Mitochondrial Dynamics during Development

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Abstract

Mitochondria are dynamic membrane-bound organelles in eukaryotic cells. These are important for the generation of chemical energy needed to power various cellular functions and also support metabolic, energetic, and epigenetic regulation in various cells. These organelles are also important for communication with the nucleus and other cellular structures, to maintain developmental sequences and somatic homeostasis, and for cellular adaptation to stress. Increasing information shows mitochondrial defects as an important cause of inherited disorders in different organ systems. In this article, we provide an extensive review of ontogeny, ultrastructural morphology, biogenesis, functional dynamics, important clinical manifestations of mitochondrial dysfunction, and possibilities for clinical intervention. We present information from our own clinical and laboratory research in conjunction with information collected from an extensive search in the databases PubMed, EMBASE, and Scopus.

Keywords

Archezoan; Inner membrane; Intermembrane space; Matrix; Mitochondrial DNA; Mitophagy; Neonate; Ontogeny; Outer membrane; Parkin

INTRODUCTION

Mitochondria are membrane-bound organelles that orchestrate cellular energy production in almost all eukaryotic cells.[1,2] These organelles generate adenosine triphosphate (ATP) through oxidative phosphorylation, the components of which are partially encoded in their own genome.[3] Mitochondria are not only the cellular 'powerhouses', but also play

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critical roles in supplying intermediary metabolites, temperature maintenance, regulation of Ca^{2+} homeostasis, determination of cellular life-span, and integration of various signaling pathways.[4–11] The physiological importance of mitochondria becomes evident early, and can be seen in the developing oocyte and the embryo, in the fetus, and throughout infancy.[12–15] After birth, the increased energy requirements are associated with a significant increase in the mitochondrial number and function.[16–19]

In this review, we have summarized recent advances in our understanding of mitochondrial dynamics, the importance of the cytoskeleton, cellular signaling, cellular and organ differentiation, regulation of the function of other organelles, and cellular lifespan. The importance of mitochondria as mediators of epigenetic regulation and metabolic processes during development has been explored. The critical role of mitochondria in cellular homeostasis is evidenced by the wide range of clinical manifestations involving multiple organ systems seen in mitochondrial diseases. We present our own clinical and laboratory research, combined with an extensive search in the databases PubMed, EMBASE, and Scopus. To avoid bias, keywords were identified from discussions in our own group and from PubMed's Medical Subject Heading (MeSH) thesaurus.[20]

Mitochondrial Ultrastructure

Mitochondria are dynamic intracellular organelles seen in all eukaryotic organisms; one exception might be the oxymonad monocercomonoides, which are obligate animal symbionts that live in the intestinal tracts of vertebrates.[21] Human tissues contain mitochondria with a high degree of numerical heterogeneity; erythrocytes do not contain any, whereas hepatocytes and muscle cells may contain hundreds to thousands per cell.[5,22,23] These numbers vary not only across various tissues, but also during development, cell cycle, and stress.[24]

Mitochondria have been traditionally viewed as 0.5–1 μm ovoids, where the number per unit volume seems to be inversely related to size.[1,25–27] However, the mitochondrial morphology varies between different cell types; cultured endothelial cells contain a mitochondrial reticulum around the nucleus (Fig. 1A). Similar to prokaryotes, mitochondria are uniquely covered in bilayered membranes. These organelles multiply by binary fission and consistently, electron micrographs show many mitochondria as a dumbbell or racket-shaped: Two larger halves with a narrow bridging tube prior to the separation of the daughter organelles.[28–31] Electron micrographs show the mitochondrial membranes, cristae, and matrix (Fig. 1B).

Advanced cellular imaging shows foci where mitochondria appear tubular and as forming a network (Fig. 1C) with active division and fusion.[32,33] The mitochondrial content and morphology are altered by cellular stress. In living cells, the net mitochondrial content or the mitochondrial mass depends on the balance between mitochondrial biogenesis and degradation. Changes in spatiotemporal positioning, which have been described as the mitochondrial dynamics, and mitochondrial morphology are governed by mitochondrial fusion, fission, and motility.[34–36] The dynamics can be seen in sub-nanometer resolution with cryo-electron tomography.[32,33] There may be unique orientations and distribution in different types of cells, and a close association with microtubules in some regions.[37,38] In

sites where the energy requirements are relatively high, mitochondria may appear more static and provide ATP directly on-site.[39] However, in other regions, there may be prominent motility either in surveillance for foci with high energy needs or in actual energy production once those are found.[36] Fluorescence microscopy combined with quantitative image analysis is a useful method to study the amount and morphology of mitochondrial organelles within cells (Fig. 1D).[40] Dynamin-related guanosine triphosphate hydrolases (GTPases) may play an important role in mitochondrial motility.[41] Even if the mitochondrial network gets damaged during isolation from cells, some fragments may continue to show respiration and ATP synthesis.[3] The mitochondrial membrane protects the structure and electrical potential of these organelles.[42]

Structural Models

The following section summarizes current information on various compartments in mitochondria. The location of these key elements is shown in Figure 2:

- An outer mitochondrial membrane (OMM) that is freely traversed by ions and small molecules.[3] It is highly porous, and hence no electrical potential difference is detectible across this membrane layer.[3] There are nearly 200 proteins, but the following are some of the best characterized:[43]

  - Translocase of the outer mitochondrial membrane (TOM):[44] The TOM complex is comprised of a large number of subunits, and it recognizes, segregates, and translocates precursor proteins to different sites within the mitochondria (Fig. 3);

  - Topogenesis of mitochondrial outer membrane β-barrel proteins/sorting and assembly machinery (TOB/SAM): proteins such as Tom40, Tob55/ Sam50; and mitochondrial distribution and morphology protein 10 (Mdm10) form channels in OMM;[45,46]

  - Mitochondrial import complex (MIM): it inserts α-helical proteins in the OMM independently of the TOM complex;[47] and

  - Endoplasmic reticulum-mitochondria encounter structure (ERMES).[48]

  - Adenine nucleotide translocator (ANT), has been referred to by various other terms such as the ADP/ATP translocase, ADP/ATP carrier protein, or mitochondrial ADP/ATP carrier. It exchanges free ATP with free ADP across the inner mitochondrial membrane (IMM). Adenine nucleotide translocator is the most abundant carrier protein in the IMM;

  - Mitochondrial porins, which are also referred to as the voltage-dependent anion channels (VDACs)–1, –2, and –3, are located on the OMMs and a class of porin ion channels;[49,50] and

  - Apoptosis regulators bax and bak. These play an important role in maintaining the cell cycle and in the formation of mitochondrial pores.[51] Many other enzymatic systems are being identified.[52]

- An inter membrane space (IMS) between the inner and outer membranes contains about 5% of the mitochondrial proteins in an aqueous medium (3.8 μL/mg protein).[3,53,54] The large physical size of the OMM pores makes the IMS largely continuous with the cytosol;[55,56] Proteins synthesized on cytosolic ribosomes traverse these pores and bind carriers.[57–61]

  The IMS may contain many pro-apoptotic factors such as the cytochrome c.[62] Other proteins may display CX_3C or CX_9C motifs.[63] The machinery for import and assembly of IMS proteins mitochondrial intermembrane space assembly (MIA) can bring in large proteins that may be up to 11 kDa in size.[59,64]

- An IMM separates the IMS from the mitochondrial matrix. It is very selectively permeable to most molecules, and therefore, carries many specialized transporters.[3,65,66] Anelectrochemical membrane potential of about 180 mV has been documented across the inner membrane.[67] The membrane is also a site for oxidative phosphorylation, which is used to create electrochemical gradients for ATP synthesis.[68] The IMM is extensively folded, where numerous invaginations called cristae increase its total surface area.[3] These cristae are separated from inner boundary membranes by junctions, and the ends are partially closed by transmembrane proteins that bind opposing membranes.[3,69–71] Cristae also affect the overall chemiosmotic function of mitochondria.[65]

- The major role of the IMM is to facilitate molecular transport and signaling for oxidative phosphorylation and ATP synthesis.[69,71] A junctional protein, the inner mitochondrial membrane translocase protein (IMMT), is expressed in the nucleus and is transported to the IMM, where it maintains the electrical potential and the structural invaginations seen in the inner membrane.[72–74] On the matrix side, the crystal membranes are studded with small proteinaceous F_1 particles, which promote proton-gradient-driven ATP synthesis.[3] The electron transport chain on the cristae includes 5 complexes: complex I nicotinamide adenine dinucleotide, hydrogenated (NADH) (NADH: coenzyme Q oxidoreductase), complex II (succinate: coenzyme Q oxidoreductase), complex III (coenzyme Q: cytochrome c oxidoreductase), complex IV (cytochrome c oxidase) and ATP synthase.[62,75,76] Overall, the cristae membranes are dynamic and can reshape in seconds. Cristae membrane remodeling is regulated by the mitochondrial contact site and cristae organizing system (MICOS) complex, optic atrophy-1 (OPA1), F_1F_0 ATP synthase, and the lipid microenvironment.[77–81]

- The matrix in the core of these organelles is enclosed within the IMM. This gel-like material contains DNA, ribosomes, soluble enzymes, small organic molecules, nucleotide cofactors, and inorganic ions.[3] The pH of 7.8 in the matrix is higher than the 7–7.4 seen in the IMS.[82,83] The water content, about 0.8 μL/mg protein, is lower than that in the IMS.[84] The restricted permeability of the IMM may regulate the osmotic balance.[85] The aquaporin conduits in the membrane may also play a role.[86] The matrix is the site for the tricarboxylic acid (TCA) cycle (citric acid cycle, Krebs cycle) metabolism for ATP production (Fig. 4).[87] It contains the key regulators, including citrate

synthase, isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, fumarase, and malate dehydrogenase; succinate dehydrogenase, located on the IMM, is an exception.[88,89]

- Mitochondrial DNA (mtDNA) is comprised of one or more double-stranded, mainly circular DNA in the matrix. Mitochondrial DNA (mtDNA) encodes for 2 ribosomal ribonucleic acids (rRNAs), 22 transfer RNAs (tRNAs), and 13 proteins involved in the mitochondrial respiratory chain.[90] It is rich in guanine and cytosine and contains 37 genes with about 17,000 base pairs.[91]

The mtDNA accounts for about 1% of the total DNA in a cell. In humans, only 13 proteins are encoded in mtDNA; all are central, hydrophobic subunits of the respiratory chain complexes/ATP synthase.[92] In total, there are 1,500 estimated different mitochondrial proteins; >99% of these proteins are likely encoded in the nucleus, synthesized in the cytosol, and imported into the mitochondria.[93,94]

Human mitochondria contain a unique protein translation machinery with ribosomes, transfer-RNAs (tRNAs), and associated protein factors that resemble those seen in bacteria.[95,96] However, mitochondria make surprisingly little use of their specialized protein production machinery. Most of the mitochondrial proteins are synthesized in the cytoplasm and then imported into the organelle by protein translocases.[57] Most of the mitochondrial proteins are transcribed in the nucleus, synthesized in the cytosol, and then imported back into the organelle.[94] More than 3,000 mitochondrial proteins have been estimated in vertebrate animals.[97] During evolution mitochondrial genes have relocated to the nucleus, whereas the translated proteins are imported back into the mitochondria to perform their function.[97–99]

Evolutionary Perspective

There are three models for mitochondrial development, where an existing cellular organism accepted proto-mitochondria.[100] There are two endosymbiotic models, and a third where mitochondria could have evolved from related predecessor organelles (Fig. 5):

- Archezoan scenario: A hypothetical primitive a mitochondrial eukaryote, termed archezoan, accepted a proto-mitochondrial endosymbiont.[97,101,102] Rigorous studies have detected artifacts and raised doubts about the validity of these hypotheses.[103]

- Symbiogenesis scenario: An archaeal cell underwent a single endosymbiotic event with an α-proteobacterium, which generated mitochondria.[104] This event was followed by the evolution of the nucleus and compartmentalization of the eukaryotic cell.[102]

- Evolution from mitochondrion-related organelles (MROs).[105] These models envisage three possible double-membrane mitochondrial precursors, which contained minimal or no DNA:

  - Hydrogenosomes: These lack a genome but may have a few incomplete elements of the TCA cycle and the electron transport chain.[106] The anaerobic metabolism seen in hydrogenosomes suggests that these

might have originated through endosymbiosis with an anaerobic bacteria such as *Clostridium*.[107] However, later studies showed that the hydrogenosomes in *Trichomonas vaginalis* may also contain several proteins resembling those in mitochondria, including chaperonins, the NADH dehydrogenase module of electron transport complex I, and components of the mitochondrial machinery for synthesis of iron-sulfur (Fe-S) clusters.[108,109] Hydrogenosomes could very well be relict mitochondria;[110]

– Mitosomes: These have been seen in anaerobic, parasitic protists such as the amoebozoons *Entamoeba histolytica* and *Mastigamoeba balamuthi*. These organisms were initially considered to be amitochondriate and unable to generate ATP.[105,111] However, these contain several proteins similar to those seen in mitochondria and hence could be evolutionarily related to conventional mitochondria.[97,109] Compared to mitochondria, the metabolic capacity of mitosomes is relatively limited;[112]

– Transitional MROs: These are seen in anaerobic ciliates *Nyctotherus ovalis*, and *Blastocystis* spp., which are related to the brown algae, diatoms.[97] There is a possibility of a shared origin between mitochondria, hydrogenosomes, and mitosomes.[113] These MROs can generate H_2 via an ATP-producing, hydrogenase-mediated pathway.[114] The genome is relatively limited, and there are not many mtDNA-encoded genes similar to those seen in the respiratory complexes III, IV, and V.[115] These MROs also lack the ability to generate ATP via coupled electron transport and oxidative phosphorylation.[116] The MRO genome can contain organellar translation systems (rRNAs, tRNAs, ribosomal proteins) and a partial electron transport chain with subunits of electron transport complexes I and II.[111]

Evolutionary Precursors of Mitochondria

Mitochondria are generally believed to have evolved about 1.6–2 billion years ago from α-proteobacteria, a subgroup of the purple non-sulfur bacteria (Fig. 6).[81–83] These bacteria were internalization into host cells and then differentiated through several transitional forms of proto-mitochondria.[117–119] Increasing information places mitochondrial precursors in the order *Rickettsiales*, which is a subgroup of α-proteobacteria that include obligate intracellular bacterial parasites such as *Rickettsia, Ehrlichia,* and *Anaplasma*.[120] Phylogenomic analysis based on the 32 genes shared by mitochondria and these bacteria show similarities with the order *Rickettsiales*.[121] These similarities identify mitochondria to possibly be a sister clade of the *Rickettsiaceae*/*Anaplasmataceae* families, subtended by the free-living α-proteobacterium HIMB59 and the *Holosporaceae* family.[122]

Mitochondria also seem to show a sister-clade relationship with a group of free-living bacteria known as the Stramenopila, Alveolata, and Rhizaria (SAR)-11 group.[121] These are ubiquitous, free-living, small carbon-oxidizing bacteria with an estimated global population

of 2.4×10^{28} cells, present in nearly 25% of all oceanic plankton.[123,124] If confirmed, this relationship would suggest an alternative source of mitochondria in addition to those from *Rickettsiales*.[125] However, these findings need confirmation through accurate reconstruction of genome trees and evolutionary models, better statistical support without stochastic noise, identification of composition biases in the sequence data, or systematic errors such as long-branch attraction.[126–131]

Unfortunately, the identification of these relationships has been difficult.[130,132,133] There are many restrictions such as (a) weakness of the phylogenetic signal: Signals from small subunit rRNAs have weakened with time due to saturated mutations;[134] (b) long-branch attraction: Mitochondria and the obligate intracellular α-proteobacteria have more rapid rates of evolution than the free-living bacteria, and therefore, there are more artifacts;[135] and (c) sequence composition bias: AT-rich genome sequences in mitochondria can result in errors in phylogenetic reconstruction.[136]

Evolution of Prokaryotic Host Cells into Eukaryotic Ancestors

The evolutionary sequence in which the proto-mitochondrial bacteria entered an endosymbiotic relationship with prokaryotes is still uncertain. To place cellular evolution in perspective, prokaryotes are known to have acquired eukaryotic characteristics with differentiation.[117] The first eukaryotic common ancestor (FECA) matured through several stages to be identified as the last eukaryotic common ancestor (LECA) about 1–1.9 million years ago (Fig. 7).[113,137–139] These ancestor cells showed many features similar to modern eukaryotes.

Cells in the superphylum Asgard, which were the immediate descendants of the FECA, are considered to be the most likely hosts of the proto-mitochondria.[113,140] Some alternative host lineages have also been considered in the superphylum Planctomycetes, Verrucomicrobia, or Chlamydiae.[103,141] However, if the host cells were indeed proven to be Asgardian, these cells most likely evolved first to the domain archaea, and then to phyla such as Crenarchaeota, Thaumarchaeota, and Korarchaeota.[142] With some capability of metabolizing oxygen, these cells have been viewed as evolutionarily closer to eukaryotes and termed eocytes.[143–145]

The eukaryotic ancestors continued to differentiate during this process. The LECA possessed most of the eponymous components of eukaryotic cells, including the nucleus with nuclear pores, associated complexes, and nuclear lamina.[146] This nucleus is believed to have contained linear chromosomes with telomeres, encoding about 4,000 genes containing spliceosomal introns.[147] It likely possessed complex gene regulatory mechanisms, including RNA interference systems and small non-coding RNAs, and histone packaging that affected the accessibility to chromatin.[148] Transcription was uncoupled from translation and involved extensive RNA processing (including intron splicing, capping, and polyadenylation).[149] This ancestor also had an elaborate protein regulation and recycling system composed of a proteasome and a ubiquitin signaling system.[150]

The cellular environment of the LECA was compartmentalized with endomembrane systems such as the endoplasmic reticulum, the golgi apparatus, endosomes, lysosomes,

and peroxisomes.[137] It displayed exocytic and various endocytic pathways such as phagocytosis.[151] There was an actin-tubulin cytoskeleton that enabled intracellular trafficking, cell motility, and a complex cell cycle.[152] The last eukaryotic common ancestor was likely able to synthesize phospholipids composed of glycerol 3-phosphate and fatty acids, as well as sterols and sphingolipids.[153] These cells also show many genes of bacterial origin that were likely acquired when the mitochondrial ancestor was engulfed.[154]

The host cells are covered in a bilayered lipid membrane, a simple cell wall (S-layer) rich in *N*-glycosylated proteins, and a relatively well-developed cytoskeleton with homologs of actin and tubulin.[155] During evolution into eukaryotes, the three most important changes were the acquisition of the nucleus, the endomembrane system, and the mitochondria.[154] However, the sequence of these events remains unclear. There are at two possibilities:

- Syntrophic consortium model: Simultaneous fusion of a symbiotic community that included the cytoplasm, nucleus, and mitochondria.[156]

- Endospore model: The nucleus evolved when a cell engulfed a sister following cell division. This model resembled endospore development in Gram-positive bacteria. Mitochondria were acquired later.[103] This model is so not well-supported by evidence.[62]

The nucleus was most likely not acquired from the internalization of another organism; phylogenomic analyses of the eukaryotic genome support the presence of an archaeal and a proteobacterial genome, but not the other genome donor(s) expected in nuclear endosymbiotic models (Fig. 8).[155] Such endosymbiotic models would also require supplemental theories to explain the origin of the endomembrane system, the physical continuity of inner and outer nuclear membranes, and the formation of nuclear pores.[62,104] Hence, the most compelling models suggest an autogenous origin of the nucleus. Infoldings/pinched-off sections of the plasma membrane formed the endoplasmic reticulum (ER) like internal compartments that later became organized around the chromatin to form the inner and outer nuclear envelope and enclosed a proto-nucleus.[155]

Acquisition of Mitochondrial Precursors into Host Cells

Mechanistic Perspective—Phylogenetic data suggest that the proto-mitochondria were likely acquired through an intimate mutualistic association between the archaeal host cells with bacterial ancestors of mitochondria that lived on the surface of these cells.[103] During evolution, these bacteria have exchanged genes to achieve lower GC contents.[157] The strongest evidence of this evolutionary process is the close homology between bacterial and mitochondrial respiratory chain complexes.[158,159] The mitochondrial endosymbiont gradually became less complex in its genome and proteome.[97,113] It also adapted gradually to anaerobiosis.[103] There are two possible mechanisms:

- Outside-in models: The symbionts living on the host surface might have been internalized in cell membrane vesicles (Fig. 9A). The inner and outer nuclear membrane was formed by the ER lamellae and the perinuclear space by the ER cisternae.[160] There is also a possibility that these bacteria could have been phagocytosed into food vacuoles, and then entered the cytoplasm by lysing the

vacuolar membrane.[161] The cell membrane covering these symbionts contributed to the formation of the nuclear membrane;[155]

- Inside-out model: The host cells generated extracellular protrusions (blebs) to increase the total surface area[155] (Fig. 9B). The ancestral prokaryotic cell body remained intact as the eventual nuclear compartment during this evolution into eukaryotes.[155] The protrusions then fused and contained the cytoplasm and an endomembrane system, which evolved to make the outer nuclear and plasma membranes.[155] The mitochondrial precursors were initially trapped within the ER but then penetrated the ER membrane to move into the cytoplasm.[155] Finally, the formation of a continuous cell membrane closed off the ER from the exterior.[162]

The base of the cytoplasmic protrusions might have been stabilized by proteins homologous to the highly conserved coat protein II (COPII) in the outer ring of the nuclear pore.[163] Exchange of materials such as hydrogen, sulfur, hydrogen sulfide, organic acids, and ATP may have expanded these protrusions.[155] The blebs likely stabilized an outer ring of nucleoporins in the cell wall.[155] Proteins such as the linker of nucleoskeleton and cytoskeleton (LINC), which physically connect the cytoskeleton with the nucleoskeleton, might have stabilized the nuclear envelope and promoted nuclear bleb formation.[164]

Most structural lipids in eukaryotic cell membranes resemble bacterial, not archaeal lipids. Bacterial and eukaryotic membrane lipids carry glycerol-3-phosphate lipids with ester-linked, straight-chain fatty acids, whereas archaea contain a glycerol-1-phosphate backbone and ether-linked fatty acids (Fig. 10).[154,165] Additionally, eukaryotes and some bacteria, but not archaea, produce triterpenoids (for example, hopanoids and sterols) that modulate membrane fluidity.[166] Eukaryotes may have acquired bacterium-like lipids from mitochondria.[154] The genes for lipid biosynthesis from proto-mitochondria may have been transferred prior to the development of vesicle trafficking systems and phagocytosis.[155]

The analysis of archaeal lipids has provided some support to the possibility that phagocytosis evolved after the acquisition of mitochondria. Archaeal membranes typically retain their physical properties across a wide range of temperatures, whereas bacterial and eukaryotic membranes retain structures best at a narrow range of physiological temperatures.[167] These properties might be important for optimizing phagocytosis.

Phylogenetic Perspective—Mitochondria are seen in most eukaryotic host cells as the two may have evolved together.[97] Consequent improvements in efficiency in metabolic processes and the encoding of interacting gene products have created an obligate codependence. However, the number of mitochondria per cell has changed through evolution and differs across phyla.[168] Many unicellular eukaryotes contain only a few mitochondria, whereas others can contain up to 10^5.[169] The number of mitochondria can vary in multicellular eukaryotes from 80 to 2,000 per cell.[168]

In proto-mitochondria, the electron transport chain and pathways for β-oxidation of fatty acids were likely present, indicating that the mitochondrial endosymbiont had an aerobic metabolism.[170] The pathways for the synthesis of lipids, biotin, heme, and Fe-S clusters

were also present.[113] This proto-mitochondria might have been capable of facultative aerobic respiration.[113]

Unlike the mitochondrial genome, the proteome shows only limited similarity with that in α-proteobacteria.[98] The mitochondrial ribosome also shows a high degree of evolutionary retailoring.[171,172] In many eukaryotes, the mitochondrial large- and small subunits have become smaller than their bacterial counterparts, and many new ribosomal proteins have been added.[97] The structure that was originally an RNA-rich complex has now become enriched in proteins.[171]

Mitochondrial Biogenesis—This process includes the growth and division of pre-existing mitochondria. Mitochondria are believed to have evolved from an α-protobacteria endosymbiont that became incorporated in a host cell.[173] Due to this bacterial origin, mitochondria contain a characteristic genome and also show auto replication.[174] Mitochondrial proteins are encoded by the mtDNA and specifically-encoded structures in the nuclear genome (described above).[94]

Major Molecular Components—A large number of mitochondrial proteins, nearly 1,000–1,500 are encoded in the nucleus.[175] The mRNAs are transcribed in the nucleus and translated into the cytosol. Most precursor proteins, whether folded or not, pass through the mitochondrial membranes assisted by protein translocases.[57] Many of these folded proteins are tagged with an *N*-terminal, positively-charged presequence.[176,177] Once this presequence is cleaved off by a matrix protease, these proteins may get folded with the aid of molecular chaperones.[176] Proteins moving to the other mitochondrial compartments may be transported by different protein-import pathways.[178] Many precursor proteins that do not contain the *N*-terminal signals may carry the targeting information within the actual protein sequence.[179] The mitochondrial membrane potential and the action of matrix Hsp70 (heat-shock protein 70) regulate this translocation.[180]

As mentioned above, the translocase of the outer membrane (TOM) protein is a universal entrygate for all proteins entering the mitochondria.[44] Many different pathways diverge at this point:

- translocase of the inner membrane (TIM), which sorts matrix-targeted precursors;[181]

- presequence translocase-associated motor (PAM) regulates matrix Hsp70 action to drive precursors into the matrix;[182]

- sorting and assembly machinery (SAM) on the outer membrane inserts β-barrel proteins into the outer membrane.[183]

These processes are an integral part of mitochondrial biogenesis, which may involve not only increased number but the size and mass. Mitochondrial biogenesis can also be altered by environmental stress as malnutrition, low temperature, oxidative stress, and cell division.[184]

An important regulator of mitochondrial biogenesis is peroxisome proliferator-activated receptor-gamma coactivator ([PGC]-1alpha) [PPAR (peroxisome proliferator-activated receptor)-γ coactivator-1α].[185,186] Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha stimulates the formation of new mitochondria by inducing UCP (uncoupling protein) 2, nuclear respiratory factor (NRF)-1, and NRF-2.[175] Nuclear respiratory factor (NRF)-1 and NRF-2 then induce key mitochondrial enzymes.[187] These also interact with Tfam, which drives transcription and replication of mtDNA and many nuclear-encoded mitochondrial components.[184] Nuclear respiratory factor (NRF)-1 activates the transcription of δ-ALAS (δ-aminolevulinate synthase), and NRF-2 that of cyclo-oxygenase (COX) IV.[188,189] Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha also interacts with other modulators of transcription such as PPARs, thyroid hormones, glucocorticoids, estrogen and ERRs (estrogen-related receptors)-α and -γ.[190,191] The ERRs are orphan nuclear receptors that target the gene networks involved in energy homoeostasis, and in mitochondrial biogenesis and function.[192–194] Mitochondrial subdivision also involves the dynamin-like and the fis-type proteins.[41] Regulation of the numerical density of mitochondria in various cells: Metabolic needs may regulate the mitochondrial mass via-a-vis the cellular size across the cell cycle and the total body weight according to a power law.[168,195] In some tissues, the organelles appear as discrete units and the number and size may be related to the cell size. The cells resemble single-celled eukaryotes and may follow linear or sublinear scaling for mitochondria, not Kleiber's power law (an animal's metabolic rate scales to the 3/4 power of the animal's mass).[196,197] Some cells show context-dependent mitochondrial morphology, and sometimes a large filamentous organelle reticulum.[34] The size of these organelles may not consistently scale strongly with cell size in single-celled eukaryotes, suggesting that the number of mitochondria per cell may be more important than the size of these organelles as a means of modulating cellular energetic requirements.[168] There might be a possibility of having an optimal per-cell mitochondrial mass given the cell size and the nature of mitochondrial biogenesis.

In humans, the mitochondrial count varies across different tissues and organs.[10,168] Mature erythrocytes do not contain any, whereas metabolically-active organs such as the liver, kidney, heart, and brain tissues contain large numbers.[198] Mitochondria are important for metabolic functions and also for cellular maintenance.[199,200] Many mitochondrial genes have been transferred to the nuclear genome during evolution. These relocations might have improved the numerical efficiency, proximity to up- and/or downstream genetic systems, or improved utilization of cytoskeletal space by preventing redundancy in transcription sites.[201]

Even though there might be some variance in the expression of a subset of genes expressed in the mitochondria, most of these genes are transcribed at a specific, constitutive level.[91] One reason might be that the entire circular mitochondrial genome involves one strand at a time.[202] The number of mitochondria may also be important because of the variations in the lability of these organelles and that of energetic constraints across tissue types.[203]

Intercellular transfer of mitochondria: Mitochondria and mtDNA can be transferred between cells.[204] Transient focal cerebral ischemia can release mitochondria from astrocytes, which enter adjacent neurons via a calcium-dependent mechanism involving CD38 and cyclic ADP ribose signaling. This can amplify the survival signals.[205,206] Horizontal transfers of mtDNA

have also been noted in cancer cells; extracellular vesicles containing mtDNA can pass through tunneling nanotubes and connexin 43 gap junctions between cells.[207,208]

Epigenetic Changes Involved in Mitochondrial Biogenesis—The epigenetic landscape is extensively reprogrammed during embryonic and fetal development.[209] Paternal genome also shows considerable DNA demethylation after fertilization.[210] Depletion of mtDNA leads to alteration in the metabolism of amino acids including methionine, leading to increased DNA methylation.[211] *S*-adenosylmethionine (SAM) acts as a co-factor in these methylation reactions; SAM is produced from methionine by methionine-adenosyl transferases (MATs).[212,213] Interestingly, the development of the embryo prior to implantation requires appropriate histone demethylation mediated by the JMJ (*jumonji*, or the Jarid2) deamylase, which removes the methyl group from lysine residues. The JMJ demethylases catalyze the histone demethylation in an α-ketoglutarate-dependent manner.[214,215] Thus, mitochondria regulate demethylation via α-ketoglutarate through the oxidation of glucose and glutamine in the mitochondrial citric acid cycle.[216]

Chromatin remodeling is also important in embryonic epigenetic programming.[216] Histone acetylation relaxes the condensed chromatin and promotes gene transcription.[217] Contrarily, deacetylation of histone condenses the chromatin and suppresses transcription.[217] Histone acetylation by specific histone acyltransferases requires acetyl-CoA, which is the product of oxidative decarboxylation of pyruvate produced by glycolysis, β-oxidation of fatty acids, and amino acid metabolism, and then shuttled out of mitochondria in the form of citrate, acetyl-CoA precursor.[218] In human embryonic stem cells, increasing acetylation suppresses differentiation, while inhibition of acetyl-CoA production from glucose results in the loss of pluripotency. The availability of nicotinamide adenine dinucleotide (NAD^+) controls the activity of the conserved NAD^+-dependent histone deacetylases, the sirtuins (SIRTs).[219] SIRTs are involved in blastocyst development as the inhibition of SIRT activity decelerates blastocyst development. NAD^+ can be synthesized de novo from the amino acid tryptophan or through the NAD^+ salvage pathway from nicotinamide.[220] However, cytoplasmic NAD^+ levels are normally very low, and blastocyst development and placental and fetal growth can be maintained only when NAD^+/NADH-reducing equivalents shuttle into mitochondria through either malate-aspartate or mitochondria glycerol 3-phosphate dehydrogenase.[221] Histone acetylation during development deserves further study.

Mitochondrial Function—The following section summarizes currently available information on various aspects of mitochondrial function(s) (Table 1):

Energy production: Mitochondria play an important role in energy production and its storage as ATP.[3] Glucose is broken down during glycolysis in the cytoplasm into two molecules of pyruvate, which are then translocated to the mitochondria by membrane-bound permeases.[222] There, pyruvate dehydrogenase processes these molecules via oxidative decarboxylation to produce acetyl coenzyme A (acetyl-CoA), which triggers the TCA as described above.[216] Metabolites enter the TCA cycle as acetyl-CoA, α-ketoglutarate, succinyl-CoA, fumarate, and oxaloacetate. Nicotinamide adenine dinucleotide (NAD), a coenzyme central to metabolism, is reduced to form hydrogenated NAD (NADH).[223]

The mitochondrial respiratory chain has been conserved through evolution (as shown in Table 1 and details depicted in Fig. 11). Complex I and II oxidize NADH and Flavin adenine dinucleotide ($FADH_2$), respectively, and transfer the resulting electrons to ubiquinol, which carries electrons to Complex III (Fig. 12).[224] Complex III shunts the electrons across the intermembrane space to reduce cytochrome c (ubiquinone), which brings electrons to complex IV.[225] Complex IV or cytochrome *c* oxidase (COX) is the last electron acceptor of the respiratory chain, involved in the reduction of O_2 to H_2O. This multimeric complex includes multiple structural subunits encoded in two different genomes, several heme groups (heme *a* and heme a_3), and coordinated copper ions (Cu_A and Cu_B). About four electrons are removed from four molecules of cytochrome *c* and transferred to molecular oxygen (O_2) and four protons, producing two molecules of water. About eight protons are removed from the mitochondrial matrix (although only four are translocated across the membrane), contributing to the proton gradient.[226] Finally, mitochondrial ATP production is the main energy source for intracellular metabolic pathways. Complex V is a multi-subunit oxidative phosphorylation complex.[227] There are two functional domains, including (a) F1, in the mitochondrial matrix; and (b) the F0, located in the IMM.[228] This energy created in the proton electrochemical gradient is utilized to phosphorylate ADP to ATP.[227]

Reduced NAD^+ (NADH) is used by enzymes embedded in the mitochondrial cristae to produce ATP.[229] Beta-oxidation of fatty acids also produces acetyl-CoA, NADH, and reduced flavin adenine dinucleotide ($FADH_2$; FAD is a redox-active coenzyme involved in several metabolic pathways).[230] Oxidative degradation of certain amino acids can also contribute to this process; the mitochondria are also the key regulators of the biosynthesis of amino acids, lipids, and gluconeogenesis.[231] Under normal conditions, over 90% of ATP is made in mitochondria[232] but most of the genetic machinery needed to produce ATP has been translocated to the nucleus during evolution.[233] Only about 3% of the mitochondrial proteins are needed to synthesize ATP.[229]

Flavin adenine dinucleotide ($FADH_2$) is another energy carrier that is produced in the mitochondrial matrix and is processed by oxidative phosphorylation in the electron transport chain to regenerate FAD.[234] Protons are pulled into the intermembrane space by the energy of the electrons going through the electron transport chain. In the electron transport chain, 4 electrons are accepted by oxygen and the protons return to the mitochondrial matrix through the protein ATP synthase.[224] The energy is used to activate ATP synthase, which then facilitates the passage of a proton to produce ATP.[234] The difference in pH between the matrix and intermembrane space creates an electrochemical gradient by which ATP synthase can facilitate the passage of protons into the matrix.[3] The oxidation of NADH and $FADH_2$ also produces GTP from succinyl-CoA synthetase-mediated signaling.[216]

In oogonia, mitochondria are the prime source of energy.[235] These mitochondria have a dense matrix and a few arch-like or transverse cristae, and are usually seen in the central cytoplasm.[236] Mitochondria in metaphase I and II of oocytes still resemble those in the germinal vesicle, with an even distribution in the cytoplasm and aggregation around the smooth ER.[236] At the pronuclear stage, mitochondria conglomerate around the pronuclei, and this persists up to syngamy.[237] In the 8-cell embryo, the morula, and the blastocyst, mitochondria are relatively less electron-dense and show clear areas in the matrices. In

expanding blastocysts, trophoblast, embryoblast, and endodermal cells, mitochondria look elongated with the IMM arranged into transverse cristae.[3,236]

Growing oocytes preferentially utilize pyruvate to make ATP, and early embryos also use pyruvate, lactate, and amino acids to support development. [238–240] Mature oocytes contain the highest mitochondrial DNA copy number and mass of any cell.[241] Fertilized oocytes have even higher mtDNA copy numbers, Inhibition of mitochondrial metabolic activity blocks the maturation of oocytes and the subsequent embryonic development. [136,242–247] In humans, embryo development and implantation rates are closely correlated with ATP levels, and inhibiting mitochondrial activity suppresses embryonic stem cell differentiation. [247,248] After birth, there is a rapid increase in the density and activity of mitochondria in the heart and other metabolically active organs.[249] The expression of mitochondrial respiratory chain genes is also increased.[17]

The density of mitochondria in cells does seem to be important. Fibroblasts and other cells from obese mothers have been shown to carry fewer mitochondria, which relates to higher levels of triglycerides, free fatty acids, and more lipids.[250] The paucity of mitochondria alters the placental lipid metabolism and transfer of the lipids to the fetus, causing lipid-related diseases such as newborn adiposity.[251] Likewise, the reduced mitochondrial function has been noted in brain injury in newborns. [252] Decreased mitochondrial proteins may lower neonatal pyruvate dehydrogenase and oxidative phosphorylation activity, and increase the risk of morbidity.[253] Metabolic shifts are also important for the function of cardiomyocytes. Mutations in mtDNA and mitochondrial dysfunction were associated with dilated cardiomyopathy via transcription factor A, mitochondrial (TFAM).[254]

Changes in mitochondrial function based on maternal age: Mitochondria have important roles in oocyte maturation, fertilization, and early embryo development.[255] In women of advanced reproductive age, aging oocytes often show less ATP and mtDNA copy number, mutations in mtDNA, and ultrastructural abnormalities.[256]

Urea Cycle—The initial steps of the urea cycle take place in the mitochondrial matrix, particularly in hepatocyte and renal epithelium (Fig. 13).[257] In the first step, the carbamoyl phosphate synthetase I enzyme utilizes two ATP molecules to convert ammonia into carbamoyl phosphate.[258] In the second, ornithine transcarbamylase converts carbamoyl phosphate and ornithine into citrulline.[259] Subsequent steps continue in the cytoplasm until ornithine is re-transported into the matrix.[257]

Transamination—Oxaloacetate can be transaminated to produce aspartate and asparagine in the matrix.[260] Similarly, transamination of α-ketoglutarate produces glutamate, proline, and arginine.[261]

Metabolic Regulation—The concentrations of ions, various metabolites, and energy charge in mitochondria are closely regulated. Ca^{2+} ions regulate the TCA cycle (as shown in Fig. 4) by activating pyruvate dehydrogenase, isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase.[262] The concentration of intermediates and coenzymes in the matrix also influences the rate of ATP production.[263] NADH can inhibit TCA enzymes α-ketoglutarate

dehydrogenase, isocitrate dehydrogenase, citrate synthase, and pyruvate dehydrogenase.[264] Adenosine triphosphate inhibits isocitrate dehydrogenase, pyruvate dehydrogenase, the electron transport chain, and ATP synthase.[265] In contrast, ADP acts as an activator.[266]

Apoptosis—Mitochondrial apoptosis is the most common form of programmed cell death.[267] It is mediated through proteins of the B-cell lymphoma-2 (bcl-2) family.[268] There are two sub-classes of bcl-2 proteins: (a) the pro-apoptotic bcl-2 associated X-protein (bax) and bcl-2 antagonist/killer 1 (bak) proteins, which oligomerize to create "pores" on the OMM in response to apoptotic stimuli.[269] Through these pores, proteins from the mitochondrial intermembrane space (IMS) reach the cytoplasm and activate the caspase cascade;[51,270,271] (b) anti-apoptotic bcl-2 proteins such as bcl-2, bcl-x_L or myeloid cell leukemia (MCL)-1, which inhibit bax and bak signaling.[272]

Apoptosis is induced when various conformations of activated bax accumulate on the mitochondrial surface.[267] The ratio of mitochondrial/cytosolic levels of bak and bax determine the cellular response to apoptosis stimulation.[273] Increasing information suggests that bax, either alone or complexed with other proteins such as cytochrome c, Smac/direct IAP binding protein with low pI (Diablo), HtrA Serine Peptidase 2 (HtrA2)/Omi, and apoptosis-inducing factor (AIF), forms pores in the OMM to release IMS proteins.[274] Bcl-2 associated X-protein (Bax) can also modulate the function of permeability transition pore complexes formed with other mediators such as the voltage-dependent anion channels (VDAC–1, –2, –3; mitochondrial porin), the adenine nucleotide transporter cyclophilin D, and the F_1F_o ATP synthase.[275] These complexes promote the transport of nucleotides, phosphocreatine, Ca^{2+}, and other small ions across the OMM.[276] Some investigators have noted the resemblance between active bax/bak and the holin proteins that are involved in host cell membrane lysis by bacteriophages.[277,278] The bax/bak oligomers form membrane lesions, which release endolysin, a muralytic enzyme, through these lesions to attack the cell wall.[278,279]

Ionic Content of Various Tissues—Mitochondria can absorb calcium ions and play an important role in the regulation of calcium content in various cells.[11,280] Increased intracellular calcium can regulate many cellular processes. In neurons, these levels can alter neurotransmitter release.[281] It can also alter other processes such as endocrine changes. muscle function, and coagulation.[282] In infants, mitochondria can alter non-shivering thermogenesis in brown fat through proton leaks.[283]

Mitochondrial Genetic Defects in Neonates

Epidemiology and Clinical Features—Mitochondrial dysfunction affects one in 6, 000 – 8, 000 newborns.[284–286] The diseases may occur in patterns consistent with autosomal recessive, autosomal dominant, mitochondrial, and random mutations.[287,288] Young infants require mitochondrial energetic metabolism to support rapid growth. Key organs such as the muscle, heart, and brain require mitochondrial function/aerobic metabolism for adaption to extra-uterine life.[289] Disorders of mitochondrial metabolism caused by defects in fatty acid oxidation; pyruvate metabolism; and those in the respiratory chain, including mitochondrial complex I, II, III, IV, and ATP synthase, can become symptomatic in the neonatal period.[230]

Mutations of both nuclear genes and mtDNA can cause mitochondrial dysfunction with adverse, outcomes in neonates.[224–228,290]

Neonatal-onset mitochondrial disease is associated with considerable, early mortality.[291] In a recent study, Ebihara et al.[285] reviewed the records of 281 patients with mitochondrial disease. The multisystem disease was noted in 194, Leigh syndrome in 26, cardiomyopathy in 38, and hepatopathy in 23 patients. Of the 321 with initial symptoms, 236 were recognized to have illness within two days of birth. The disorders were recognized by altered mitochondrial respiratory chain enzyme activity rate in 182, and abnormal oxygen consumption rate in 89. The remaining 10 patients were diagnosed using a genetic approach. Genetic analysis showed 69 to have nuclear DNA variants in 36 genes; 11 of 15 had mtDNA variants in 5 genes, and 4 had a single large deletion. Cyclo-oxygenase (Cox) proportional hazards regression showed significant differences in survival in those with Leigh syndrome [hazard ratio (HR) = 0.15, 95% confidence interval (CI) 0.04 to 0.63, p = 0.010] and in others with a molecular diagnosis (HR = 1.87, 95% CI 1.18 to 2.96, p = 0.008).

In the outpatient setting, mutations of mitochondrial complex I mutations can be seen with Leigh Syndrome, lethal infantile mitochondrial disease, lactic acidosis, MELAS syndrome, and Leber's Hereditary Optic Neuropathy.[292,293] Mutations in succinate dehydrogenase (SDH)-A, -B, and -AF1 genes in Complex II can cause mitochondrial leukoencephalopathy, cardiomyopathy, infantile leukodystrophy, and Kearns-Sayre syndrome.[294] Mutations in Complex III can cause severe lactic acidosis with hypotonia, irritability, and muscle wasting.[295] Complex III deficiency is mainly caused by mutations in maternally-transmitted mitochondrial chaperone BCS1 (BCS1L), Ubiquinol-Cytochrome C Reductase-Binding Protein (UQCRB), Ubiquinol-Cytochrome C Reductase Complex III Subunit VII (UQCRQ) and mitochondrially-encoded Cytochrome B (MTCYB) genes.[296,297] Mutations in Complex IV are associated with neonatal hypertrophic cardiomyopathy, liver dysfunction, myopathy, hypotonia, developmental delay, and encephalopathy.[294] The biogenesis and assembly of cyclooxygenase (COX) in Complex IV depends on numerous ancillary factors, including copper chaperones, all nuclear-encoded.[298,299] Specifically, disease-causing mutations were found in the gene encoding the Surfeit locus protein 1 (SURF1), which is essential for the formation of early assembly intermediates.[300,301] Mutations in Complex IV have been associated with neonatal encephalopathy, respiratory distress, pulmonary hypertension, lactic acidosis, peripheral neuropathy, dysmorphism, and cataracts.[302] Defects in ATP synthase can also cause fatal encephalopathy in neonates.[303,304]

Pyruvate dehydrogenase complex (PDHc) catalyzes the oxidative decarboxylation of pyruvate to produce acetyl-CoA and initiates the TCA cycle.[305] Pyruvate dehydrogenase complex (PDHc) deficiency is most often due to mutations in the first component of the enzyme complex, pyruvate dehydrogenase E1α (responsible for 70% of PDH deficiencies).[306] There is a spectrum of clinical presentations in E1α mutations;[307] the most severe mutations can manifest with lactic acidosis within a few hours of birth.[308] Other infants may show hypotonia, lethargy, feeding, respiratory difficulties, and encephalopathy.[309,310]

Mitochondrial Disorders

- *Infections*: The sepsis syndrome is a systemic host inflammatory response accompanied by organ dysfunction in response to invading microbial pathogens.[311] The host recognizes both danger and pathogens through its pattern recognition receptors on immune cells.[312] These receptors bind to pathogen associated molecular patterns (PAMP) and danger (DAMP) associated molecular patterns derived from microbes and host tissues, respectively.[313] These DAMPs and PAMPs activate the formation of inflammasomes, which bind to the apoptosis-associated speck-like protein (ASC) containing a caspase recruitment domain (CARD).[314–316] This forms a platform for the activation of caspase-1 and induction of interleukin (IL)-1β and IL-18.[317,318] Caspase-1 triggers mitochondrial damage.[319] It also inhibits mitophagy, a process that clears damaged mitochondria, leading to accumulation of defective mitochondria and damaged cells.[319] Mitochondrial DNA (mtDNA) has also been detected in the extracellular traps formed by innate immune leukocytes in these infected lesions.[320,321]

- *Oxidative phosphorylation*: Mitochondria are the site of oxidative phosphorylation in eukaryotes; the energy is produced by means of electron flow between four enzymes, of which three are proton pumps, in the inner mitochondrial membrane.[322] NADH generated in the TCA cycle is oxidized and activates the electron transport chain, which is comprised of complexes I–IV, and ATP synthase.[158,216] Acute inflammation may curtail these pathways.[323] Tumor necrosis factor (TNF) induces microRNAs that damage the mitochondrial complex-I, inhibit oxidative phosphorylation, and reduce ATP levels.[324,325]

- *Inflammation:* Inflammatory stimuli can promote mitochondrial fragmentation by increased protein unfolding, ER stress, phosphorylation of pro-fission proteins, and decreased respiratory capacity.[326–330] There is also increased oxidative stress; mitochondrial complex III generates superoxide during the ubiquinone (Q)-cycle.[331] Some lesions may show mitochondrial fission, mitophagy, and decreased fusion.[330,332,333] The intrinsic dynamicity of mitochondria also plays a role in proinflammatory signaling, identifying these organelles as a central platform for the control of innate immunity and the inflammatory response.[334]

During inflammation, cytokines such as TNF, interleukin (IL)-1, and IL-18 can promote necroptosis, a form of programmed necrosis mediated by various cytokines and pattern recognition receptors (PRRs).[335–338] Cells dying by necroptosis show necrotic phenotypes, including swelling and membrane rupture, and release damage-associated molecular patterns (DAMPs), inflammatory cytokines, and chemokines, thereby mediating extreme inflammatory responses.[339] Mitochondrial proteins such as the phosphoglycerate mutase (PGAM)-5 and dynamin-related protein (Drp)-1 have been identified as important activators of the receptor-interacting serine-threonine kinase (RIPK)-3 and consequent mitochondrial fission and necroptosis.[340–342] Mitochondrial reactive oxygen species (ROS) may regulate TNF-mediated cell death in other diseases.[343–345]

Mitochondrial mediators such as the DNA polymerase γ (POLG) and the protein growth factor erv1-like can alter physiological mediators for cellular self-renewal and suppress signaling mediators such as the octamer-binding protein 4 (OCT4), nanog homeobox (NANOG), and the putative thiosulfate sulfurtransferase (SSEA).[346–350]

- *Mitophagy in birth asphyxia and neurological disorders*: In asphyxiated infants with hypoxic-ischemic encephalopathy, neural energy failure is being increasingly documented.[351] Currently, the options for timely diagnosis and treatment are limited. Mitochondrial dysfunction with increased permeability, altered dynamics with changes in fission and fusion, mitophagy, and biogenesis have been observed in many studies.[352–355] Mitoprotective therapies may help prevent/treat brain injury and reduce the incidence of lifelong disabilities.[355,356]

In other neurological disorders, mitochondrial transmembrane potential loss with the involvement of PTEN (phosphatase and tensin homolog)-induced putative kinase 1 (PINK1), which then recruits Parkin, the E3 ubiquitin ligase, to the damaged mitochondria.[357–360] The BCL2 (B-cell lymphoma 2 genes)-interacting protein 3-like (BNIP3L), a mitophagy receptor that recruits LC3 family proteins to the damaged mitochondria, can be altered. [361,362] The FUN14 domain-containing 1 (FUNDC1) is another mitophagy receptor located on the outer mitochondrial membrane.[363,364]

- *Mutations in mitochondrial genes*: Many deletions and duplications in the mitochondrial genome can be seen sporadically. These may develop *de novo* or during early development (Table 1):[365–367]

Leber's hereditary optic neuropathy (LHON) is the most common, maternally-inherited mitochondrial disorder in the respiratory chain, which causes degeneration of retinal ganglion cells, associated axons, and optic atrophy within a year of disease onset.[368,369,319] An intriguing feature of LHON is that only 50% of males and 10% of the females with the mtDNA mutations actually become symptomatic.[370] This incomplete penetrance and gender bias imply that additional mitochondrial and/or nuclear genetic factors must be modulating the phenotypic expression of LHON.[371] It typically begins as a unilateral progressive optic neuropathy with the central visual loss with sequential involvement of the fellow eye months to years later.[220] In about 90% of clinical cases, the disease is associated with three mutations in mtDNA complex I subunit genes, namely the G3460A, G11778A, and T14484C. These mutations are absent or very rare among normal controls.[371–374]

Pearson syndrome is a rare fatal mitochondrial disorder caused by single large-scale mitochondrial DNA deletions. Most patients present with sideroblastic anemia during infancy, followed by multi-organ dysfunction including lactic acidosis, pancreatic insufficiency, renal tubulopathy, failure to thrive, muscle hypotonia, and endocrine disorders.[375,376] Bone marrow cytology shows vacuolization in erythroid and myeloid precursors and ring-sideroblasts; the diagnosis is established by the detection of mitochondrial DNA deletions.[375,377,378] Most cases have a lethal outcome. Some survivors go on to develop Kearns-Sayre syndrome, a progressive cardio-encephalo-myopathy caused by a large deletion or rearrangement of mtDNA.[379–382]

Leigh syndrome, also termed subacute necrotizing encephalomyelopathy, is a rare, inherited progressive neurodegenerative disorder that usually manifests in infancy or early childhood.[383,384] Many cases can be diagnosed in early infancy and present with developmental delay, pyramidal and extrapyramidal symptoms, leukodystrophy, and brainstem dysfunction.[385,386] Neuroimaging shows focal, symmetrical, necrotic lesions in the thalamus, the brainstem, and the posterior columns of the spinal cord. Histopathology shows symmetric spongiform lesions with degeneration of basal ganglia, particularly in the corpus striatum; and demyelination, vascular proliferation, and astrocytosis in the brainstem.[387–389] The lesions typically appear hyperintense on T2-weighted MRI.[390] Pathogenic mutations are often seen in flavoprotein of complex II.[391]

Alpers-Huttenlocher syndrome manifests with seizures, developmental delay, hypotonia, and liver disease.[326,327] It is a maternally-inherited disease with variable penetrance. It is usually caused by mutations in polymerase gamma (POLG).[392,393] Mutations in mitochondrial tRNA synthetase genes, including the phenylalanyl-tRNA synthetase 2, mitochondrial (FARS2), asparaginyl-tRNA synthetase 2, mitochondrial (NARS2), and the prolyl-tRNA synthetase 2, mitochondrial (PARS2) have also been linked.[394,395]

A syndrome associated with MELAS syndrome is caused by mutations in mitochondrial transfer genes such as the mitochondrially-encoded tRNA leucine 1 (MT-TL1).[396,397] It is characterized by mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes.[398,399]

OUR CURRENT UNDERSTANDING

Mitochondria provide energy and regulate key cellular events not only during the embryonic, fetal and neonatal period, but and throughout life.[4] After birth, the newborn infant's organs may show major changes in the number and function of mitochondria.[400] There is some evidence that epigenetic changes in mitochondrial DNA during the perinatal period may be protective.[401,402] These changes are most noticeable in the muscles, heart and brain.[403] Disorders of mitochondrial metabolism related to nuclear/mtDNA defects in mitochondrial complexes I, II, III, IV, and ATP synthase may present in the neonatal period.[404,405]

There is a need for focused studies of mitochondrial function and its modulators in the fetal/neonatal period to ascertain the need for interventions.[406] We still have major gaps in our understanding of the long-term effects of mitochondrial dysfunction in neonatal period and infancy.[353] A framework is needed to focus future research on altered mitochondrial function as a mechanism of perinatal adaptation.

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KEY POINTS

- Mitochondria are highly-dynamic, membrane-bound organelles that generate most of the chemical energy in eukaryotic cells.

- These organelles most likely evolved about 2 billion years ago from α-proteobacteria, a subgroup of the purple non-sulfur bacteria. These precursors of mitochondria likely belong to the order *Rickettsiales*.

- Besides the primary role in energy generation, mitochondria also perform numerous other cellular functions to support metabolism, epigenetic regulation, and cell cycle.

- In this article, we have summarized the ontogeny, ultrastructure, structure-function correlation, biogenesis, and clinical manifestations of mitochondrial dysfunction.
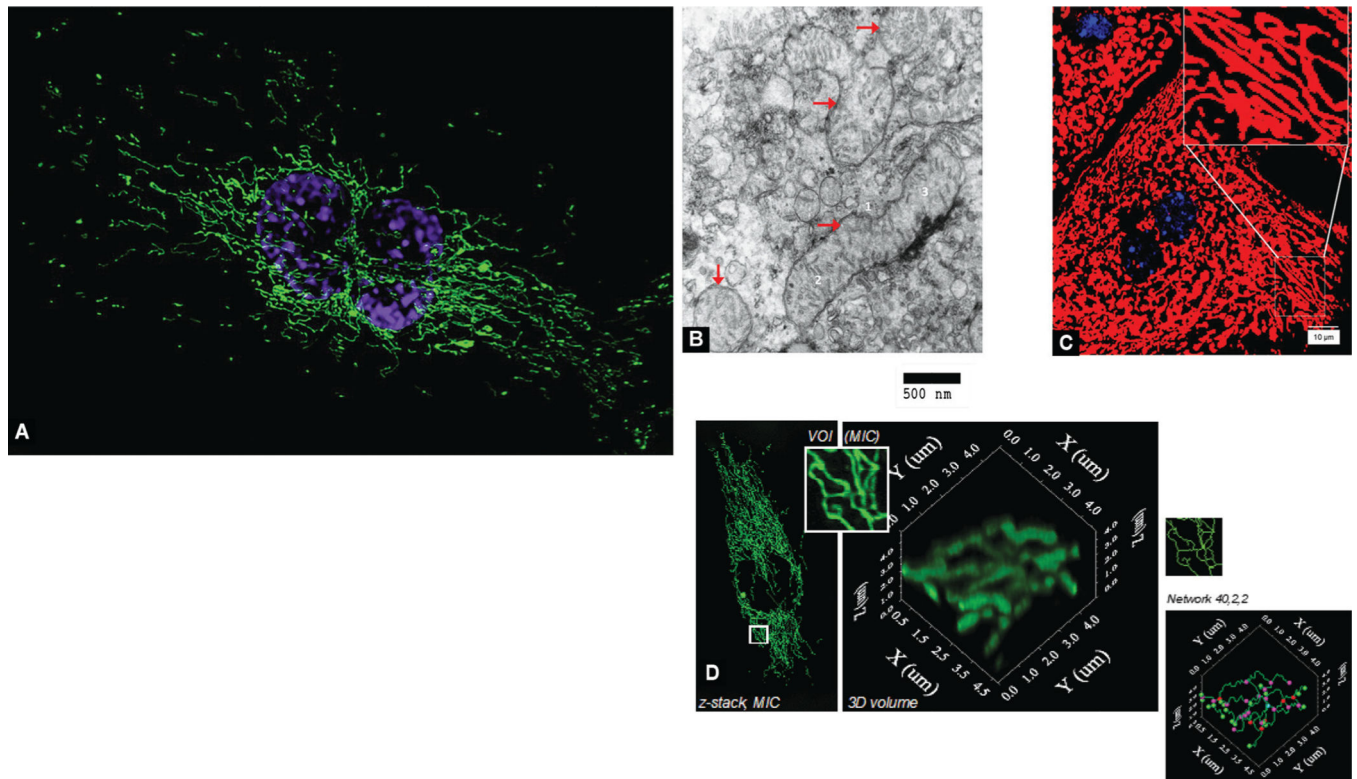
Figs 1A to D:

Panoramic view of mitochondria. (A) Mitochondria in a cultured dividing endothelial cell. The image shows a cultured mitotic human vascular endothelial cell (HUVEC) expressing mitochondrial green fluorescent protein (GFP). Nuclei (blue/purple) were stained with DAPI. Mitochondrial morphology varies between different cell types; this dividing endothelial cell displays a mitochondrial reticulum around recently-duplicated nucleus; (B) Transmission electron microscopy of mouse liver cells show mitochondria (indicated with red arrow). Mitochondrial membranes, 1; cristae, 2; and the matrix, 3 can be seen; (C) Mouse primary hepatocytes stained with MitoTracker Red, a red-fluorescent dye that stains mitochondria in live cells and its accumulation is dependent upon membrane potential. The dye is well-retained after aldehyde fixation; (D) Quantitative image analysis of mitochondria in a human vascular endothelial cell. VOI, Volume-of-interest; MIC, 3-dimensional light microscopic image (described in Nikolaisen et al, DOI: 10.1371/journal.pone.0101365)
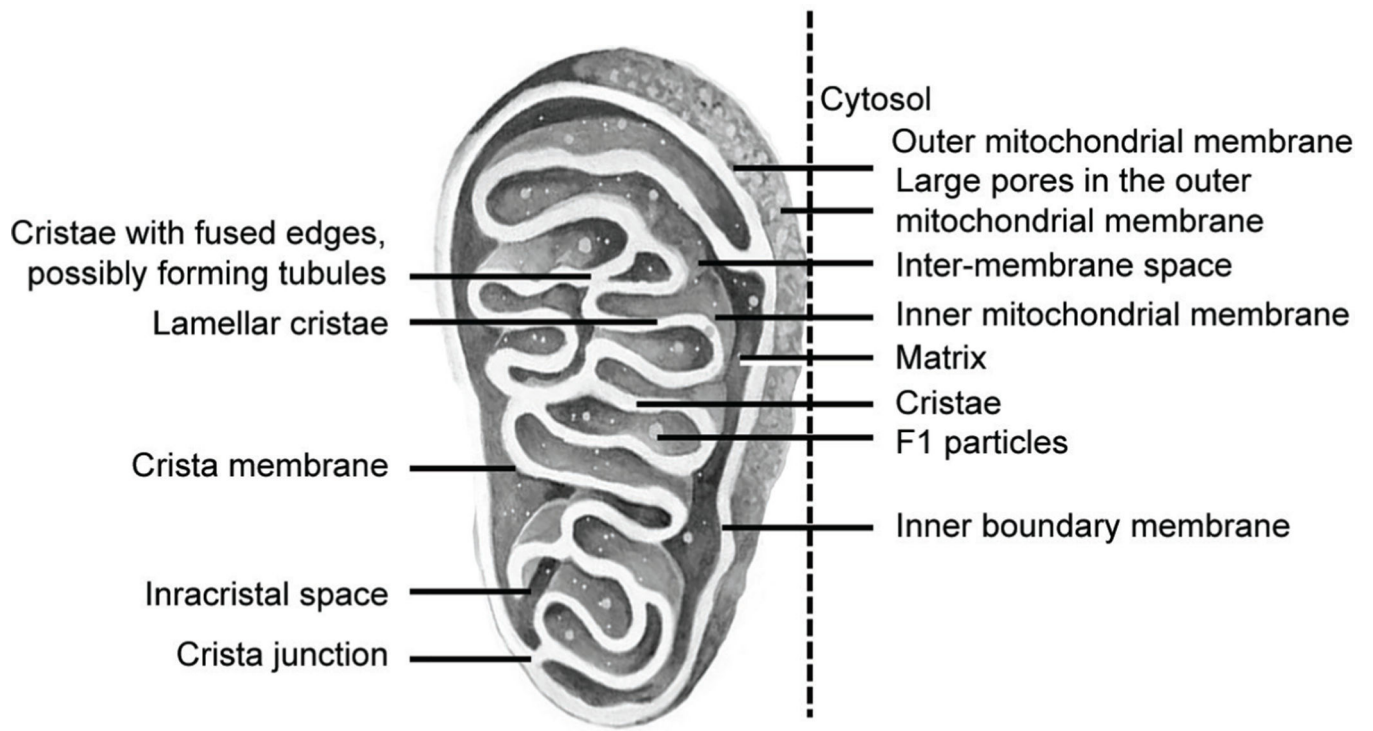
Fig. 2:
Graphical depiction of mitochondrial infrastructure showing the location of the most important/better-known elements
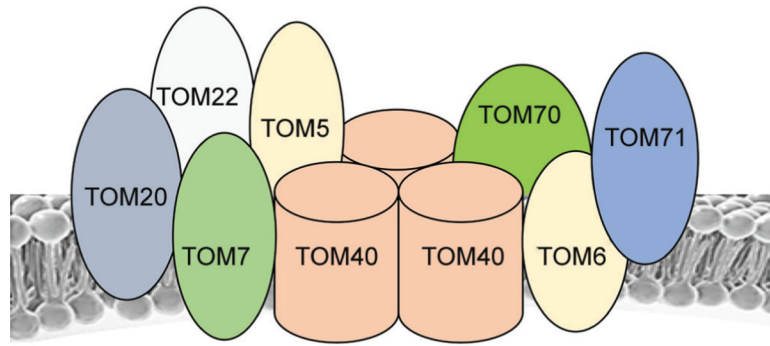
Fig. 3:

Translocases of the outer mitochondrial membrane (TOM): The TOM complex is comprised of many subunits; It recognizes, segregates, and translocates precursor proteins to various sites within the mitochondria
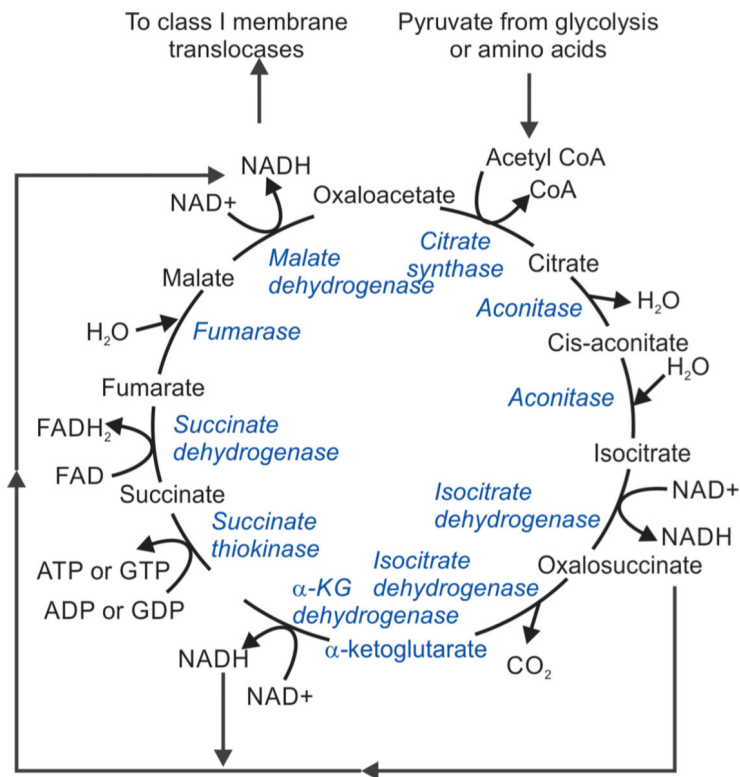
Fig. 4:

Graphical depiction of the TCA cycle. Metabolites enter the TCA cycle as acetyl-CoA, and progress to form α-ketoglutarate, succinyl-CoA, fumarate, and oxaloacetate. Nicotinamide adenine dinucleotide (NAD), a coenzyme central to metabolism is hydrogenated to form NADH; KG = ketoglutarate. Enzymes are depicted in blue font
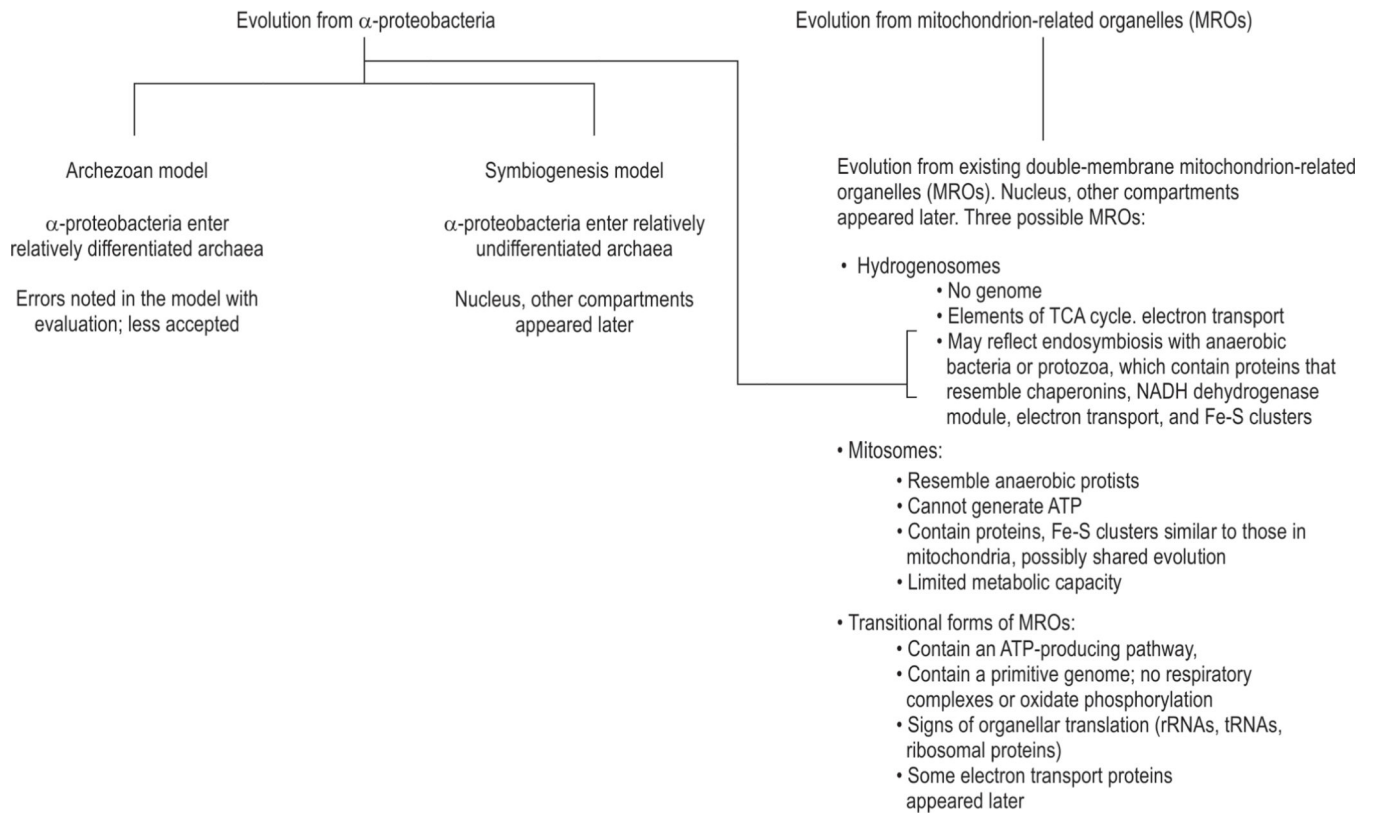
Fig. 5:

Existing models for mitochondrial development. Two endosymbiotic models suggest that proto-mitochondria entered an existing cellular organism. The third suggests that mitochondria evolved from related organelles that already existed in host cells
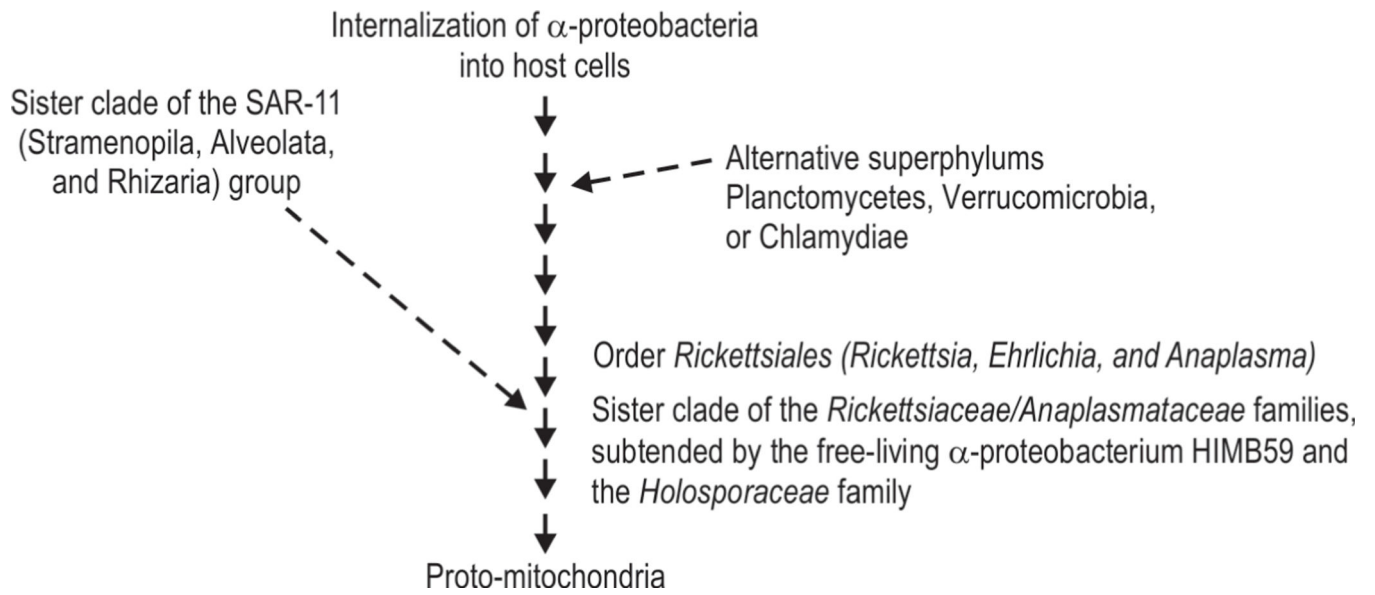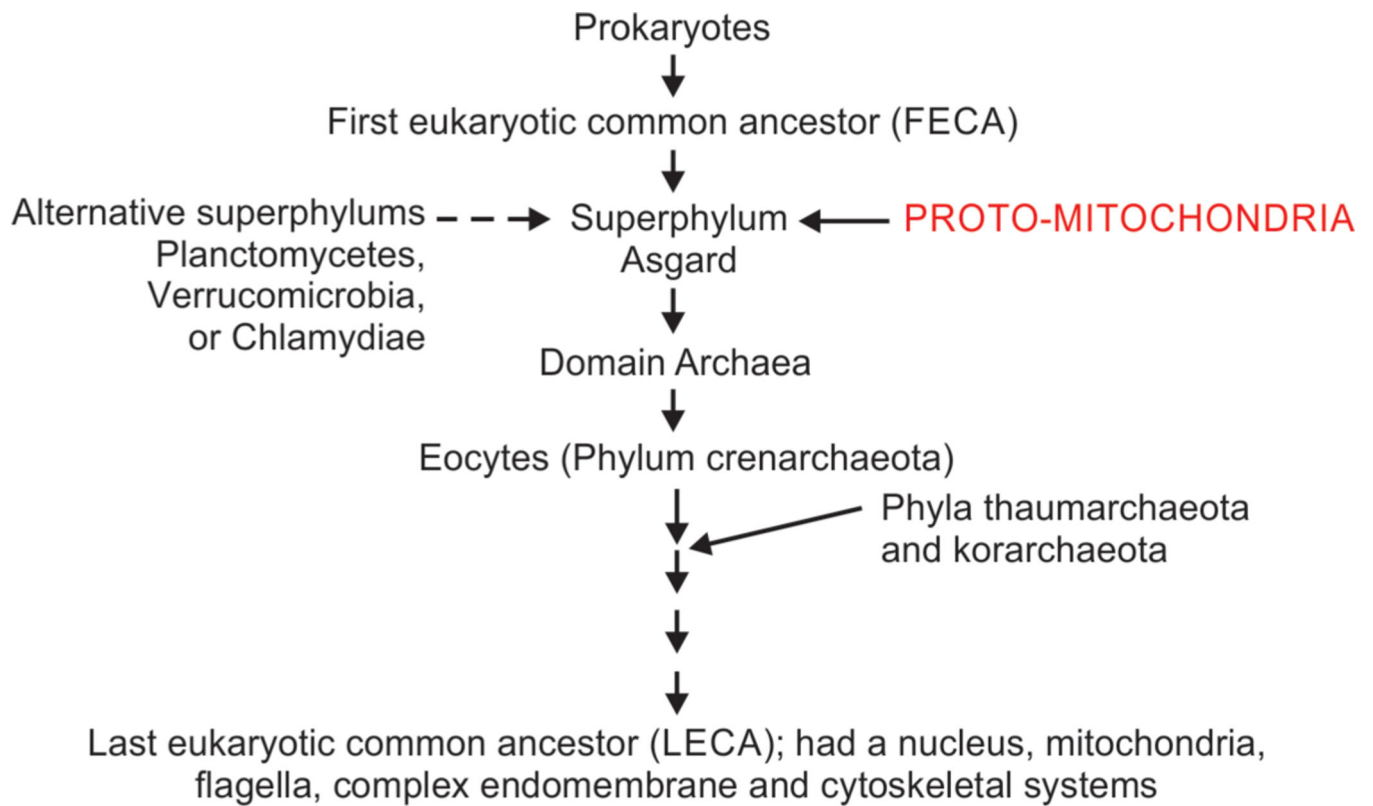
Fig. 6:
Proteo-bacteria evolved into mitochondria following internalization into host cells

Fig. 7:

Evolution of an endosymbiotic relationship between eukaryotic ancestors and proto-mitochondrial bacteria. The first eukaryotic common ancestors (FECAs) likely matured into the superphylum Asgard and internalized proto-mitochondrial bacterial ancestors. However, there is a possibility that the FECAs could have originated in other super-phyla. These cells matured over time, and the last eukaryotic common ancestors (LECAs) seen about 1–1.9 million years showed a nucleus, mitochondria, flagella, complex endomembrane, and cytoskeletal systems

Host (cytoplasm) could be an archaeon, a proteobacterium, or a bacterium of the superphylums Planctomycetes, Verrucomicrobia, or Chlamydiae.

It was most likely a prokaryotic and internalized other structures via phagocytosis

Less likely

Nucleus → **Cytoplasm-endomembrane system** ← **Mitochondria**

The nucleus could have originated from a phagocytosed archaeon, spirochete, or a membrane-bound virus. However, increasing information has refuted this model

Less likely

Mitochondria, derived from phagocytosis of α-proteobacteria

To note:

- *Archaea lack nuclei and are prokaryotes*

- *Spirochetes are long, helically coiled, gram-negative bacteria*

- *Planctomycetes are widely distributed bacteria; role in global carbon and nitrogen cycles. Seen in biofilms*

- *Verrucomicrobiota are widely distributed gram-negative rods*

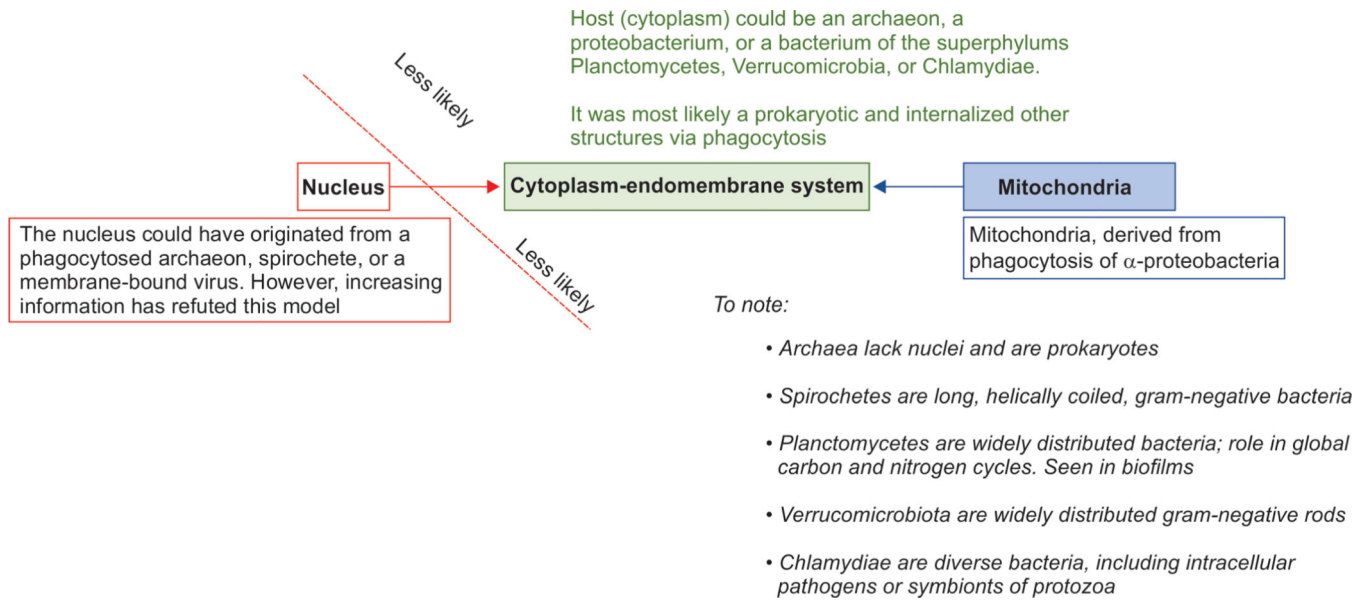- *Chlamydiae are diverse bacteria, including intracellular pathogens or symbionts of protozoa*

Fig. 8:
Differentiating host cells internalized proto-mitochondrial bacterial ancestors. There have been considerations that the nucleus could also have originated in a phagocytosed archaeon, spirochete, or a membrane-bound virus. However, increasing information has refuted these possibilities and favor an endogenous origin of the nucleus
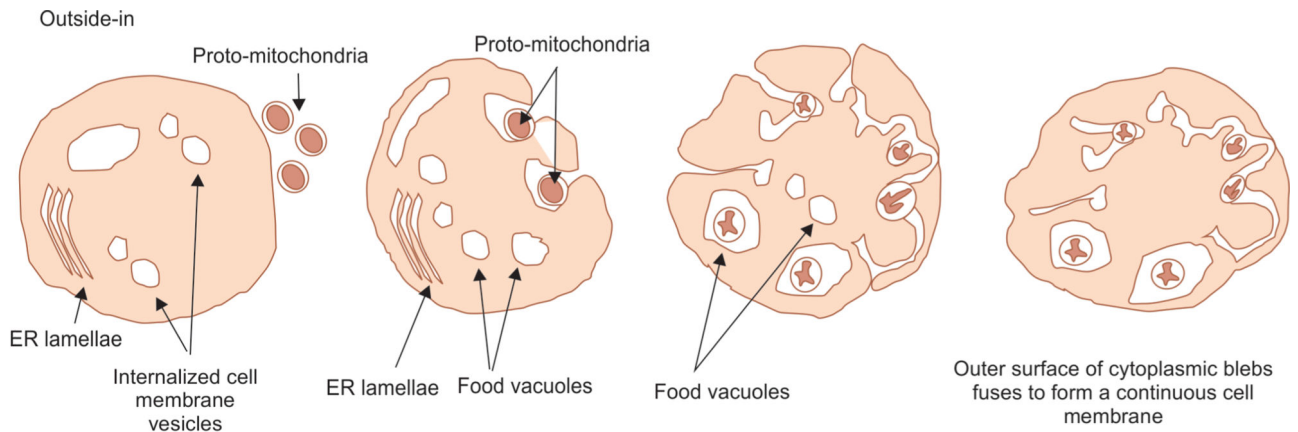
Autogenous outside-in model (visualized as entrapment at the eukaryotic cell membrane)	Endosymbiotic outside-in model (visualized as phagocytosis at the eukaryotic cell membrane)	Final structure in eukaryotic cells
Original cell membrane	Original cell membrane	Cell membrane
Internalized cell membrane vesicles	Internalized cell membrane vesicles	ER
Outer surface of ER lamellae	Food vacuole membranes	Outer nuclear membrane
ER cisternae	Food vacuoles	Perinuclear space
Inner surface of fused ER lamellae	Outer cell membrane of symbiont	Inner nuclear membrane

A
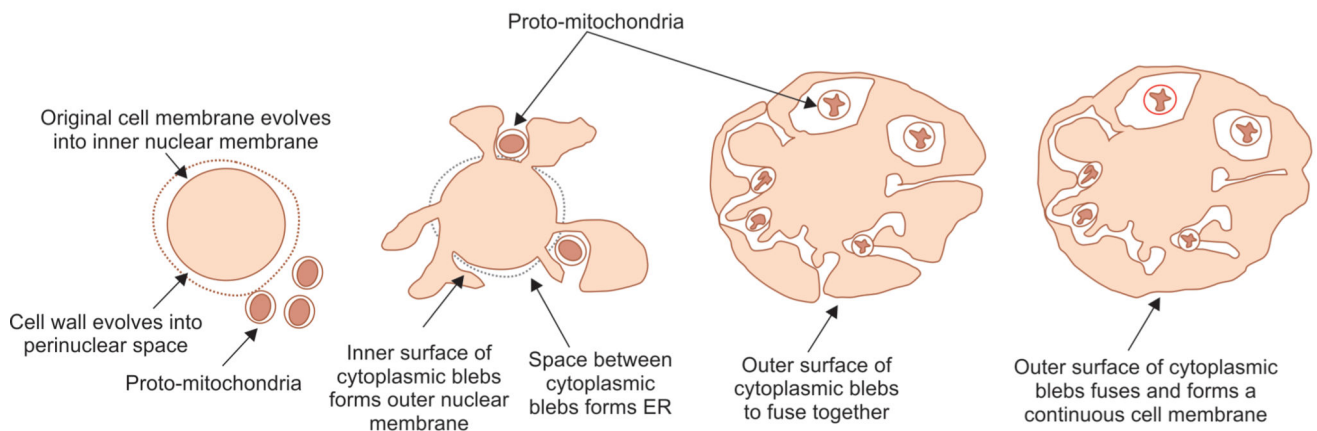
Inside-out model (visualized as starting at the eukaryotic nuclear membrane)	Final structure in eukaryotic cells
Original cell membrane	Inner nuclear membrane
Cell wall	Perinuclear space
Inner surface of cytoplasmic blebs	Outer nuclear membrane
Space between cytoplasmic blebs	ER
Outer surface of cytoplasmic blebs	Cell membrane

B

Figs 9A and B:

Evolution of mitochondria. (A) Outside-in model: Symbionts could have been internalized in cellular vesicles. The inner and outer nuclear membrane may have originated in the endoplasmic reticulum lamellae, and the perinuclear space in the ER cisternae. There is also a possibility that these bacteria could have been phagocytosed into food vacuoles, and then entered the cytoplasm by lysing the vacuolar membrane; (B) Inside-out model: host cells generated extracellular protrusions (blebs). The ancestral prokaryotic cell body remained intact as the eventual nuclear compartment during this evolution into eukaryotes. The

protrusions fused and formed the cytoplasm and an endomembrane system, which evolved to make the outer nuclear and the plasma membranes. The mitochondrial precursors moved from the ER into the cytoplasm. Finally, the formation of a continuous cell membrane closed off the ER from the exterior
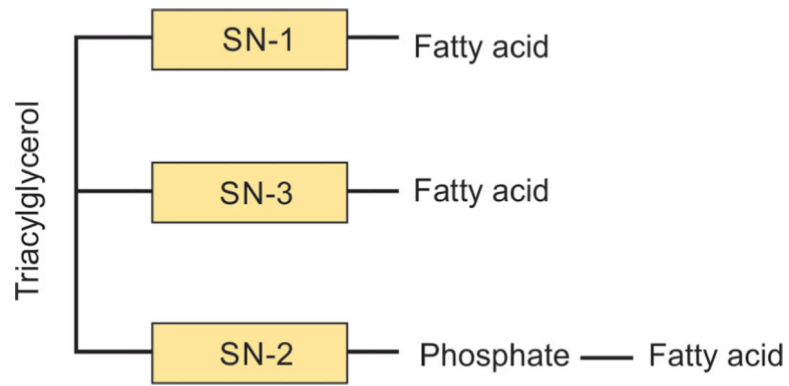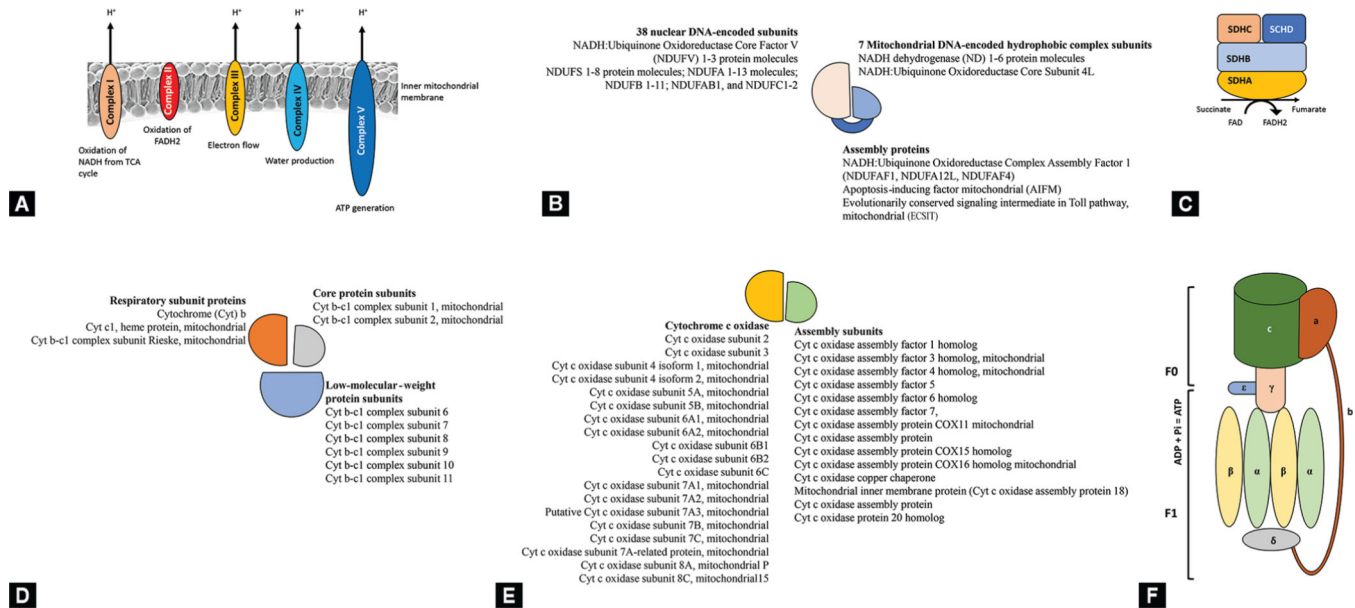
Fig. 10:
Bacterial and eukaryotic membranes carry glycerol-3-phosphate lipids with ester-linked, straight-chain fatty acids, unlike the glycerol-1-phosphate backbone seen in archaea; SN, Stereospecific numbering

Figs 11A to F:

Mitochondrial genes. (A) Overall pattern of organization in the 5 mitochondrial gene complexes; (B) Complex I is comprised of 38 subunits that are encoded in the nuclear DNA, 7 in mitochondrial DNA, and several assembly units. This complex oxidizes NADH by transferring electrons to ubiquinol. NADH stands for "nicotinamide adenine dinucleotide (NAD) + hydrogen (H); (C) Complex II converts succinate to fumarate and reduces FAD to $FADH_2$ during this process. The released electrons are transferred to ubiquinol. SDH = succinate dehydrogenase. The figure shows four components of the SDH complex, A-D; (D) Complex III (coenzyme Q: cytochrome *c* – oxidoreductase, or the cytochrome bc_1 complex), contains 11 subunits: 3 respiratory subunits, 2 core proteins and 6 low-molecular-weight proteins; (E) Complex IV (cytochrome *c* oxidase or cytochrome AA3), contains two hemes, a cytochrome a and cytochrome a_3, and two copper centers, the Cu_A and Cu_B centers; and (F) Complex V (mitochondrial ATP synthase) is a multisubunit oxidative phosphorylation complex. Complex V is composed of two functional domains: F_1, which is situated in the mitochondrial matrix, and F_o, located in the inner mitochondrial membrane. Complex V uses the energy created by the proton electrochemical gradient to phosphorylate ADP to ATP. ADP, Adenosine diphosphate; ATP, Adenosine triphosphate; Pi, inorganic phosphate
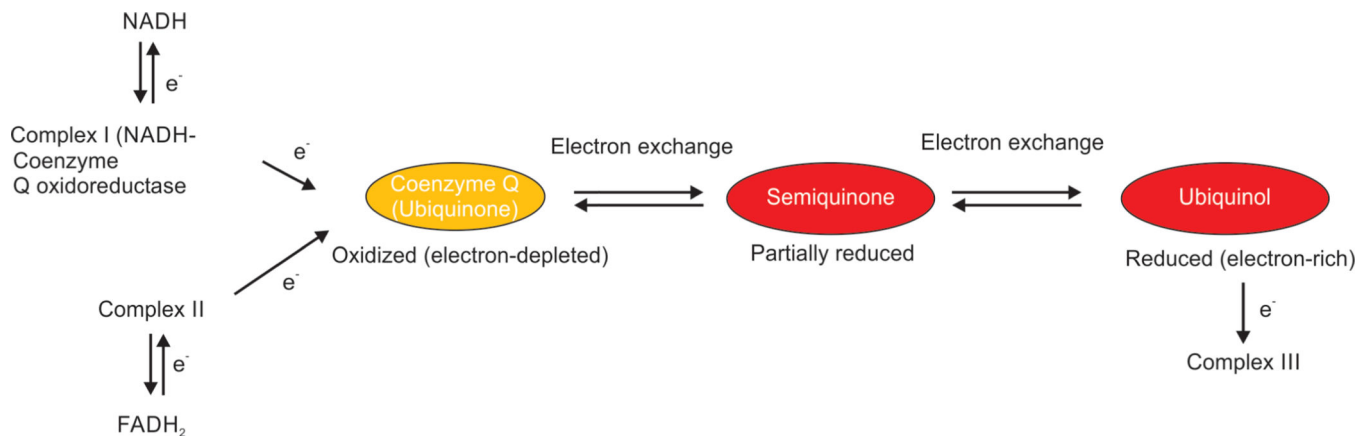
Fig. 12:

Ubiquinol is an electron-rich (reduced) form of coenzyme Q (ubiquinone). The term most often refers to ubiquinol-10 that has a 10-unit tail; it exists in three redox states, the fully reduced (ubiquinol), partially reduced (semiquinone or ubisemiquinone), and fully oxidized (ubiquinone) forms. Ubiquinol can serve a redox function in cellular energy production and in antioxidant protection based on the ability to exchange two electrons in redox cycles. Complex I (NADH-Coenzyme Q oxidoreductase, or NADH dehydrogenase) can accept high energy electrons from NADH, and complex II interacts with $FADH_2$.
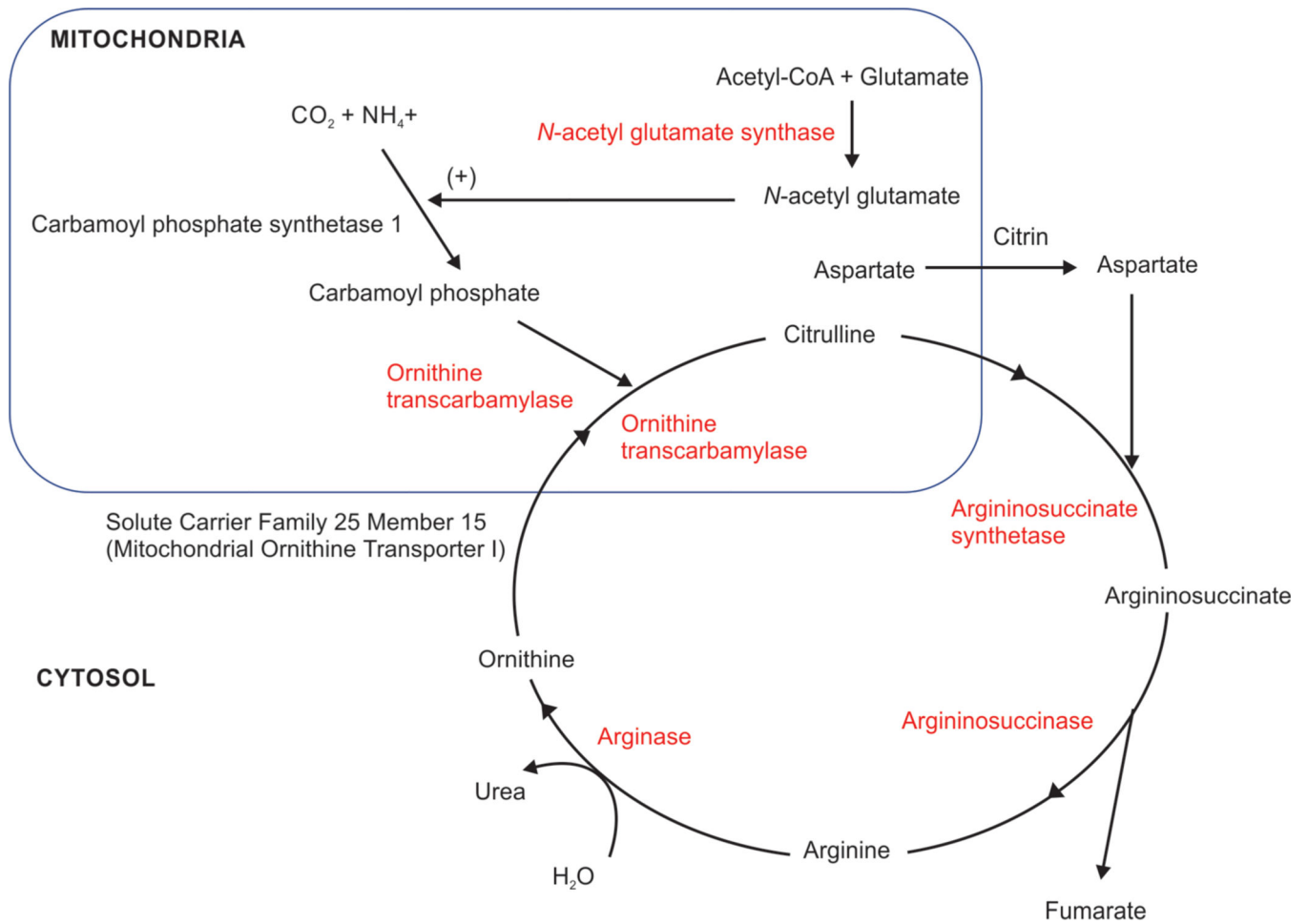
Fig. 13:
The initial steps of the urea cycle take place in the mitochondrial matrix. Carbamoyl phosphate synthetase I (CPS I) combines ammonia with carbon dioxide to from carbamoyl phosphate and ornithine transcarbamylase promotes citrulline synthesis. *N*-acetyl glutamate (NAG) synthase increases the formation of NAG, which activates CPS I.

Table 1:

Genetic components of mitochondria and associated inherited disorders seen in young infants

		Composition of the gene/gene complex	Clinical features
Mitochondrial respiratory chain complex	Complex I	Complex I contains 33 genes that have been mapped to various autosomes, 1 to the X chromosome, and 7 to mtDNA	Lethal infantile mitochondrial disease, lactic acidosis, Leber's Hereditary Optic Neuropathy, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome
	Complex II	Complex II (succinate: ubiquinone oxidoreductase) is the smallest complex in the respiratory chain and is composed of 4 subunits of the succinate dehydrogenase in the nucleus: SDHA, SDHB, SDHC, and SDHD	Leigh syndrome, mitochondrial leukoencephalopathy, Kearns-Sayre syndrome, cardiomyopathy, infantile leukodystrophy
	Complex III	Complex III contains 11 subunits, and only one, cytochrome b is of mitochondrial origin	Lactic acidosis, hypoglycemia, ketosis, hyperammonemia, cardiomyopathy, multisystemic dysfunction, encephalopathy; growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death (GRACILE) syndrome
	Complex IV	Complex IV is comprised of 4 cytochrome c oxidase genes, which form a large transmembrane protein complex. It is the last enzyme in the respiratory electron transport chain located in the mitochondrial membrane. It converts molecular oxygen to water and helps establish a transmembrane electrochemical potential that the ATP synthase then uses to synthesize ATP	Steatosis, encephalopathy, myopathy, hypertrophic cardiomyopathy, hepatomegaly, liver dysfunction and hypotonia, delayed motor development, mental retardation
	Complex V	Complex V contains 24 genes. Synthesizes ATP using energy provided by the proton electrochemical gradient across the IMM. It is an F-type ATPase and consists of two structural domains: F1, a soluble portion situated in the mitochondrial matrix; and F0, which spans the IMM. Protons pass from the inter membrane space to the matrix through F0, which transfers the energy created by the proton-motive force to F1; ADP is phosphorylated to ATP	Severe neonatal encephalopathy, neonatal respiratory distress, lactic acidosis, peripheral neuropathy, dysmorphism, cataract, pulmonary arterial hypertension, bilateral cataracts, Reye-like syndrome
Fatty acid metabolism	Carnitine palmitoyltransferase I		Hypoketotic hypoglycemia, hyperammonemia, elevated transaminases, and mild metabolic acidosis
	Carnitine-acylcarnitine translocase		Hypoglycemia, seizures, cardiomyopathy, cardiac arrhythmia, and apnea
	Carnitine palmitoyltransferase II		Nonketotic hypoglycemia, hepatomegaly, encephalopathy, seizures, respiratory distress, and metabolic acidosis. cardiomyopathy and arrhythmia
	Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency		Hypertrophic cardiomyopathy and fasting hypoketotic hypoglycemia
	Short-chain acyl-CoA dehydrogenase (SCAD) deficiency		Hypotonia, muscle weakness, and seizure
	Neonatal long-chain 3-ketoacyl CoA thiolase (LCKAT) deficiency		Lactic acidosis, pulmonary edema, and cardiomyopathy
Amino acid metabolism	Phenylalanine hydroxylase Cystathionine synthase Branched chain ketoacid dehydrogenase		Phenylketonuria Homocystinuria/Homocystinuria Maple syrup urine disease Hartnup disease

	Composition of the gene/gene complex	Clinical features
	SLC6A19 solute carrier family 6, member 19	
Pyruvate metabolism	PDHA1	Lactic acidosis, hypotonia, Seizure
	Pyruvate carboxylase	Hypercitrullinemia and hyperlysinemia
Krebs cycle metabolism	Dihydrolipoyl dehydrogenase	Severe persistent lactic acidosis, respiratory difficulties, seizures, dystonic movements, hypoglycemia, lethargy, hypotonia, vomiting, constipation, failure to thrive, and feeding difficulties
	α-ketoglutarate dehydrogenase	Choreoathetosis, opisthotonos, spasticity, hypertrophic cardiomyopathy, hepatomegaly, and sudden death
	Fumarase	Lethargy, microcephaly, hypotonia, axial dystonia or opisthotonos, areflexia, or developmental delay
Pathological disorders caused by complex genetic alterations	Deletions with combinations of Class I, II, III	Steatosis, fibrosis/cirrhosis
	Syndromes due to deletions and duplications in the mitochondrial genome. Usually sporadic, heteroplasmic, and unique. Frequently occur between directly repeated sequences, suggesting that many occur because of de novo arrangements during oogenesis or early development	Syndromes described in text