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# Mitochondria, Chloroplasts in Animal and Plant Cells: Significance of Conformational Matching

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Many commonalities between chloroplasts and mitochondria exist, thereby suggesting a common origin via a bacterial ancestor capable of enhanced ATP-dependent energy production functionally linked to cellular respiration and photosynthesis. Accordingly, the molecular evolution/retention of the catalytic  $Q_o$  quinol oxidation site of cytochrome *b* complexes as the tetrapeptide PEWY sequence functionally underlies the common retention of a chemiosmotic proton gradient mechanism for ATP synthesis in cellular respiration and photosynthesis. Furthermore, the dual regulatory targeting of mitochondrial and chloroplast gene expression by mitochondrial transcription termination factor (MTERF) proteins to promote optimal energy production and oxygen consumption further advances these evolutionary contentions. As a functional consequence of enhanced oxygen utilization and production, significant levels of reactive oxygen species (ROS) may be generated within mitochondria and chloroplasts, which may effectively compromise cellular energy production following prolonged stress/inflammation conditions. Interestingly, both types of organelles have been identified in selected animal cells, most notably specialized digestive cells lining the gut of several species of Sacoglossan sea slugs. Termed kleptoplasty or kleptoplastic endosymbiosis, functional chloroplasts from algal food sources are internalized and stored within digestive cells to provide the host with dual energy sources derived from mitochondrial and photosynthetic processes. Recently, the observation of internalized algae within embryonic tissues of the spotted salamander strongly suggest that developmental processes within a vertebrate organism may require photosynthetic endosymbiosis as an internal regulator. The dual presence of mitochondria and functional chloroplasts within specialized animal cells indicates a high degree of biochemical identity, stereoselectivity, and conformational matching that are the likely keys to their functional presence and essential endosymbiotic activities for over 2.5 billion years.

**MeSH Keywords:** **Chloroplasts • Kleptoplasty • Mitochondria • MTERF • PEWY • Reactive Oxygen Species • Stereospecificity**

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## Background

Mitochondria and chloroplasts represent endosymbiont models of complex organelle development driven by evolutionary modification of permanently enslaved primordial bacteria [1–4]. Over diverse eukaryotic phyla mitochondria and chloroplasts either alone or together provide a concerted amplification of cellular energy production via shared biochemical pathways. Cellular dysregulation of these two distinct organelles may generate potentially dangerous reactive oxygen species (ROS) due to compromised complex bioenergetics energy production, systemic oxidative stress and compounded pro-inflammatory processes. Importantly, genetically- or biochemically-mediated failure of mitochondrial function in human populations represents a potentially dire factor in the etiology of major disease states that include Type II diabetes, atherosclerosis, rheumatoid arthritis, Alzheimer's Disease, and cancer progression [5–21]. In sum, these compelling mechanistic and clinical data suggest that the extent of mitochondrial/chloroplast regulatory signaling may vary over the lifetime of the eukaryotic cell according to physiological demand and bioenergetics requirements [22,23].

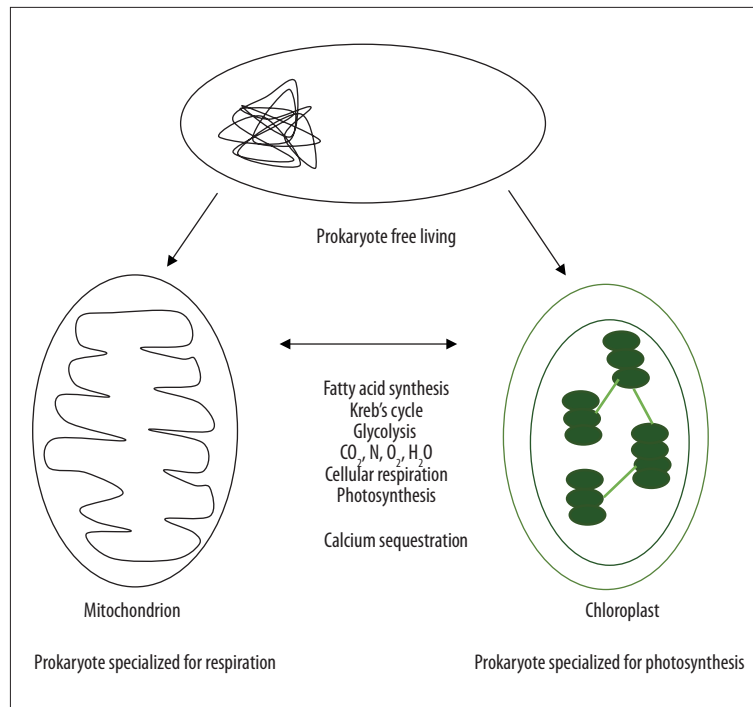
Interestingly, a tumor cell may be viewed as a phenotypic reversion to the last common eukaryotic ancestor of the host cell, i.e., a facultative anaerobic microbe with unlimited replication potential [24]. For example, anaerobic mitochondria in gill cilia of *M. edulis* have evolved to utilize the phenotype of a facultative anaerobe, demonstrating that this primitive type of respiration has been evolutionarily conserved [25,26]. Accordingly, anaerobically functioning mitochondria may represent a re-emergence or evolutionary retrofit of primordial metabolic processes.

It has become recently apparent that mitochondria have discrete microenvironments composed of complex intracellular membrane structures with distinct functional identities determined by segregated biochemical pathways [27] (Figure 1). 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 shared regulatory, bioenergetic, and chemical substrate pathways. Commonalities of energy processing in both plants and animals have become even stronger by the finding that chloroplast can be found in animal cells. The discovery of kleptoplasty, a functional chloroplast in cells of a non-photosynthetic host [28] is a remarkable phenomenon [28–31]. It is also found in metazoans, i.e., the sacoglossan sea slug. Of equal importance is the longevity of functional kleptoplasts in the host, suggesting again the common significance of bidirectional communication and the many commonalities in molecules exist so that this phenomenon can

take place and work. These sea slugs extract and incorporate functional chloroplasts from Ulvophyceae into their gut cells [32], allowing their derived “food” to be gained for months. The dependence on specific algae strongly suggests common bidirectional communication is responsible for these phenomena.

The ability of a chloroplast to function as a symbiotic bioenergetic organelle within the intracellular milieu of a representative invertebrate, i.e., the Sacoglossan sea slug, was previously identified as a unique phenomenon unlikely to occur in vertebrates [28–32]. Recently, the observation of internalized algae within embryonic tissues of the spotted salamander strongly suggest that developmental processes within a vertebrate organism may require photosynthetic endosymbiosis as an internal regulator [33]. Accordingly, it appears that green algae and spotted salamander embryos have an intimate endosymbiotic relationship and algae are able to invade the embryonic tissues and cells of the salamander and eventually degrade as the larvae develop over time [33]. Although endosymbiotic algal cells go through degradation, the cells can also encyst on the inner capsule wall which is detected through 18S rDNA amplification in the reproductive tracts of the adult salamanders, thereby allowing for the transfer of genes from one generation to the next [33]. Due to the dense accumulation of algae within the embryo, a distinct green color is exhibited which leads to beneficial effects for the embryo. Requisite physiological effects include lowering embryonic mortality, larger embryo size, and earlier hatching times. It is still unclear if the algae and the embryo have a true bidirectional symbiotic relationship because there is evidence that the algae have no increase in oxygen levels, but they may benefit from the embryos when their nitrogenous waste is released. In any event, this phenomenon defines a distinctive relationship between developmental processes in a defined vertebrate organism and eukaryotic algae.

A careful examination of the biomedical literature has yielded many examples of existential commonalities between mitochondria and chloroplasts, which include free living bacteria [34]. Formally known as the PEWY motif in mitochondrial complexes, cyt b displays four tetrapeptide residues (PDWY, PPWF, PVWY and PEWY) employed in catalytic reactions, which is now identified as the  $Q_o$  motif. PEWY, which is present in chloroplasts and mitochondria, and PDWY which is present in Gram-positive bacteria both associate with the redox potential of quinone species [34]. These data suggest that when electron transfer occurs from a low-high potential throughout evolution that the cyt bc1 complex with PEWY being the  $Q_o$  motif will function best with a high potential and ubiquinone as its substrate [34]. For PDWY as the cyt b complex, a low potential and menaquinone will function the best. In sum, the molecular evolution/retention of the catalytic  $Q_o$  quinol oxidation site of cytochrome *b* complexes, functionally underlies the common



**Figure 1.** The prokaryotic cell is characterized by a general lack of highly structured intracellular organelles but displays intracellular regions of functionality with some membrane enhancements, e.g., mesosome. We surmise that with time this relatively simple structure became more elaborate, adding membrane surface area to perform work, enhancing a major function like respiration. In all probability the stimulus was solar energy, causing the photolysis of water. This cell was driven in this direction because it provided a new coping strategy for, counter-intuitively, DNA advancement. This evolving cellular architecture could not survive on its own given the presence of by products it produced, e.g., ROS, which are basically toxic to unprotected intracellular components, notably DNA. This evolutionary self protection mechanism was further advanced when oxygen levels increased as a result of photosynthesis. In all probability the cellular oxygen toxicity issue was partly solved by having a “bacterium” develop in a “bacterium”, becoming a eukaryotic cell, which could harvest specific bond energy. This also aided in ROS protection with a more structured and protected environment for this new intracellular relationship to evolve, having a plentiful energy supply for novel DNA expression. Accordingly, a major free radical and free radical creator was effectively removed via chloroplasts, which originated in a similar manner as mitochondria. Thus, it is not surprising to find both types of “bacteria” in the same cell and others where only one is present. Furthermore, given this close involvement, enslavement was not an issue in this circumstance because each “cell” used the same or similar chemical messengers, stabilizing what appears to be a precarious relationship. Indeed, bidirectional communication served as the process for eukaryotic cellular communication/cooperation, which allowed for metazoan evolution. Interestingly, metazoan evolution is still highly dependent on the intracellular communication with its endogenous bacterial components from which it evolved, e.g., intracellular and extracellular (gut microbiome). The vulnerability expresses itself in “mitochondrial dysfunction” in that it can be so complicated and diverse depending on the tissue region affected. We further surmise that hypoxia plays a major role in triggering mitochondrial dysfunction since this entire relationship depends on a continuously ongoing energy processing system[2,21]. Briefly, the evolutionary advancement of eukaryotic cells requires this homeostatic energy balance to maintain its multicomponent and faceted existence. Any deviation from the thermodynamically stabilized life form creates a pathology wherever it occurs. This process may also represent the deleterious mechanisms that may be associated with aging.

retention of a chemiosmotic proton gradient mechanism for ATP synthesis in cellular respiration and photosynthesis.

The relationship between photosynthesis and respiration can vary, thereby demonstrating their dynamic nature. For example, when tomato fruit ripen, their chloroplasts will change into photosynthetically inactive chromoplasts that can produce ATP through a respiration process known as chromorespiration [35]. Oxygen consumption through chromorespiration can

be stimulated by NADH and NADPH, and is also sensitive to the plastidial terminal oxidase inhibitor octyl gallate. Isolated chromoplasts are also sensitive to multiple molecules such as the cytochrome *b<sub>f</sub>* complex inhibitor 2,5-dibromo-3-methyl-6-isopropyl-p-benzoquinone [35]. Cytochrome *f* was identified in the chromoplast as was cytochrome *c<sub>6</sub>* and their expression increases in ripened tomatoes suggesting that they may be acting as electron acceptors for the cytochrome *b<sub>f</sub>* complex. During ripening, mitochondrial numbers significantly decrease

in the fruit tissue [35]. In order to compensate for this strong decrease, the number of chromoplasts will functionally increase during the later stages of ripening, thereby demonstrating critical modification of energy processing.

Importantly, plants require imported oxygen to carry out most of their biochemical reactions such as respiration even though they lack the ability to distribute oxygen to the cells [36]. To compensate for the lack of this distribution mechanism, plants often display steep oxygen gradients that may be impaired due to environmental distress [36]. Thus, plants require different physiological responses to manage the variations of oxygen levels available to them and display metabolic adaptations in energy requirements. As a key example, physiological demand is coupled to activation of the cellular glycolytic pathway to generate ATP production when oxidative phosphorylation is compromised [27]. Cellular oxygen levels have been demonstrated to regulate the expression of Group-VII ethylene response factors (ERFs), a family of transcription factors involved in the regulation of hypoxia-inducible genes that include *HRE1* and *HRE2* [36]. Furthermore, the functional integrity of mitochondria and chloroplasts are critically linked to cellular oxygen requirements, as regulated by the N-end rule signaling pathway due to the impacted loss. The N-end rule signaling pathway represents a cellular response mechanism that requires ubiquitin ligation linked to proteasomal degradation via covalent modification of N-terminal amino acids [36].

Finally, the array of complex control mechanism by which organellar gene expression (OGE) promotes respiration, photosynthesis and plant development is actively under investigation [37]. Presently, several required components have been identified that have been functionally associated with OGE processes. Nucleus-encoded proteins have important roles in OGE by promoting various required functions such as splicing, transcription, RNA processing and regulation of translational processes. Normative OGE is regulated by the family of mitochondrial transcription termination factors (mTERF). Mammalian mTERFS were originally proposed to specifically terminate transcription, but further biochemical and molecular studies indicate that three out of the four mTERFS possess important regulatory activities necessary for ribosomal biogenesis and antisense transcription termination. Approximately 30 members of the mTERF family have been identified throughout plant evolution, but still little is known about how photosynthetic organisms are using mTERFs and OGE [28]. In sum, the dual regulatory targeting of mitochondrial and chloroplast gene expression by mTERF proteins to promote optimal energy production and oxygen consumption further advances the evolutionary importance of OGE processes.

## Conclusions

It is now established that the same set of functional genes are encoded in both the plastid and mitochondrial genomes, which express the same conserved proteins in the electron transport chain [38]. Thus, it is strongly implied that OGE processes are critically linked to shared stereo-selective biochemical pathways. Maier and colleagues refer to this as an example of parallel and convergent evolution. The ongoing processes underlying biologically meaningful evolutionary modification of the organellar genome can be partly attributed to regulatory stability of intracellular redox processes. As such, a hypothesis of evolutionary modification of intracellular redox regulation predicts that there is a specific location for the plastids and mitochondria genes that encode for bioenergetics membrane proteins that are functionally related to respiration or photosynthesis [38]. The dual evolution of the plastid and mitochondria genomes will effectively drive the retention of functionally similar sets of ribosomal protein genes which are functionally required for proper ribosomal assembly.

It has been recently proposed that archaeobacterium and eubacterium precursors led to the origin of eukaryotes [39,40]. Conversely, mitochondria arose from an alpha-proteobacterium and a eukaryote [40,41]. Plastids arose in a similar manner but from cyanobacterium and a eukaryote [40]. Hence the eukaryotic cell was “developed”. The developmental primacy of photosynthesis was probably due to abundant sunlight and coincident appearance of requisite photovoltaic chemical processes. Furthermore, the byproducts of these processes, i.e., glucose and oxygen, introduced a major change in the biosphere with the associated evolutionary development of complex cellular respiratory processes and with major potential problems involving oxygen toxicity. In light of these changes, both photosynthetic and respiratory processes were driven by the potential for bacteria to further enhance the intracellular membrane microdomains segregated according to functional physiological criteria.

Accordingly, the respiratory “bacterium” evolved and remained in place because of its existential brokerage of molecular oxygen and the use of glucose as an initial fuel source in the bioenergetics of ATP production. In this regard, photosynthetic priming events promoted evolutionary acceleration of intracellular membrane differentiation, selective for plastid-like structures. This major contention is supported by the observation that many organelles can be found in both plant and animal cells and that their molecular biology/bioenergetics share basic chemical processes.

The dual expression of mitochondria and functional chloroplasts within specialized animal cells indicates a high degree of biochemical identity, stereoselectivity, and conformational

matching that are the likely keys to their functional presence and essential endosymbiotic activities for over 2.5 billion years [3,42–44]. Thus, conformational matching imposes a high degree of rigidity on the systems, allowing for their retention in evolution. Another component of the conformational matching hypothesis is that this phenomenon also occurs via a chemical messenger and its receptor with the added fact that both must be expressed simultaneously and appropriately on the right target [3,42–44]. Therefore, all the conformational

dependent substrates and enzymes impose a rigidity on change in general, which does not favor change. However, change can and does occur because slight changes may be tolerated, giving rise to modified systems, e. g., the catecholamine pathway.

### Conflict of interests

The authors declare no conflict of interests.

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