

Contributions of mitochondrial fission proteins to mitophagy

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Contributions of mitochondrial fission proteins to mitophagy

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Parkinson's disease & PD-related disorders

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Research Abstract

DESCRIPTION (provided by applicant): Mitochondria are fundamentally important for human health and disease. Mitochondrial fission and fusion play key roles in maintaining a healthy mitochondrial network. Fusion can compensate for small amounts of damage to mitochondria

through complementation, while fission helps shed severely damaged portions of mitochondria for degradation through mitophagy. Here, we propose to study the contributions of mitochondrial fission proteins to mitophagy. The key player in this process is Drp1, a Dynamin-related protein that is recruited to mitochondria by Mff, a receptor for Drp1 on the surface of mitochondria. New data from our lab and that of our collaborator Dr. R. Youle (NIH) suggests that another mitochondrial outer membrane, Fis1, also plays a critical role during this process. Fis1 recruits the Rab7GAP TBC1D15 to mitochondria where it acts to attenuate Rab7 function and promotes recruitment of autophagic isolation membrane. Mutations in TBC1D15 and Fis1 have similar effects on mitophagy. We will address key questions raised by the hypothesis that Fis1 helps guide orderly disposal of defective mitochondria during mitophagy. Specific aims are: 1. Identify upstream triggers for stress-induced fission. Our preliminary data suggests that the requirements for Fis1 depend on upstream triggers for fission. CCCP bypasses Fis1 function, while ROS producing chemicals, such as Antimycin A and Paraquat, do not. We will investigate the possible roles of ROS-signaling pathways in this process. 2. Investigate changes in the fission machinery. Fis1 can bind to TBC1D15, but it was previously also shown to interact with Drp1 and key components of the ER-mitochondrial interface. We will test whether Fis1 interactions with TBC1D15 and other proteins are modulated by different fission inducing conditions and will look for additional changes in the fission machinery using a range of biochemical approaches. 3. Investigate downstream effects on degradation. The effects of Fis1 and TBC1D15 suggest a role in the attenuation of Rab7 function mitophagy. We will determine how TBC1D15 accesses Rab7 and which stages of mitophagy are affected by these proteins. 4. Investigate the functions of Fis1 and its binding partners in neuronal cells. We will test whether Fis1 and TBC1D15 or the closely related protein TBC1D17 affect mitophagy in neuronal cell lines and primary neurons as they do in cancer cell lines. Ultimately, our experiments will help understand how mitochondria respond to stress. This stress response is critical for human diseases, such as Parkinson's. More insight into these processes could help develop treatments by providing new ways to promote mitophagy where and when it is acutely needed.

Lay Summary

PUBLIC HEALTH RELEVANCE: Mitochondria are small power plants within cells. Their roles in energy production and oxygen consumption also subject them to a lot of damage. Mitochondria compensate by dividing and fusing with other mitochondria. Fusion helps replenish damaged components, while fission helps eliminate the most badly damaged mitochondria. Fission and fusion have been linked to major human diseases, such as Parkinson's, where the process of mitochondrial elimination has gone awry. We propose to study the roles of specific fission proteins in this process, with the long-term goal of restoring the ability to eliminate damaged mitochondria.

Further information available at:

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United States of America

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Parkinson's disease & PD-related disorders

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