Recent Research Reveals Possible Dimer Structure of Human MiD51

Members: Alexis Coffeen, Theodore Holdmann, Alyssa Jodarski, Sarah Laudolff, Logan Meyer, Theresa Oliver, Chloe Smith, Bekah Tilstra, Elizabeth Walters, Cora Williams
Advisor: Josh Demski
Mentors: John Egner, Amber Bakkum, Medical College of Wisconsin

Mitochondrial Fission and Fusion

Mitochondria go through a constant cycle of fusion and fission regulated by an array of membrane and cytosolic proteins. A balance of mitochondrial fusion and fission is necessary to meet the energy demands of the cell, to maintain calcium homeostasis and to allow for cellular processes such as apoptosis and mitophagy. Mitochondrial fission is accomplished by recruitment of dynamin related protein (Drp1) to the mitochondrial membrane by MiD51 and other mitochondrial membrane proteins. At the mitochondrial membrane surface, Drp1 multimerizes creating a ring like structure which constricts and leads to fission. One important function of fission is depolarizing damaged mitochondria which facilitates mitophagy and maintains cell heath. Fission also creates smaller mitochondria that are more capable of generating reactive oxygen species important in homeostatic oxygen sensing. Disordered mitochondrial dynamics of MiD51 have been implicated in cardiovascular diseases, specifically pulmonary arterial hypertension (PAH). Dysregulation of the balance between fission and fusion, where fission exceeds fusion, has been documented in PAH. Inhibition of fission, by inhibiting Drp1, prevents cell cycle progression, arresting the cell in the G2M phase, and also induces apoptosis of the pulmonary artery smooth muscle cells (PASMCs).

Does Human MiD51 Form a Dimer?

MiD51 belongs to the nucleotidyltransferase fold superfamily of proteins. MiD51 is a globular protein anchored on the mitochondrial outer membrane, and is organized into three domains; a disordered domain, an N-terminal domain containing a binding pocket for ADP/GDP, a recruitment region for Drp1, and a C-terminal domain. In mice, MiD51 forms functional dimers. It has been shown in mice that point mutations in interface residues prevent dimer formation. MiD51 monomers will recruit DRP1 however they fail to release DRP1, preventing mitochondrial fission. Human dimeric MiD51 has never been crystallized, but is believed to exist based on the dimeric crystal structure of the mouse homolog and data.

Summary

MiD51 has been implicated in heart disease, specifically PAH. Several strategies have been used to therapeutically target Drp1 as a preclinical treatment for PAH. Pharmacological inhibition of Drp1 activity produced encouraging results, regressing experimentally induced PAH in a xenotransplantation murine model. More research is needed to fully understand how the oligomeric state of MiD51 affects Drp1 GTPase activity in humans. Gaining a more complete understanding of the form and function of these proteins may eventually lead to more effective targeted treatments.

Citations

Looks good to me, Laconia! John & Amber, we look forward to your review. Thank you!

Anonymous, 3/29/2018

I changed question to read Does Human MiD51 form a dimer? This question has bigger impact than previous wording, but when presenting, you can stress/emphasize the human part.

Anonymous, 3/29/2018