

Greenfield High School SMART Team

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Not-So-Mighty Mitochondria: Neonatal Lethality Due to Drp1 Malfunction

PDB: 4BEJ

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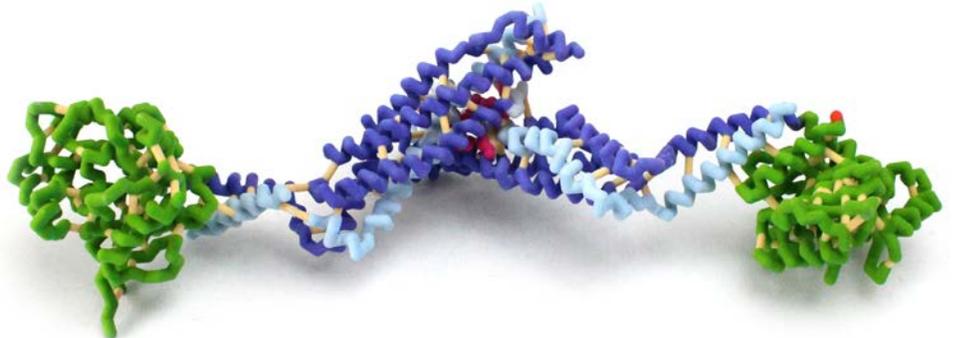
Format: Alpha carbon backbone

RP: Zcorp with plaster

Description:

Cells require mitochondria to produce cellular energy, allowing work to be done. Defective mitochondrial function can impair proper cell function, even leading to neurodegenerative diseases,

such as Parkinson's and Alzheimer's disease, and neonatal lethality. The defect stems from imbalances between mitochondrial fission (splitting) and fusion (combining), resulting in abnormal mitochondrial morphology. Dynamin related protein 1 (Drp1) is a GTPase (enzyme that breaks down GTP) that results in fission of mitochondria by forming tubular spirals around the outer mitochondrial membrane in order to split one mitochondrion into two. The Greenfield SMART Team modeled Drp1 using 3D printing technology to investigate its structure. The structure of Drp1 is ordered by the following four components: GTPase Domain (G Domain), Middle Domain, B-Insert, and GTPase effector domain (GED). The G Domain hydrolyzes GTP and interacts with other G Domains on neighboring Drp1s, while the Middle Domain is the primary site of dimerization. The B-Insert regulates Drp1 assembly, and the GED helps activate the G domain. Drp1 in the cytosol is a dimer; when recruited to the outer mitochondrial membrane Drp1 forms an oligomer. The specific amino acids, Met482, Glu490, Asn635, Asp638, Tyr628, and Lys642, help keep the dimer interface together due to salt bridge interactions. A mutation in Drp1, A395D, was identified as important for causing neonatal lethality due to improper assembly of Drp1 on the outer mitochondrial membrane. When Drp1 malfunctions, such as in the A395D mutation, the imbalance of fusion and fission leads to detrimental issues, such as neonatal lethality. Studying Drp1 could prevent unnecessary death and eventually lead to a better understanding of other Drp1-related neurodegenerative diseases.



Specific Model Information:

- Backbone is colored lightgray.
- GTPase (G) Domain (Glu2-Asp299) is colored green.
- Middle Domain (Cys300-Pro491) is colored blue.
- B-Insert (Asp504-Gln615) is colored gray.
- GTPase Effector Domain (GED) (Arg616-Arg705) is colored lightblue.
- Amino acids Met482, Glu490, Asn635, Asp638, Tyr628, and Lys642 involved in dimerization of Drp1 are colored magenta.
- Mutation associated with neonatal lethality at Ala395 (A395D) is colored orange.
- C terminus (Met1) is colored red.
- N terminus (Arg705) is colored royalblue.
- Structural supports and H-bonds are colored navajowhite.

<http://cbm.msoe.edu/smartTeams/index.php>

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