THE ROLE OF MICOS COMPLEX AND ITS ASSOCIATED PROTEINS IN THE HEART

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Problem

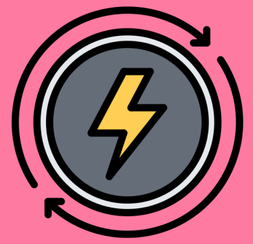
What roll does MICOS and its associated proteins play in cardiovascular diseases?

Objective

- Explain what is MICOS and discuss its functions.
- Explain some of the proteins that compose this complex.
- Evaluate proteins associated with MICOS.
- Investigate how this complex is affected, and the role it plays in cardiovascular diseases.

Mitochondria

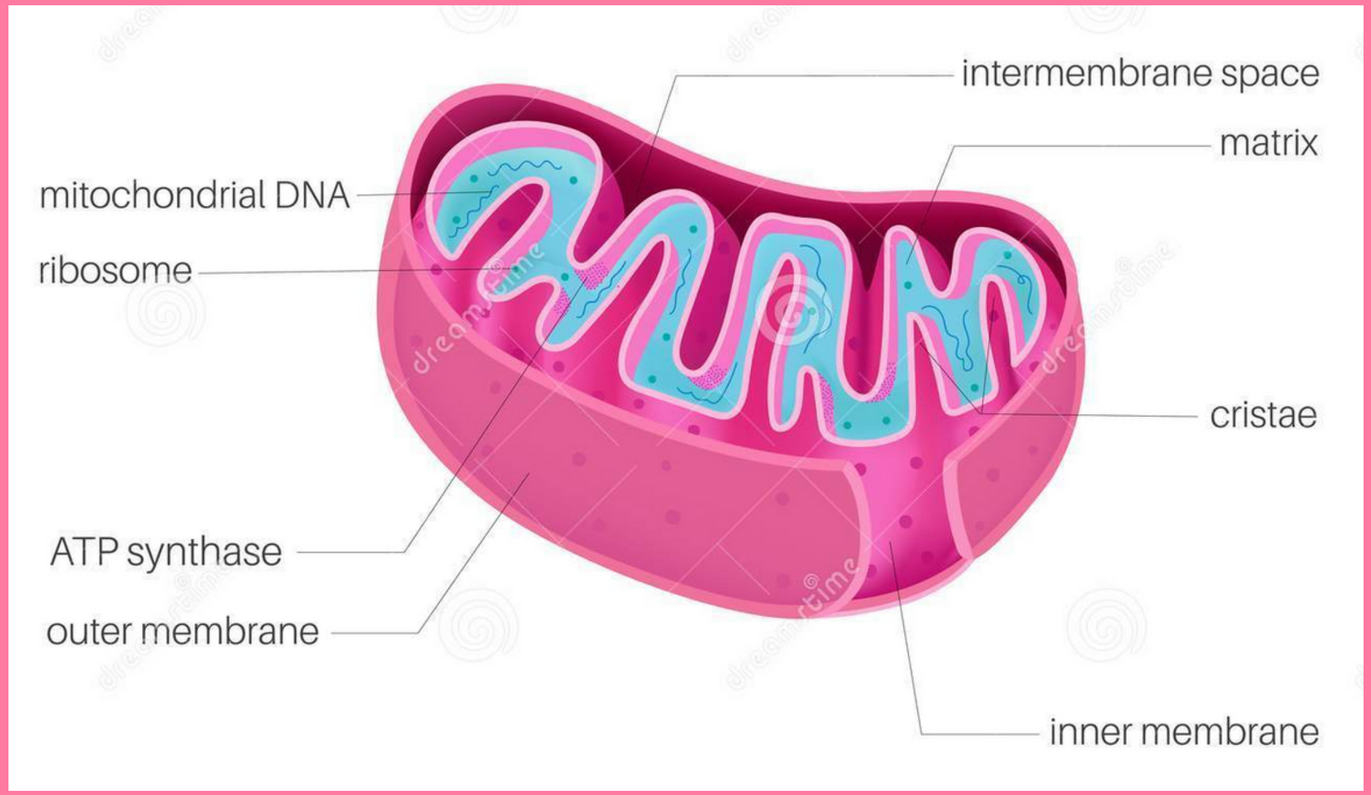
- Generates the chemical energy needed to stimulate all biochemical reactions in the cell.



- This chemical energy, adenosine triphosphate (ATP), powers millions of cells that carry out important processes in the human body.

- Malfunctions in the mitochondria mean alterations of these ATP distribution processes etc., resulting in severe damages to the human body, specifically in the heart.

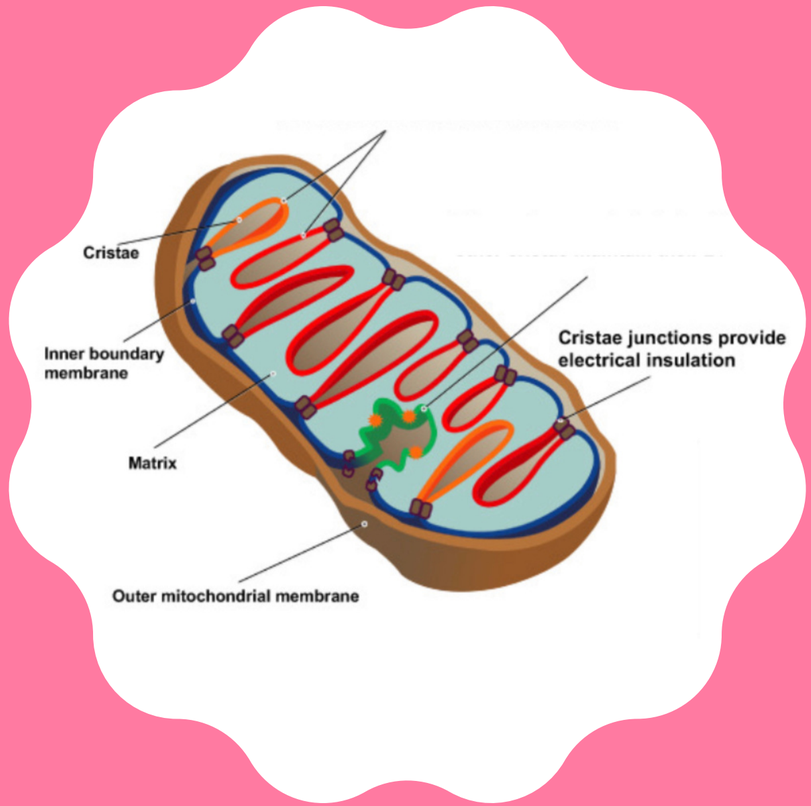
Mitochondrial Structure



Where do malfunctions in the mitochondria start?

- Malfunctions are due to abnormalities in the mitochondrial structure.

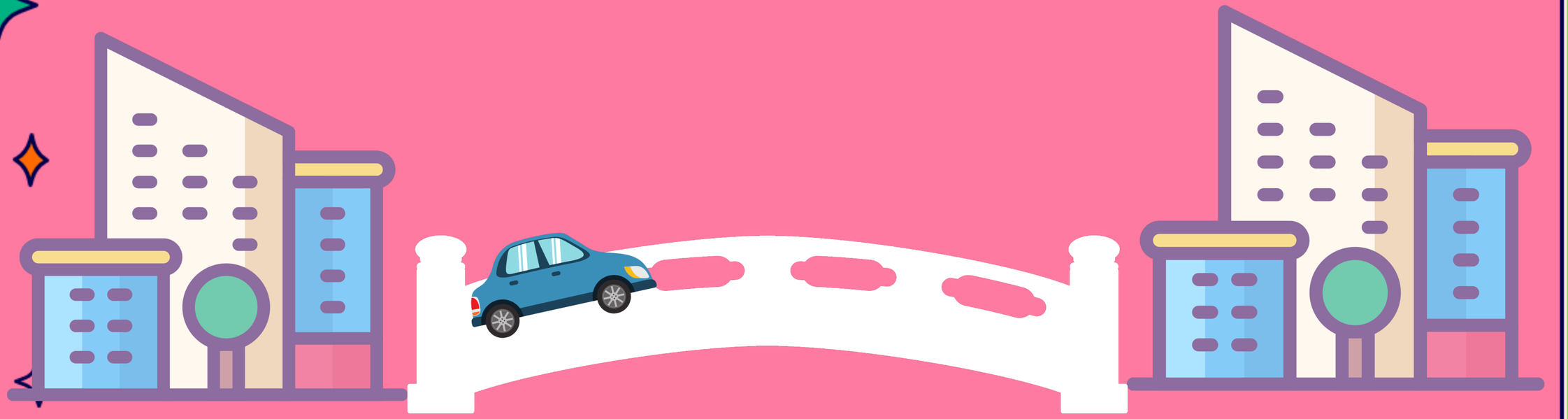
- These could lead to severe damages in the human body, including diseases involving the nervous and cardiovascular systems.



Imagine this....

Worker's home

The factory he works at



MINI Teodoro Moscoso

MICOS

Multi-subunit protein that plays a crucial role in:

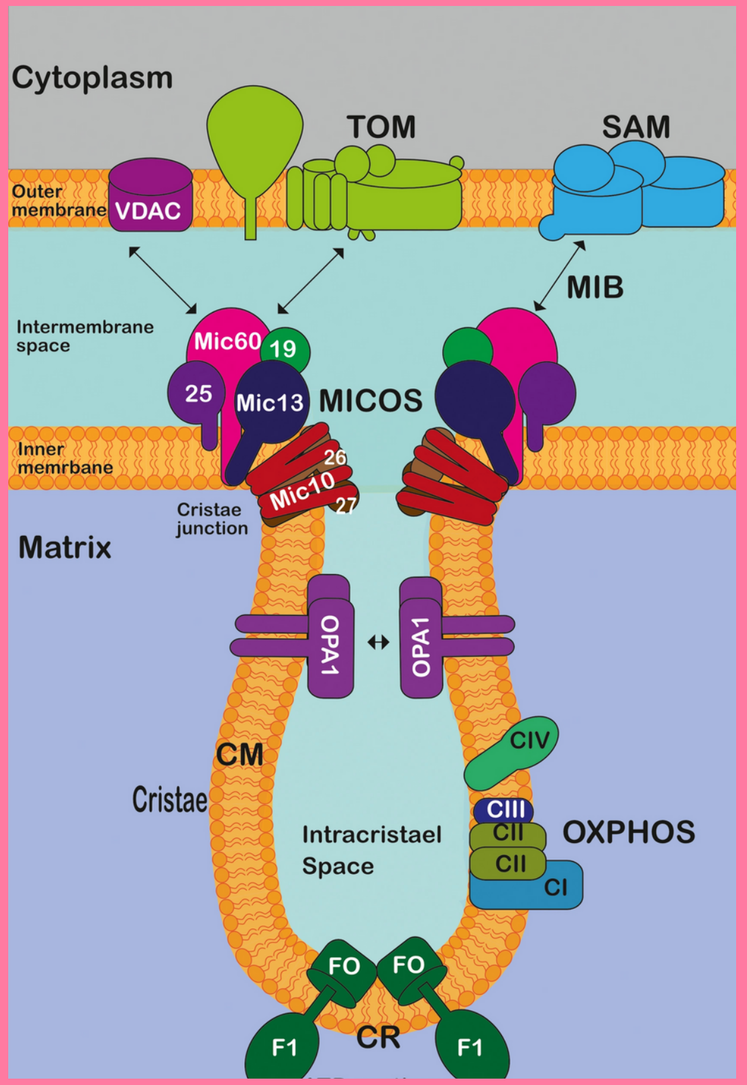
- Maintaining mitochondrial architecture (cristae junctions etc.) and controling overall mitochondrial function and stability.
- Overseesing maintenance of inner and outer membrane contact sites (key interactor).
- Communicating in a large network of interacting proteins and protein machineries.
- MICOS has various subunits and related proteins, which work with this complex to maintain mitochondrial function.

Human	Yeast	Proposed function	References
MICOS (mitochondrial contact site and cristae organizing system)			
MIC60 (mitofilin, IMMT = inner mitochondrial membrane protein, MINOS2)	Mic60 (Fcj1 = formation of crista junction protein 1)	Contact site formation, membrane bending, maintenance of crista junctions, facilitates protein and lipid biogenesis	[21–23, 27, 29, 34, 38, 41, 42, 51, 54, 55, 57, 60–62, 65, 68, 71, 83, 139, 140]
MIC19 (CHCHD3 = coiled-coil helix coiled-coil helix domain-containing protein 3, MINOS3)	Mic19 (Aim13 = altered inheritance rate of mitochondria, Mcs19)	Myristoylated inner membrane protein, regulates Mic60 function and MIB complex	[21–25, 27, 35, 38, 41, 54, 63, 64, 66, 67, 71, 74, 76, 77, 212]
MIC25 (CHCHD6 = coiled-coil helix coiled-coil helix domain-containing protein 6)	-	Paralog of Mic19 in metazoa	[27, 40, 41, 63, 67, 75]
MIC10 (MINOS1)	Mic10 (Mcs10, Mio10, Mos1)	Oligomerization, membrane bending, maintenance of crista junctions	[21–23, 25, 27, 30, 37, 38, 56–58, 78, 109, 110, 139, 188]
MIC13 (QIL1)	Mic12 (Aim5 = altered inheritance rate of mitochondria, Mcs12)	Connecting the MIC60 and MIC10 subcomplexes	[21–23, 27, 28, 47–49, 53, 58, 81, 188]
MIC26 (APOO = apolipoprotein O, MIC23)	Mic26 (Mio27, Mcs29, Mos2)	Regulatory role in MIC10 subcomplex	[21–23, 27, 39, 41, 57, 58, 78, 79, 188]
MIC27 (APOOL = apolipoprotein O-like)	Mic27 (Aim37 = altered inheritance rate of mitochondria, Mcs27)	Regulatory role in MIC10 subcomplex	[21–23, 27, 36, 38, 39, 41, 53, 57, 58, 78, 188]
F_1F_o-ATP synthase			
ATP5I (ATP5ME, ATP5K, subunit e)	Su e (Atp21, Tim11)	ATP synthase dimerization, membrane curvature	[90, 93, 94, 97, 98, 100]
ATP5L (ATP5MG, subunit g)	Su g (Atp20)	ATP synthase dimerization, membrane curvature	[90, 93, 94, 97, 98, 100]
Su k (DAPIT = diabetes-associated protein in insulin-sensitive tissues)	Su k (Atp19)	ATP synthase dimer stabilization, oligomerization	[93, 96, 99, 105, 106]

Human	Yeast	Proposed function	References
Further proteins involved in inner membrane architecture			
OPA1 = optic atrophy 1	Mgm1 = mitochondrial genome maintenance 1	Mitochondrial inner membrane fusion and morphology, cristae biogenesis	[9, 116–119, 130, 133]
PHB (prohibitin 1)	Phb1 (prohibitin 1)	Lipid and protein scaffold of the inner membrane	[172, 195, 213–217]
PHB2 (prohibitin 2)	Phb2 (prohibitin 2)	Lipid and protein scaffold of the inner membrane	[172, 195, 213–217]

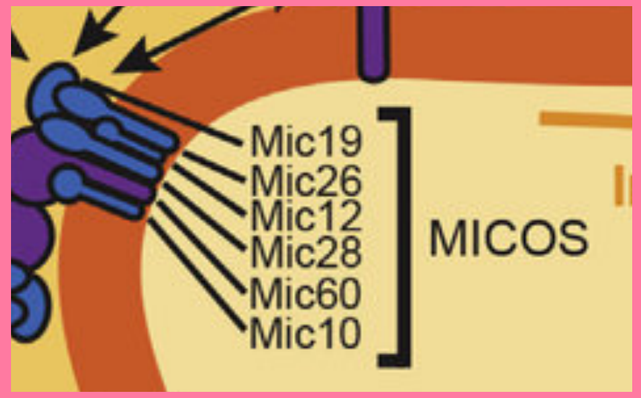
MIC-60 PROTEIN

- Known as the mitofilin or heart protein
- Core component for the assembly and maintenance of MICOS
- Key interactor with outsider proteins (kinase Pink1)
- Bridge or main communicator between outer membrane and inner membrane of the mitochondria (b-barrel proteins)
- Deletion, or lack of the protein results in direct damage to the inner membrane (poor ultrastructure)
- Overexposure of the protein causes an unregulated amount of cristae branching and cristae junctions

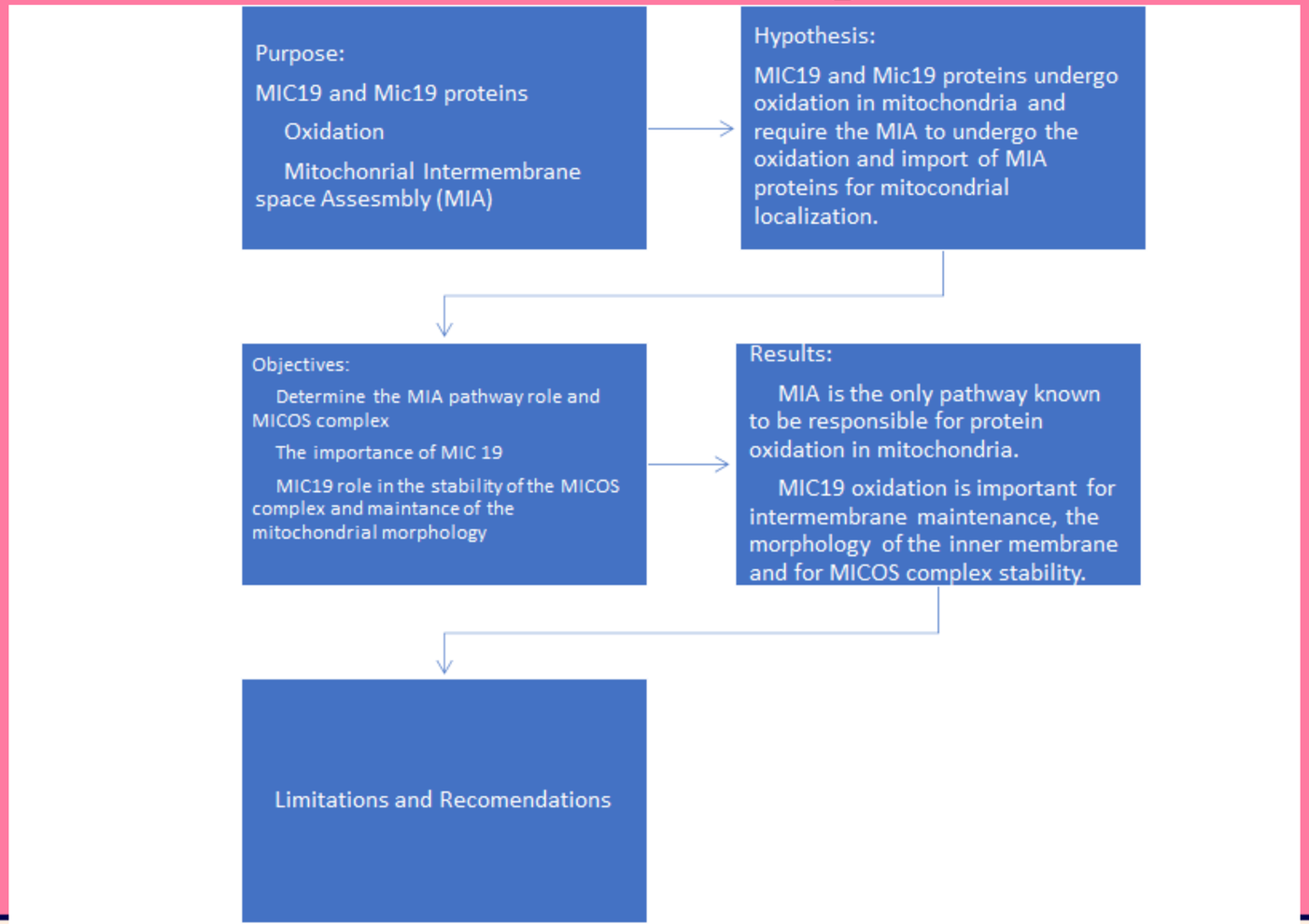


MIC19

- MIC19 is a peripheral protein of the inner membrane and component of the MICOS complex.
- This protein maintains mitochondrial work and its related with the mitochondria in many ways.
- MIC19 undergoes oxidation in the mitochondria and provides stability in contact sites and cristae.
- Mic19 works together with OMM proteins.
- MIC 19 is also related to cardiolipin, which is in the heart. Cardiolipin joins with MIC19 and helps to assemble and stabilize the MICOS complex.

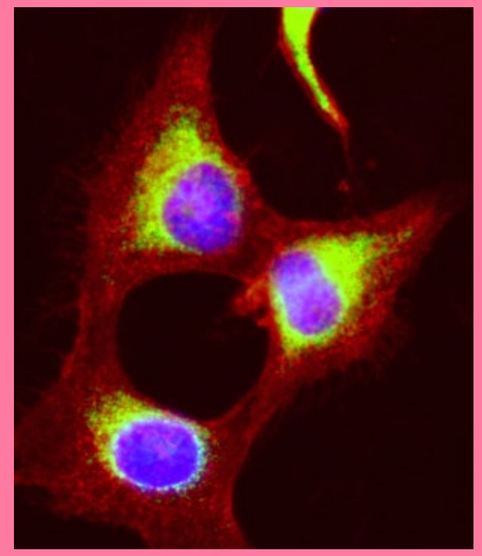


Does human and S. Cerevisiae MIC19 proteins undergo oxidation in mitochondria requiring the Mitochondrial Intermembrane space?



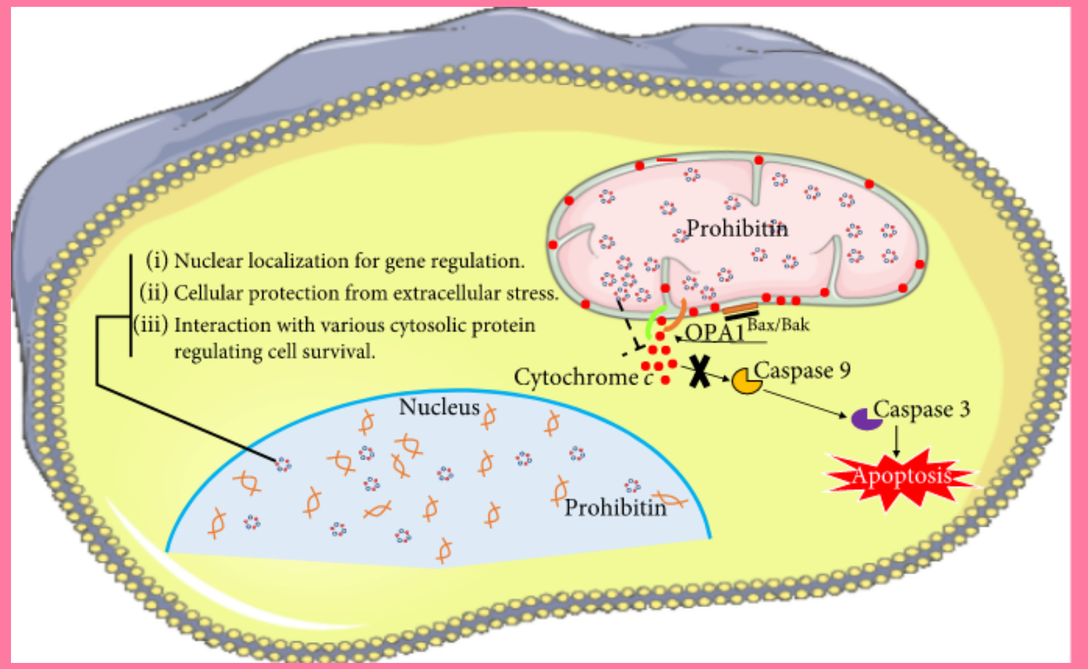
Prohibitin Protein

- Prohibitin 1 & 2 are proteins which express themselves in different tissues and organelles.
- They can determine the cell fate, death, or life.
- Prohibitin 2 plays a key role in the cellular energy metabolic homeostasis.
- Loss of Prohibitins has resulted in fragmented and disorganized mitochondria.
- Depending on the cellular localization, Prohibitin 1 & 2 have distinctive functions, but are more hard working on the mitochondrial function.



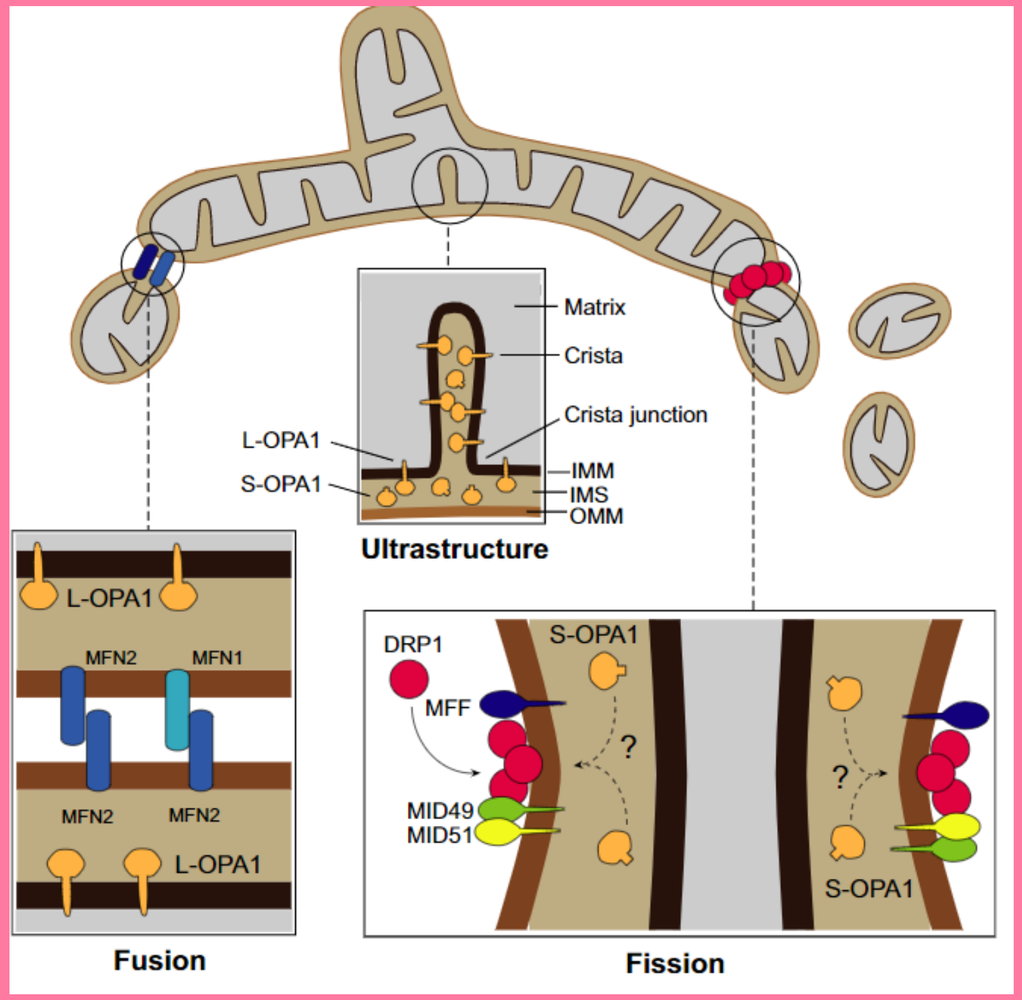
Prohibitin Protein in the Heart

- PHB alterations have been found in aging and cancer, neurodegenerative, kidney and cardiac diseases.
- PHB1 in cardiomyocytes has been shown to protect cells from oxidative stress-induced mitochondrial apoptosis.
- They preserve the cytochrome c release and mitochondrial membrane permeability, which eventually can lead to cell death.

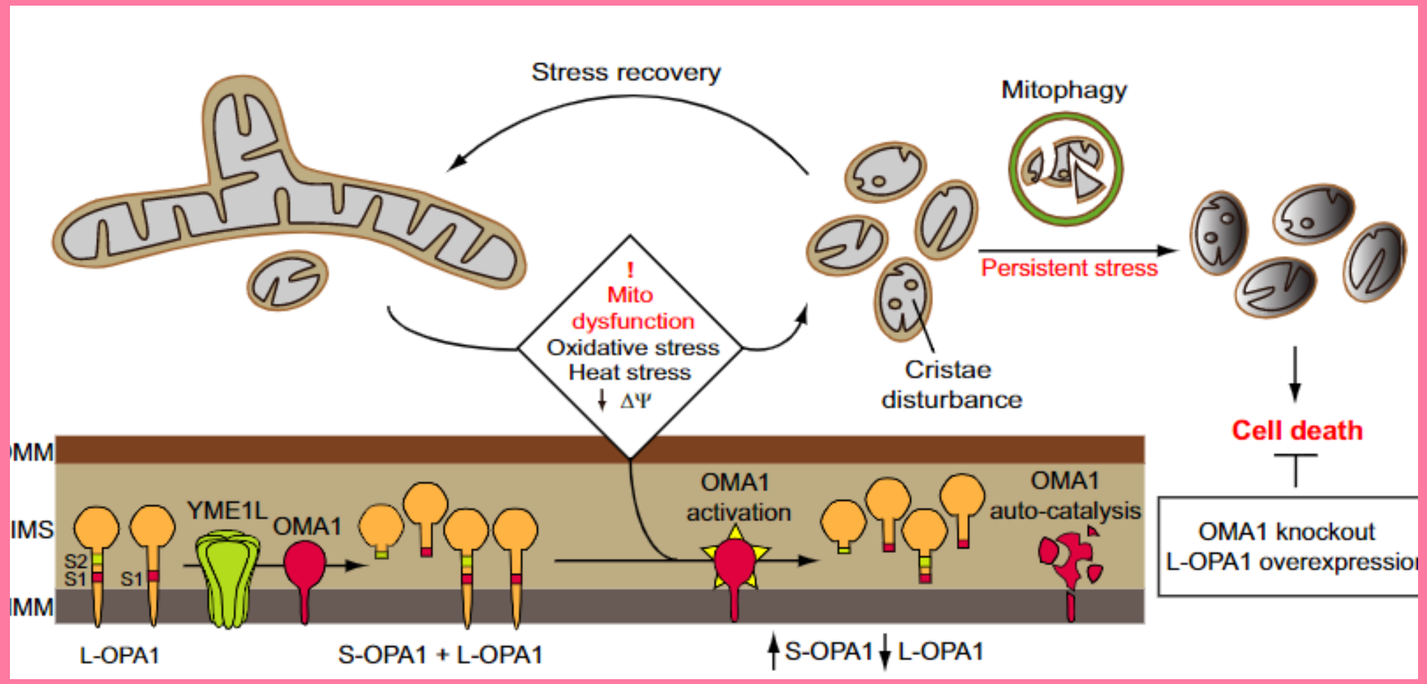


OPA1

- Is the only protein responsible for the fusion of the IMM.
- OPA1 preserves cellular death and organizes mitochondrial cristae.
- Maintains mitochondrial morphology and energetics.



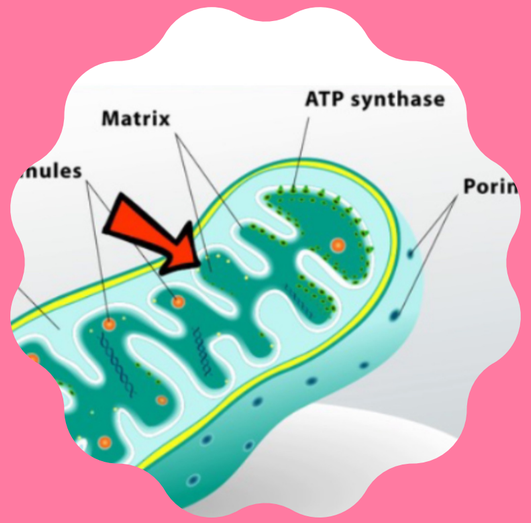
OPA1

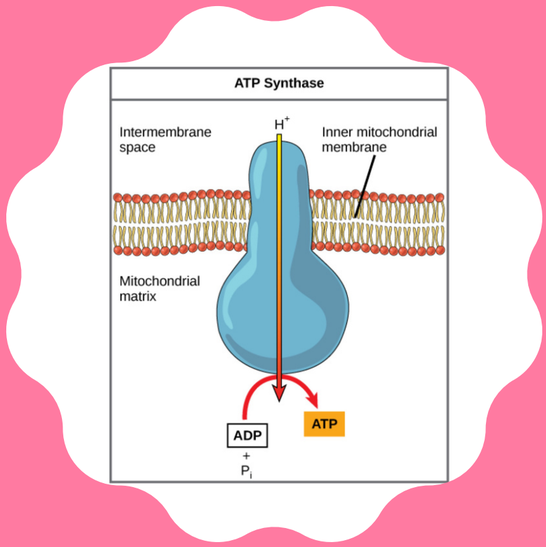


- OPA1 is composed of two different isoforms.
- Loss of the OPA1 fusion property may cause apoptosis.
- Apoptosis is a mechanism of cellular death.

ATP Synthase

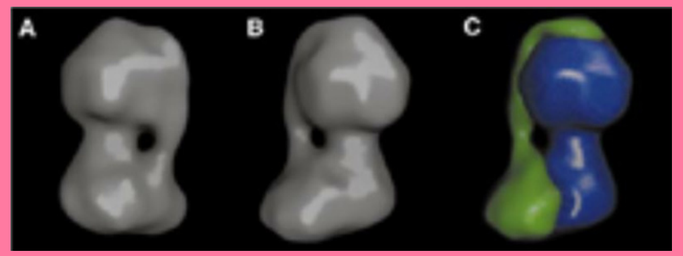
- Also known as Complex V, ATP synthase is dedicated to the production of ATP.
- This occurs through a process called ATP synthesis and it takes place in the mitochondrial matrix.
- ATP is made from adenosine diphosphate (ADP) and inorganic phosphate (Pi).
- Complex V also serves as the opposing force to MICOS and creates the positive curvatures in cristae.
- ATP synthase is crucial to sculpt cristae and maintain mitochondrial functions.

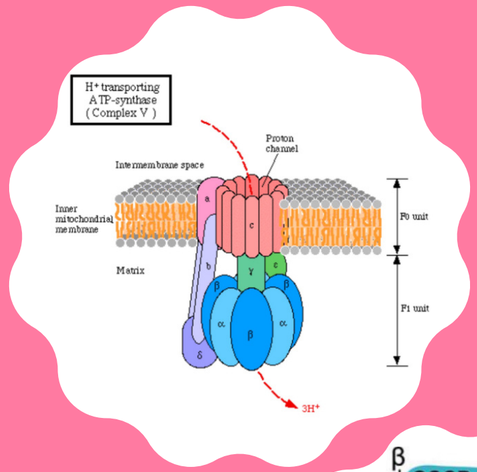


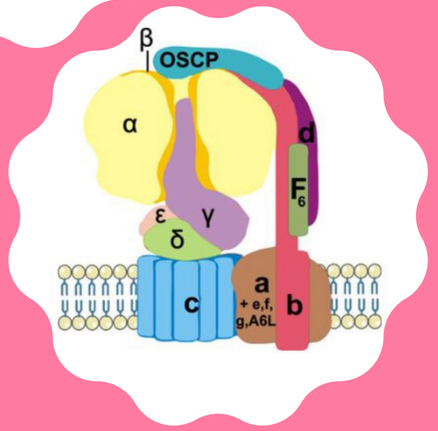


ATP Synthase

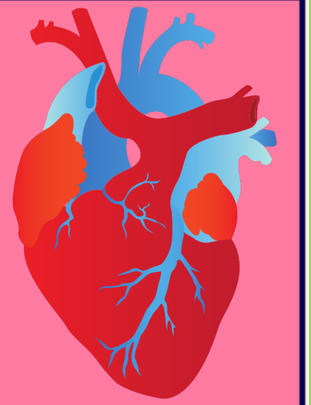
- ATP synthase is divided into two functional domains: F1and Fo.
- Within these domains, there are many subunits, and they all have their specific function in the production of ATP.
- The heart has a high production and consumption rate of ATP which is required to maintain its continuous mechanical work.
- Problems in all the ATP generating processes may severely affect contractile function of the heart directly.
- Alterations in cardiac metabolism can affect the progression to heart failure by mechanisms beyond ATP supply.





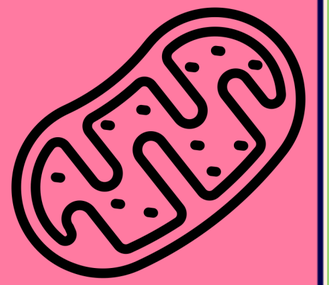


Discussion



- Both **Apoptosis and Necrosis** can cause heart failure

- The absence of **Mic-60** may cause unwanted organelle abnormalities that can lead to Ischemia/ Reperfusion (strokes)



Limitations

- The specific relation between MICOS and its related proteins with the heart is still to be determined.
- There is not much research conduced in this area.
- The research that does exist, has been done in yeast.

Recommendations

- We recomend that a deeper study of this complex and its related proteins be held in future investigations
- We also suggest future experiments be done on animal cells to better relate the effects of these proteins in cardiovascular diseases
- The separation or enhancement of one certain protein and the way it reacts in the specimen

Conclusion

- The proteins discused in this presentation are crucial for the stability of cristae structure, and therefore play a critical role in mitochondrial formation and stability.
- ATP synthase is in charge of producing ATP and, without it, the mitochondria would fail to keep its form and perform its function accordingly.
- PHB1 has escencial pleiotropic functions that require signaling for their porper function.
- OPA1 is one of the most important proteins, providing the cell life.
- Mic-60 and Mic-19 are key components of MICOS, establishing a proper and functional mitochondrial cristae, specifically during problems of IR when mitochondria are susceptible.

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