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Mitochondria and Chloroplasts Shared in Animal and Plant Tissues: Significance of Communication

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Mitochondria have long been recognized as the main source of energy production for the eukaryotic cell. Recent studies have found that the mitochondria have a variety of dynamic functions aside from the production of energy. It communicates bidirectionally with other organelles in order to modulate its energy balance efficiently, as well as maintain homeostasis, ultimately prolonging its own and the cell's longevity. The mitochondria achieves this level of regulation via specific and common bidirectional chemical messengers, especially involving the endoplasmic/sarcoplasmic reticulum (ER/SR), deoxyribonucleoside triphosphates (dNTP's), ATP and the generation of reactive oxygen species (ROS). Its communication network is also involved in stress associated events. In this regard, the activation of the Bax family proteins and the release of cytochrome c occurs during cellular stress. The communication can also promote apoptosis of the cell. When mitochondrial abnormalities cannot be dealt with, there is an increased chance that major illnesses like type 2 diabetes, Alzheimer's disease, and cancer may occur. Importantly, functioning chloroplasts can be found in animals, suggesting conserved chemical messengers during its evolutionary path. The dynamic capacity of mitochondria is also noted by their ability to function anaerobically. Indeed, this latter phenomenon may represent a return to an earlier developmental stage of mitochondria, suggesting certain disorders result from its untimely appearance.

MeSH Keywords: bcl-X Protein • Calcium • Chloroplasts • Mitochondria • Nitric Oxide • Reactive Oxygen Species

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Background

The mitochondrion is an endosymbiont model of complex organelle development driven by evolutionary modification of permanently enslaved primordial purple non-sulphur bacteria [1,2]. Over diverse eukaryotic phyla, mitochondria provide a concerted amplification of cellular energy production. Mitochondria, at the expense of the extra energy provided, generate potentially dangerous reactive oxygen species (ROS). The manifestation of compromised cellular energy production, either due to oxidative stress and compounded pro-inflammation or genetically- or biochemically-determined mitochondrial abnormalities, represents a major contributing factor to the symptomatology of major illnesses including schizophrenia, diabetes type 2, and Alzheimer's disease, to name a few [3–19]. Taken together, this suggests that mitochondrial regulatory signaling, incoming and outgoing, may vary over the lifetime of the eukaryotic cell.

Illustrating the above point is the fact that a tumor cell may be viewed as a phenotypic reversion to the last common eukaryotic ancestor of the host cell, i.e., a facultative anaerobic microbe with unlimited replication potential [20]. Interestingly, anaerobic mitochondria in gill cilia of *M. edulis* have evolved to utilize the phenotype of a facultative anaerobe, demonstrating that this primitive type of respiration has been evolutionarily conserved [21,22]. Accordingly, anaerobically functioning mitochondria may represent a re-emergence or evolutionary retrofit of primordial metabolic processes. Thus, it is quite evident that cytosolic and mitochondrial communication is, and must be, bidirectional and part of the process that enslaves this bacteria so that the relationship works smoothly.

In this regard, chloroplasts also represent enslaved bacteria that have a similar cytoplasmic relationship, dependent on chemical messengers [23]. Given the shared chemical messengers between the two, and interrelationships between the common energy processes, it is not surprising that additional commonalities are emerging. Furthermore, it is no surprise that mitochondria are present in both plants and animals, implying major commonalities in regulation, energy production, substrates employed, etc. This common presence of mitochondria, with similar functions and structure, underscores how close our life forms are. The enslavement process should be equally similar, if not the same.

Recently, as just noted, the commonalities of energy creation (translocation of chemical bond energy) and utilization have become even stronger by the finding that chloroplasts can be found in animal/eukaryotic animal cells. The discovery of kleptoplasty, a functional chloroplast in cells of a non-photosynthetic host [24] is a remarkable phenomenon [24–27]. It is also found in metazoans, in the sacoglossan sea slugs. Of equal importance is the longevity of functional kleptoplasts in the host, suggesting again that the common significance of bidirectional communication, and the many commonalities in molecules, exists so that this phenomenon can take place and work. These sea slugs extract and incorporate functional chloroplasts from Ulvophyceae into their gut cells [28], allowing their derived "food" to be gained for months. The dependence on specific algae strongly suggests common bidirectional communication is responsible for this phenomena.

Recently, aside from the energy focus, studies have shown that mitochondria function as regulators for signal transduction and liberators of reactive oxygen species (ROS), communicating with the endoplasmic reticulum (ER) to help regulate signals, and inducing stress responses to the rest of the cell, so that they can alter their physiology if needed [29]. Furthermore they maintain homeostasis and control deoxyribonucleoside triphosphate (dNTP) pools, which helps with the mitochondrial DNA replication process. It is known that there is a communication between the cytoplasm and the mitochondria for the dNTP pool levels, however, the depth of how much they actually interact is still unclear. Recent research has tried to clarify this process through experimental procedures using both normal cells and transformed cells. The normal cells have been identified to have a strong correlation between the concentration levels of dNTP in the cytoplasm and the mitochondria, but not for the transformed cells [30].

Calcium

A specific and vital signaling process that mitochondria also perform is the adjustment of the cell's Ca^{2+} levels. Bidirectional communication with the nucleus occurs when stress is induced on the cytosol due to the changes in Ca^{2+} levels. An example of the Ca^{2+} levels changing due to a stressful situation was demonstrated in previous experiments where cellular stress was induced using mitochondrial metabolic inhibitors, such as antimycin, which affected mouse mitochondrial membrane potential [25]. Stress signals that are occurring in the mitochondria, such as ATP decline, cause changes in other cellular processes, which can affect the biogenesis of the mitochondrial membranes [31,32].

With the extensive varieties of pumps, channels and exchangers within a cell, an increase of cytoplasmic Ca^{2+} concentrations due to extracellular stimuli can occur, which further leads to responses such as proliferation, cell death or secretion. Previously, the mitochondria were thought to have a minor role with these communication processes, until a direct measurement revealed a rapid increase in Ca^{2+} occurring in the cytosol as well. Since the Ca^{2+} transporters located in the mitochondria do not have a high affinity, they require the close

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proximity of the Ca^{2+} releasing channels in the endoplasmic reticulum [33]. Calcium signaling between the sarcoplasmic and endoplasmic reticulum (SR/ER) and the mitochondria continues to play a strong role in regulating processes such as ATP production and apoptosis. The calcium transporters involved in the communication processes are directly exposed to ROS, as well as being sensitive to redox regulations. Though some mechanisms are still unclear regarding calcium and the ROS signaling, it is apparent that this communication maintains homeostasis of the cell [34].

It is surmised that the ER and mitochondria are associated with type 2 diabetes mellitus [35]. Dysfunctional mitochondria will cause stress on the ER, leading to a disruption of the Ca^{2+} concentration levels being modulated in the mitochondria. With both the dysfunctional mitochondria and the stress on the ER, insulin resistance and β-cell dysfunction occurs [35].

ATP levels in the mitochondria are controlled by the intra-mitochondrial free calcium concentration levels. Additionally, intra-mitochondrial Ca^{2+} plays an important role in controlling the opening of the large pore, i.e., permeability transition pore (PTP), which regulates apoptosis. Calcium also acts as a secondary messenger in the cytosol, signaling through Ca^{2+} transients. This, in turn, leads to the mitochondria being able to seize the Ca^{2+} from the transients to alter the shape and location of these signal transients [36].

Cytochrome C

When the mitochondrion undergoes an unexpected change or a stress-related event, it may release the hemeprotein known as cytochrome c. The cytochrome c concentration from inside the mitochondria increases and then is released to their cytosol. This release of cytochrome c demonstrates that mitochondria are also involved in inducing apoptosis of the cell [37,38].

Bax Family

Apoptosis or necrosis causes cytochrome c to redistribute from the intermembrane mitochondrial space to the cytosol space, which leads to depolarization of the inner mitochondrial membrane. When the mitochondrion tries to prevent physiological changes that are occurring, such as apoptotic stress, it signals the release of a protein known as Bcl-xL, which inhibits apoptosis by causing a decrease in the mitochondrial membrane potential. Thus, Bcl-xL expression is causing osmotic and electrical homeostasis and promoting cell survival [38]. Even though Bcl-xL acts as an anti-apoptotic gene, there is also a pro-apoptotic molecule, BAX that will help promote cell death. Its presence is a direct result of signaling between the mitochondrion and the cytosol. When a death signal is communicated to the cell, the activation of BAX can occur, causing an override of Bcl-xL or interleukin (IL)-3 leading to apoptosis of the stressed cell [39].

Bcl-2 is also a member of BAX family that can migrate from the cytosol to the mitochondria, inducing apoptosis [40]. BAX activity can be inhibited if there is pro-survival of the Bcl-2 proteins. The pro-survival of the Bcl-2 family proteins is key to the BAX being retro-translocated, and if this is inhibited, BAX will build up in the mitochondria and lead to apoptosis [40].

ROS/Oxidants

Production of ROS by mitochondria is an important communication process, involving organelles, cytosol and the nucleus. A primary ROS produced by the mitochondria is superoxide (O_2^-), which correlates/interacts with other phenomena occurring within the mitochondria. If the isolated mitochondria are not producing enough ATP, mainly at complex I, along with a reduced amount of coenzyme Q and high NADH/NAD^+ ratios, the superoxide levels will generally be higher. When levels of these molecules are reversed, the O_2^- levels are significantly lower, showing the critical importance of these molecules on ROS production [41]. Conversely, when you have an active oxidative phosphorylation system operating through Complexes I–V, then the superoxide formation is minimized. Mitochondrial oxidants are generally known to be harmful when a leakage occurs. Recently, these oxidants were shown to function as signaling molecules, stimulating communication between the cytosol and mitochondria. An increase in the release of H_20_2 from the mitochondria causes the metabolic escalation of a kinase known as JNK1, which causes the inhibition of metabolic enzymes, such as glycogen synthase, leading to regulation of the metabolic pathways [42].

Normal ROS production not only helps maintain cellular metabolism, but also has been found to help the mitochondria monitor innate immune responses. The generation of ROS is enhanced when the mitochondria are under apoptotic stress or cellular damage. By acting as a sensing organelle for innate immune responses, such as antiviral signaling and facilitating antibacterial immunity, the mitochondria can accumulate ROS, causing immune activation [43,44]. In this regard, the activation state of this organelle can be ascertained by its conformation. Mitochondrial conformational changes associated with activation, via altering shaping proteins or when retinoic acid-inducible gene I-like helicase (RLH) is activated, will exhibit an elongated shape. The mitochondria will most likely take an asymmetrical shape as well, and can also fragment if there are pro-apoptotic factors involved [38]. These shape changes appear to be important in their functional dynamics

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since they are associated with neurodegeneration, the lifespan of a cell, and also cell death. Conformational change occurs in white blood cells, endothelial cells, microglia and invertebrate immunocytes, following stimulation and is indicative of energy usage [45,46]. In general, immune cells have fewer mitochondria compared to other cells, however the conformational shape changes in mitochondria may allow it to accumulate in cellular processes requiring ATP, and in their absence, degeneration may occur [44,47,48].

ER/SR Communication

A cell's organelles must be in a certain anatomical position and conformation so that they are able to communicate with one another and function properly. Two organelles that are known to have a specific organization are the endoplasmic reticulum (ER) and the mitochondria. The research literature documents that these two organelles closely communicate in a bidirectional manner to promote regulation of physiological processes, e.g., lipid metabolism, ATP production, calcium signaling, as well as cell death [49,50]. There are still many signaling cascades that can be explored between the ER and the mitochondria that may also lead to insights into disease origin [49]. Two important tissues in which the SR/ER-mitochondria communicate bidirectionally are cardiac and skeletal muscles. With the help of Ca^{2+} signals from the SR to the mitochondria, the generation of ATP can correlate with the contractions of cardiac and skeletal tissues [51].

Nuclear Communication

Not only does the mitochondria help regulate homeostasis, but it has many transcription factors and specific cofactors that regulate its biogenesis. Though these functions are newer findings, a more recent study has found that the mitochondrion can send messages that change nuclear gene expressions, therefore altering nuclear control [52]. Through retrograde signaling, communication from the mitochondria to the nucleus provides the status of metabolic and respiratory conditions, along with the genetic instability of the mitochondria. The mitochondrial genome (mtDNA) plays a key role in the retrograde signaling when there is a lower amount of mtDNA, which causes it to not function properly due to a reduced membrane potential. This decrease in mtDNA levels is associated with various conditions like diabetes, neurodegenerative disorders, cancer and aging [53].

Chaperones play a key role in regulating the proteins that are encoded by the mitochondria DNA and nuclear mitochondrial proteins by being involved in the process of their synthesis, transportation and folding [54]. When stressed, the mitochondria and molecular chaperones will exhibit a specific response to alleviate the situation. These chaperones are encoded by nuclear DNA, demonstrating a potent communication mechanism [54].

Conclusions

The bidirectional communication that occurs between the mitochondria and the rest of the cell has a functional capacity for promoting a positive environment for the cell through primarily calcium and ATP monitoring and sophisticated internal regulatory processes. Situations such as cellular stress can affect the fidelity of the communication, which leads to changes and therefore to mitochondrial dysfunction. Even more important is the fact that mitochondria originated from bacteria, which are similar to chloroplasts, demonstrating this enslavement of both is based on common signaling pathways. These similarities are especially noted in the fact that functioning chloroplasts occur in animals. Since these enslaved organelles are really alien to their host cells, one can surmise that this communication becomes faulty with aging, and may manifest itself in many mitochondrial associated disorders, e.g., Alzheimer's, etc. Taken together, the mitochondria are more dynamic than just being the "powerhouse" of the cell, which produces an enriched amount of ATP, but also as a sophisticated and dynamic organelle that communicates bidirectionally with the rest of the cell on a moment to moment basis. This dynamic immediate relationship is manifest in the fact that mitochondria can alter their ATP producing capacity at times that demand it to do so, producing lesser amounts of ATP [2]. In all probability, this last phenomenon may be, in part, responsible for the development of chronic conditions.

Conflict of interests

All authors certify that there is no conflict of interests.

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