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Viewpoint

Maxwell's demon at work: Mitochondria, the organelles that convert information into energy?

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Mitochondria (singular, mitochondrion) are important organelles that in the center of energy production and information processing. They are primarily known as the powerhouse of the cell, as they produce most of the energy that cells need for all kinds of activities. This is done by generating the cellular energy currency, adenosine triphosphate (ATP). In addition to energy production, mitochondria play a central role in regulating signal transduction as signaling organelles. Mitochondria control Ca^{2+} homeostasis, reactive oxygen species (ROS) generation and elimination, cellular differentiation, and programmed cell death (apoptosis). They are involved in many signaling pathways including calcium, mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)-Akt, mammalian target of rapamycin (mTOR), wingless-int (Wnt), Ras, and insulin signaling pathways. There are accumulating evidences that suggest mitochondrial dysfunction is associated with a variety of diseases and aging. Mitochondria have been extensively researched in many areas. This article is not intent to provide a comprehensive review of each area of study, but rather to propose a hypothesis of information-energy conversion as a new viewpoint for future research.

Mitochondria: energy production

Mitochondria use oxygen within the cells and generate energy by metabolizing fuel molecules such as pyruvate from glucose and fatty acids from fats, through respiration.[1] The process is called oxidative phosphorylation in which ATP is formed as a result of the transfer of electrons from nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) to O_2, forming H_2O.[2] The oxidative phosphorylation requires an electrochemical proton gradient across the inner mitochondrial membrane, with three procedures occurring at the same time: electron transport, proton pumping, and ATP formation. The process is conducted by the respiratory chain (RC) complexes (Complex I, Complex II, Complex III, and Complex IV) and ATP synthase (Complex V) located in the

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inner mitochondrial membrane. Energy released by the electron transfer from NADH and $FADH_2$ to O_2 is used to pump protons (H^+) via Complex I, Complex III, and Complex IV. The proton gradient across the inner mitochondrial membrane drives ATP production via ATP synthase.[3] This process requires intact mitochondrial membrane for the proton concentration gradient and electric potential. Otherwise the oxidation may still occurs but no ATP is produced.[4]

Mitochondria: cell signaling

Oxidative phosphorylation generates reactive oxygen species (ROS) as byproducts. ROS are chemically reactive chemical species containing oxygen such as peroxides, superoxide, hydroxyl radical, and singlet oxygen. Excessive amount of intracellular levels of ROS will cause oxidative damage to components of the cell, including nucleic acids (DNA, RNA), proteins, and lipids.[5] Cells control ROS levels by balancing the generation of ROS with their elimination by a variety of antioxidant enzymes that convert ROS into less harmful forms. However, if the conversion is less efficient, or there is a dramatically increase of the levels of ROS, cells would undergo oxidative stress – the condition caused by the imbalance between the production of ROS and antioxidant defenses.[6] Oxidative stress is associated with a range of diseases such as cancer, diabetes, autism, attention deficit hyperactivity disorder (ADHD), Parkinson's disease, Alzheimer's disease, depression, heart failure, and chronic fatigue syndrome.[7–11]

On the other hand, ROS have important roles in cell signaling. ROS serve as critical signaling molecules in cell proliferation and survival. While excess ROS induce oxidative damage and promote cell death, at normal levels (amounts), ROS function as "redox (reduction–oxidation reaction) messengers" in intracellular signaling and regulation. ROS regulate several signaling pathways through interaction with critical signaling molecules, affecting a variety of cellular processes, such as proliferation, metabolism, differentiation, and survival.[6,12–14] These signaling pathways include MAPK signaling, Ras signaling, PI3K-Akt Signaling, calcium signaling, etc.[13] Disturbances of ROS-dependent cell signaling will affect the complicated signaling pathway network and trigger a range of conditions.

Mitochondria: cell death

If there are too much damages present in mitochondria, a cell undergoes apoptosis. Apoptosis is a naturally occurring programmed process that eliminate cells by activating caspases (aspartate-specific cysteine proteases, they are enzymes that degrade proteins). B-cell lymphoma 2 (Bcl-2) family of proteins are localized to the outer and inner membrane of mitochondria, and regulate the apoptosis as an important gatekeeper. The Bcl-2 family consists of anti-apoptotic members such as Bcl-2 and pro-apoptotic members such as Bcl-2 associated X (Bax) and Bcl-2 homologous antagonist killer (Bak). Once activated, the proteins Bax and Bak will promote mitochondrial outer membrane permeabilization (MOMP) which leads to the release of cytochrome C. Cytochrome C binds to apoptotic protease activating factor-1 (Apaf-1) and form apoptosomes which activate caspase-9. The caspase-9 then initiates the caspase cascade, a chain reaction of protein degradation and eventually cell death.[15,16] On the other hand, by binding to Bax and Bak, anti-apoptotic protein Bcl-2 inhibits the MOMP thus prevents the apoptosis. The behavior of the Bcl-2 proteins depends on the pro-apoptotic and anti-apoptotic signals. By responding to these signals, the Bcl-2 family of proteins act as a cell life and death decision maker. Therefore, it is the balance between the pro-apoptotic and anti-apoptotic signals that eventually determines whether cells will undergo apoptosis, survive or proliferate.

Apoptosis is vital to various biological activities including embryogenesis, development, functioning of the immune system, and aging. Apoptosis imbalance (too little or too much cell death) will trigger a variety of diseases including cancer, neurodegenerative diseases, and autoimmune disorders.[17–19] By controlling apoptosis, mitochondria not only play a key role in eliminating damaged cells, but also in development. Proper mitochondrial functioning is important to health.

Mitochondrial dysfunction: a key player in chronic diseases?

Mitochondria are found in every cell of the human body except red blood cells. Therefore, it is not surprising to see that loss of function in mitochondria, or mitochondrial dysfunction, would result in numerous conditions throughout the whole body. These conditions cross the timeframe from birth to death, including: poor growth, developmental delays,[20] learning disabilities,[21] muscle weakness, excess fatigue, exercise intolerance,[22] nervous system dysfunction,[23,24] neurological problems,[25] neurodevelopment disorders,[26] neurodegenerative disorders,[27] visual problems, hearing problems,[28] gastrointestinal disorders,[29] respiratory disorders,[30] metabolic disorders,[31] heart diseases,[32]