tomography Using a Surface Morphometrics Pipeline

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Mitochondria are highly dynamic organelles that function simultaneously as an interconnected network and as discrete organellar units with important roles in cellular energy production and stress signaling integration. Disruptions to the pathways that mediate their dynamic behavior causes mitochondrial dysfunction associated with a myriad of diseases including cancer and neurodegeneration. Despite this biomedical importance, the mechanisms mediating stress-induced adaptive remodeling across mitochondrial networks and within their individual membranes remain poorly defined. To address this, we developed a correlative and quantitative cryo-light microscopy and cryo-electron tomography workflow to map and measure changes in mitochondrial structure across multiple biological scales and distinct cellular physiologies. We show that activation of acute endoplasmic reticulum (ER) stress remodels all aspects of mitochondrial inner membrane ultrastructure (e.g., curvature, inter-membrane distance, orientation) in a manner that is dependent on bulk network morphology. We are applying pharmacologic and genetic approaches to decipher the molecular basis for these stress-induced modulations to mitochondrial structure and function. This work sets the stage for directly assessing how distinct stress states remodel organellar networks, membranes, and proteins at nanometer- scale resolution and at throughput sufficient for statistical hypothesis testing.