Review: Dynamic Mitochondrial Movement in Cells and their Linkage to Various Diseases

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1.INTRODUCTION

Mitochondria is the energy producing 'power-house' in all eukaryotic cells. Recently, dynamic mitochondrial movements have been linked to various human diseases, such as Parkinson's Diseases and Alzheimer's Diseases.

The aims of our research were:

- To explore mitochondrial movements in various cells
- To outline important links between these movements and human diseases
- To highlight treatment method developed recently using the autophagy function of mitochondria

2. MITOCHONDRIAL DYNAMICS

Mitochondria move dynamically in certain directions by motor proteins actions along the cytoskeleton. Interactions between motor proteins, adaptors and receptors are also important. Adaptors distinguish mitochondria and other organelles by binding with receptors which localize in mitochondrial outer membrane. This interacts with motor protein enables movement along cytoskeleton. Kinesin and dynein are used as microtubule motor, each driving towards opposite directions. Myosin is used as actin filament.

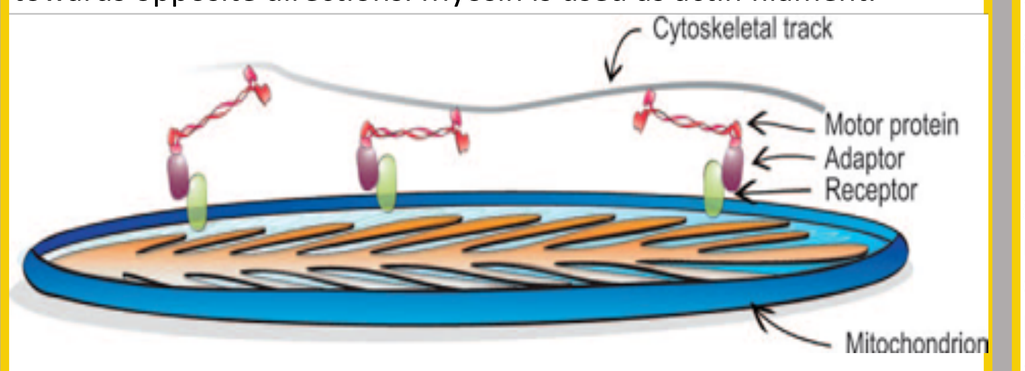

Figure 1. (Federick, R. L. et al., 2007)

MITOCHONDRIAL FUSION AND FISSION

Mitochondria exhibitfusion and fission mechanisms. Fusion involves docking, fusion of OMM, and fusion of IMM. Mfn1/Mfn2 proteins (Mitofusion1/Mitofusion2) anchored on OMM are required for the fusion and binding of OMM. OPA1 is required to tether and fuse IM M. Fission is caused by DLP1/Drp1(dynamin-like protein 1) in cytosol and hFis1(human fission protein 1) on OMM. Both fusion and fission are induced by GTPhydrolysis (Home J et al.,2009).

Many morphological defects are linked to many human diseases - thus understanding mitochondrial dynamics is important.

APOPTOSIS

Apoptosis kills the cells when they are overly replicated or damaged. The intrinsic activation pathway of apoptosis is related to mitochondria. In intrinsic pathway mitochondrial membrane potential is disrupted, causing increase in membrane permeability. As a result, apoptogenic proteins such as cytochrome c or AIF (apoptosis initiation factor) are released into cytosol which constitute apoptosome and activate caspases with protease activity (Morrision, I.M. et al.,2008). Therefore, regulating membrane permeability of mitochondria is crucial.

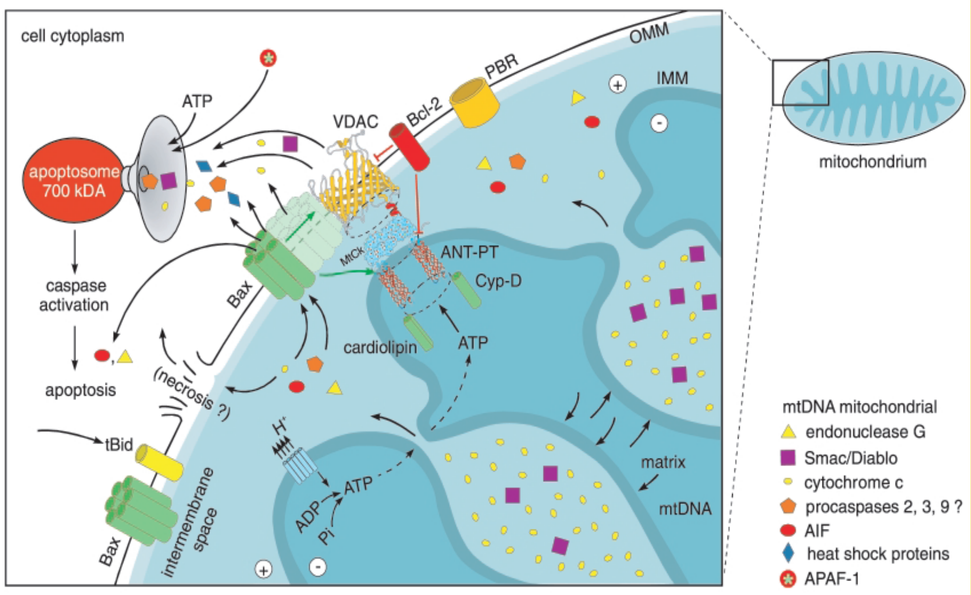

Figure 2 (Mayer, B. et al., 2003)

3. MITOCHONDRIA IN NERVE CELLS

Neurons are sensitive to changes in mitochondrial function because they consume a lot of energy, such as synaptic transmission, exon / dendritic transport, ion channels, and ion pump activity. This mitochondrial function is sensitive to the dynamics of fusion and fission. This is because the migration and distribution of mitochondria, respiration, and mtDNA are controlled through dynamics.

Alzheimer's disease(AD) – Oxidisation of synaptic mitochondria increases cyclophilin D level, defecting calcium homeostasis and clustering Aβ, causing a 'synapse disorder' that causes AD. Highly polarized cells regulate mitochondrial fission and fusion to offer energy supply but is defective in the AD brain. (Brian Duboff et al.,2013)

Parkinson's disease (PD) – a disease causing abnormal body movement due to degeneration of nigrostriatal dopaminergic neuron and accumulation of α- synuclein called lewy body (Hansruedi Büeler ., 2009). According to many studies the toxicity of dopaminergic neuron indicates mitochondria's roles in PD.

The close relationship between neurodegenerative diseases and dysfunction of mitochondria proves the potential of new treatment method

4. MITOCHONDRIA IN CANCER

Mutation of mitochondrial protein SDH and FH, enzymes for TCA cycle and tumour repressors, are critical in tumours. Germline mutations in genes encoding SDH predispose individuals to HPGL while germline mutations in FH cause HLRCC. Impaired HIF degradation due to the inhibition of its hydroxylation by PHDs is at the heart of the pathology of these tumours.

While It is clear today that many tumour cells are capable of performing oxidative phosphorylation, glucose metabolism is dramatically increased in most tumours. Increased glucose metabolism may reflect the need for rapid-production of ATP and/or of anabolic metabolites (Gogvadez, V. et al., 2009). Cancer cells display upregulated glycolysis and abnormal programmed cell death caused by hyperpolarisation, caused by ROS. So treatment for cancer is composed of stimulating downregulated apoptosis of mitochondria and normalization of mitochondrial respiratory chain activity.

Main energy source in tumor cell is glycolysis (suppress glycolysis causes ATP loss and dephosphorylase pro-apoprotic protein Bad, increasing the permeability of OMM thus apoptosis. Over generation of ROS by targeting mitochondria is useful for cancer therapy. This method is base for several traditional anti-cancer therapies. In addition, stimulating decreased mitochondrial metabolism induces overall apoptosis process. Increasing oxidative stress, increasing cytotoxicity, lowering abnormally high mitochondrial membrane potential and induces production of ROS inhibit the growth of tumor cells and remove malignant cell

5. CONCLUSION/FUTURE PERSPECTIVE

- In AD, increase in amyloid β causes mitochondria fusion-fission imbalance in neurons and for PD, defective proteins cause mitophage and problem in mitochondria transport.
- Therefore, many clinical trials are trying to control mitochondrial fission-fusion activity to normalize mitochondrial function for neurodegenerative disease therapy, but each mechanism are still unknown.
- Mitochondrial function impairment leads to metabolic reprogramming, activating glycolysis caused by imbalance on transcription factors, which can be used to determine tumor cell.
- As for cell death, mitochondrial activity is suppressed and mitochondrial resistance on apoptosis occurs in tumor cells.
- Therefore, mitochondria-localized antiapoptotic protein and mitochondrial metabolism are being studied for cancer therapy.
- There are many difficulties on developing mitochondria-targeting drugs, so as well as research on metabolism, limitations on clinical methods also needs to be overcome

6. REFERENCE

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7. ACKNOWLEDGEMENT

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