REVIEW ARTICLE

Development and Functions of Mitochondria in Early Life

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Abstract

Mitochondria are highly dynamic organelles of bacterial origin in eukaryotic cells. These play a central role in metabolism and adenosine triphosphate (ATP) synthesis and in the production and regulation of reactive oxygen species (ROS). In addition to the generation of energy, mitochondria perform numerous other functions to support key developmental events such as fertilization during reproduction, oocyte maturation, and the development of the embryo. During embryonic and neonatal development, mitochondria may have important effects on metabolic, energetic, and epigenetic regulation, which may have significant short- and long-term effects on embryonic and offspring health. Hence, the environment, epigenome, and early-life regulation are all linked by mitochondrial integrity, communication, and metabolism.

Keywords: Early life, Metabolism, Mitochondria, Mitochondrial dynamics, Neonatal development, Oocyte maturation.

Newborn (2022): 10.5005/jp-journals-11002-0013

Introduction

Mitochondria, the "powerhouses" to provide the required cellular energy, are seen to have a primary role in the oxidation of nutrients to build up proton gradients in the inner mitochondrial membrane and to make adenosine triphosphate (ATP) in eukaryotic cells.[1] Yet, the significance of mitochondria extends beyond the generation of ATP; these organelles also play central roles in the regulation of Ca^{2+} homeostasis and apoptosis, supply of intermediary metabolites, generation of heat, and the integration of various signaling pathways.[2–6] During oocyte maturation and the development of embryo prior to implantation, mitochondria go through dynamic restructuring and redistribution to support developmental processes.[7,8] After birth, many events that were previously assumed to be performed by maternal organs and placenta are actually carried out in neonatal organs such as the liver, heart, lung, and kidneys. A tremendous amount of energy is needed for these physiological processes, and hence, these are associated with a massive increase in the mitochondrial number and function.[9–12] This dynamic nature of mitochondria is essential for modulating key cellular events.

Origin of Mitochondria

The prokaryotic provenance of mitochondria is clearly distinct from the eukaryotic nuclear lineage.[13] Mitochondria were derived from a common ancestral organelle that originated from the integration of an endosymbiotic alpha-proteobacterium into a host cell related to the archaea superphylum Asgard or the Asgardarchaetoa that is capable of metabolizing oxygen.[14] It is still unclear whether it was the acquisition of mitochondria that triggered evolutionary transition of prokaryotes to eukaryotes, or if the prokaryotes had already evolved to a eukaryote-like stage (fledged eukaryotes) when mitochondrion joined in; the endosymbiotic origin of mitochondria is an important question in the study of eukaryogenesis.[14–16] The mitochondrial deoxyribonucleic acid (DNA) (mtDNA) encodes 2 ribosomal ribonucleic acids (rRNAs), 22 transfer ribonucleic acids (tRNAs), and 13 proteins that are involved in the activity of the mitochondrial respiratory chain.[17] However, there are 1,500 estimated different mitochondrial proteins,[18] and >99% of the mitochondrial proteins are likely encoded in the nucleus, synthesized in the cytosol, and imported into the mitochondria.[19]

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How to cite this article: Peng J, Ramatchandirin B, Pearah A, *et al*. Development and Functions of Mitochondria in Early Life. Newborn 2022;1(1):131–141.

Source of support: Nil

Conflict of interest: None

Cellular Functions of Mitochondria

Mitochondria are double-membrane-bound subcellular compartments. These are the "powerhouses" that provide eukaryotes with energy in the form of ATP. For glucose metabolism, after the split of glucose into two pyruvates in the cytosol, pyruvate enters the mitochondria and is oxidized to acetyl coenzyme A (CoA), NADH+H, and CO_2 by pyruvate dehydrogenase complex, and acetyl CoA is further oxidized to generate NADH+H, $FADH_2$, GTP, and CO_2 in the citrate acid cycle.

For the oxidation of amino acids, once the amino acids have broken down, the metabolites enter the citrate acid cycle as acetyl CoA, α-ketoglutarate (α-KG), succinyl-CoA, fumarate, and oxaloacetate. For the metabolism of fatty acids, the fatty acid is degraded to acetyl CoA with the latter entering the citrate acid cycle and generates NADH+H, $FADH_2$, GTP, and CO_2. NADH+H and $FADH_2$ will be used to generate ATP through oxidative phosphorylation in the mitochondrial respiratory chain. Under normal conditions, over 90% of ATP is made in the mitochondria.[20] The mitochondria are

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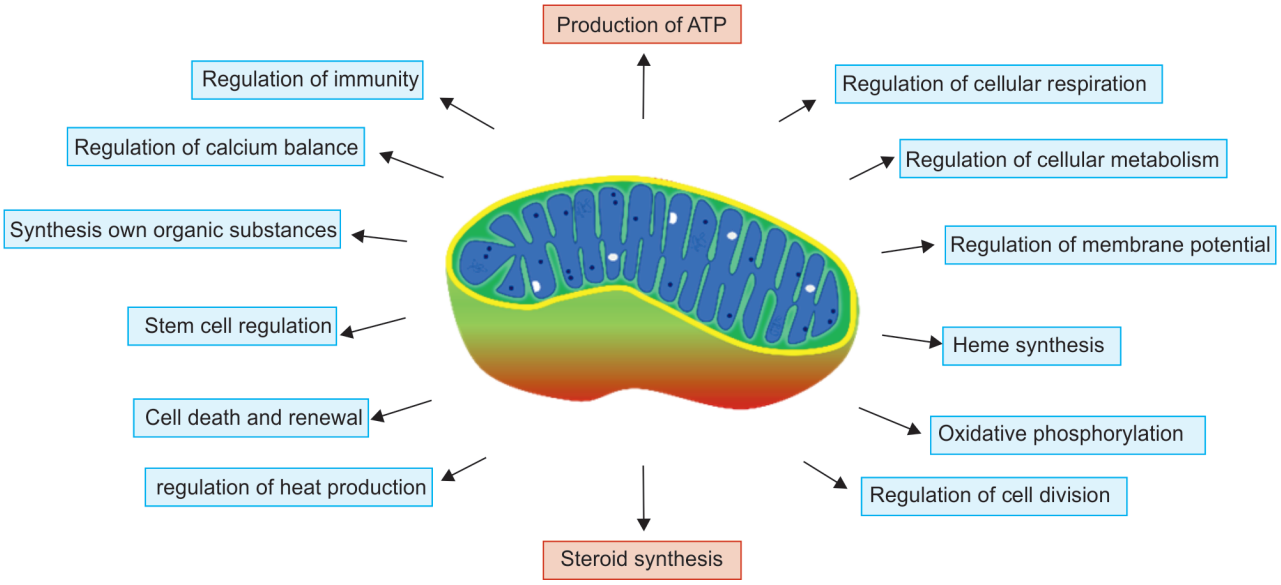

Fig. 1: Functions of mitochondria

also the subcellular compartments that regulate the biosynthesis of amino acids, lipids, and gluconeogenesis (Fig. 1).[14]

Mitochondrial Development and Functions in Embryogenesis

Mitochondria are the most abundant organelle in the oocyte and undergo significant structural and positional changes during preimplantation development.[21] These are received exclusively from the mother in uniparental inheritance; the parental mtDNA is eliminated.[22] The maternal mitochondria provide the required energy for oocyte viability until embryonic mitochondria assume their function.[23]

Mitochondria are oval or elongated in oogonia with a sparse, but even intracellular distribution. The growing oocytes show relatively dense rounded or oval mitochondria that contain a rough endoplasmic reticulum (ER). In fully grown germinal vesicle oocytes, mitochondria have a dense matrix and a few arch-like or transverse cristae and are usually not seen in the cortical part of the cytoplasm. In metaphase I and II of oocytes, mitochondria have a structure similar to that of germinal vesicle oocytes with an even distribution in the cytoplasm and aggregation around the smooth ER. At the pronuclear stage, the mitochondria are observed in a central conglomeration around the pronuclei, which persists up to syngamy. In the 8-cell cleaving embryo, the morula, and the blastocyst, mitochondria are less electron-dense and show clear areas in the matrices. In the expanding blastocysts, trophoblast, embryoblast, and endodermal cells, mitochondria look elongated with the inner mitochondrial membranes arranged into transverse cristae.[7]

Growing oocytes preferentially utilize pyruvate to make ATP via oxidative phosphorylation (OXPHOS),[24] and early embryos also use pyruvate, lactate, and amino acids to support development.[25,26] The highest mtDNA copy number and mass are found in the mature oocyte of any cell. High numbers of mitochondria in oocytes are essential for early embryonic development by providing the capacity for nutrient oxidation.[27] Fertilized oocytes have a higher mtDNA copy number than the unfertilized ones,[28] and a low mitochondrial number is correlated to fertilization failure and abnormal developments of the embryo.[22,29,30] The importance of mitochondria in embryonic development is evident in decreased fertility seen in mice with induced mtDNA mutations.[31] Inhibition of mitochondrial metabolic activity blocks maturation of oocyte and the subsequent embryonic development[32,33] as well as the growth of the fetus and the placenta in animals.[34] In humans, embryo development and implantation rates are closely correlated to ATP levels,[33] and inhibiting mitochondrial activity prevents human embryonic stem cell (ESC) differentiation.[35]

Mitochondria take up Ca^{++} under physiological conditions in a variety of cell types and are involved in Ca^{++} homeostasis.[36] Several cellular events including fertilization are regulated by the intracellular concentration of free calcium. In mammalian fertilized eggs, the Ca^{++} concentrations vary in oscillatory patterns that seem to be necessary for oocyte activation[37] and embryo development.[38] Importantly, mitochondrial ATP is needed to maintain these Ca^{++} oscillations.[39]

Development and Functions of Mitochondria in Neonates

After birth, the many functions previously assumed by maternal organs and placenta must be promptly carried out by the newborn's organs. A tremendous amount of energy is needed during the neonatal period to cope up with various energy-demanding physiological processes, and their cells show considerably increased mitochondrial number and function. To adapt to an environment with high oxygen content, the number and functions of mitochondria in the lung continue to increase during postnatal growth and development. To fulfill the function of gas exchange, postpartum mitochondria in type II alveolar epithelial cells (AECII) undergo significant morphological changes from a single and spherical shape to a complex and branched structure.[40] There are few mitochondria in the nonciliated cells of prenatal animals, but with a significant shift in mitochondrial abundance during differentiation.[41]

For a successful adaption to extrauterine life, the differentiation and proliferation of mitochondria within the neonatal liver is a key

regulatory process because the mitochondrial number and activity in hepatocytes of the fetal liver are very low.[42] The proliferation or differentiation of preexisting mitochondria to functioning mitochondria occurs rapidly after birth as well as a marked increase in mitochondrial activity concomitantly with increased ATP levels in the liver within an hour after delivery.[11] Furthermore, the expression of genes related to the mitochondrial respiratory chain activity is significantly increased in the neonatal liver.[42,43] After delivery, the neonatal kidneys must take charge of the functions of glomerular filtration, glucose reabsorption, and acid/base homeostasis previously assumed by the maternal kidneys. In the developing kidneys, mitochondrial respiration and oxygen consumption significantly increase between 21 days post coitum and 1 day postpartum, accompanied by an increase in enzymatic activity in the citrate acid cycle, fatty acid oxidation, and the levels of ATP.[12]

Importance of Mitochondria in Embryonic/Neonatal Development through the Regulation of Methylation and Acetylation of the Genome

Extensive reprogramming of the epigenetic landscape occurs to activate the embryonic genome in preimplantation embryo development. Paternal genome is also activated after fertilization through DNA demethylation.[44] Mitochondrial activity has been linked to methylation via involvement in methionine metabolism.[45] Depletion of mtDNA leads to alteration in the metabolism of amino acids including methionine, leading to increased DNA methylation.[45] *S*-adenosylmethionine (SAM) acts as a cofactor in the methylation reaction and SAM is produced from methionine by methionine adenosyl transferases (MATs).[46] In the murine embryos, knockdown of Mat2α results in 2-cell embryo arrest and reduced transcriptional activity. Furthermore, being inhibited of Mat2α or cultured in the absence of L-methionine, embryos were arrested at the morula stage and H3K4me3 levels in morula and blastocyst were much lower than those cultured under normal medium.[47] SAM supplementation promotes hatching of bovine embryo, accompanied by significant alterations in DNA methylation.[48] Consistently, in human embryonic stem cells, methionine deprivation leads to a decrease in H3K4me3 and global DNA methylation, which can be reversed by supplementation with SAM.[49]

Preimplantation embryo development requires appropriate histone demethylation mediated by the *jumonji* or the Jarid2 (JMJ) deamylase, which removes the methyl group from lysine residues.[50] JMJ demethylases catalyze the histone demethylation in an α-KG-dependent manner.[51] Thus, mitochondria regulate demethylation via α-KG through the oxidation of glucose and glutamine in the mitochondrial citric acid cycle.[52]

Chromatin remodeling also plays an essential role in embryonic epigenetic programming.[53] Histone acetylation by histone acetyltransferases (HATs) relaxes the condensed chromatin and promotes the gene transcriptions. On the contrary, deacetylation of histone condenses the chromatin and suppresses the gene transcription. Histone acetylation by HATs 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.[54] In human ESCs, increasing acetylation levels by the supplementation of precursor of acetyl CoA leads to reduced differentiation, while inhibition of acetyl CoA production from glucose results in the loss of pluripotency.[55] The availability of nicotinamide adenine dinucleotide (NAD^+) controls the activity of the conserved NAD^+-dependent histone deacetylases, the sirtuins (SIRTs).[56] SIRTs are involved in blastocyst development as the inhibition of SIRT activity leads to a significant reduction in blastocyst development.[57] NAD^+ can be synthesized *de novo* from the amino acid tryptophan or through the NAD^+ salvage pathway from nicotinamide. However, cytoplasmic NAD+ levels are very low, to maintain the NAD+ levels; NADH+H-reducing equivalents need to shuttle into mitochondria through either malate-aspartate or mitochondrial glycerol 3-phosphate dehydrogenase. This is important because blocking NADH+H into mitochondria by inhibition of malate-aspartate activity reduced blastocyst development and placental and fetal growth.[58] The significance of dynamic changes of histone acetylation and deacetylation in embryonic and neonatal development deserves further study.

Mitochondrial Dysfunction Affects Embryogenesis and Neonatal Development

Mitochondrial Dysfunction in Oocytes is Largely Responsible for Age-related Decline in Fertility

The role of mitochondria in reproduction has received increasing attention because of their importance in oocyte maturation, fertilization, and early embryo development. Less ATP and mtDNA copy number, and ultrastructural mitochondrial abnormalities are observed in mice aging oocytes.[59] Mutations of mtDNA accumulate in maternal oocytes with age.[60] In women of advanced reproductive age, oocytes have increased mtDNA deletions and mutations, which probably result in impaired mitochondrial function and subsequently lead to embryo development failure.[61]

Mitochondrial Dysfunction Causes Severe Clinical Symptoms in Neonates

Neonates require an adequate capacity of the mitochondrial energetic metabolism to support rapid growth and adaption to extrauterine life; therefore, ATP provision from the mitochondrial oxidative phosphorylation is essential. Neonates' muscles, heart, and brain are mainly dependent on aerobic metabolism that depends on mitochondrial function. Disorders of mitochondrial metabolism caused by defects in fatty acid oxidation, pyruvate metabolism, and the respiratory chain, including mitochondrial complexes I, II, III, and IV, and ATP synthase, may often present in the neonatal period. Mutations of both nuclear genes and mtDNA can cause mitochondrial dysfunction in neonates; primary and secondary mitochondrial dysfunctions are quite common in neonates.[62–64] The prognosis for newborns with mitochondrial dysfunction is often unfavorable (Table 1).[63]

Mitochondrial dysfunction affects 1 in 6,000–8,000 newborns, making mitochondrial disease almost as common as childhood cancer. Each year, about 1,000–4,000 children in the United States are born with a mitochondrial disease. Autosomal recessive inheritance, autosomal dominant inheritance, mitochondrial inheritance, and random mutations lead to mitochondrial diseases in neonates.[65] Furthermore, mitochondrial dysfunction is closely linked with obesity, diabetes, liver dysfunction, and coronary vascular disease.[66] Recent studies demonstrate that in neonates, there are 32 out of 107 patients diagnosed with mitochondrial diseases, 7 out of 73 patients are diagnosed with neonatal lactic acidosis,[64] and 11 out of

Table 1: Mitochondrial gene known to be mutated in neonatal disorder

Mutation	*Neonatal mitochondrial disorder*	*References*
Mitochondrial respiratory chain complex		
Complex I	Leigh syndrome	138, 139
	Lethal infantile mitochondrial disease	139
	Lactic acidosis	139
	Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome	140
	Leber hereditary optic neuropathy	141
Complex II	Mitochondrial leukoencephalopathy	142
	Cardiomyopathy	143
	Infantile leukodystrophy	144
	Kearns–Sayre syndrome	75
Complex III	Lactic acidosis, hypoglycemia, ketosis, hyperammonemia	145, 146
	Cardiomyopathy, multisystemic dysfunction	147
	Encephalopathy	148
	Growth retardation, aminoaciduria, cholestasis, iron overload, lactacidosis, and early death (GRACILE) syndrome	146
Complex IV	Steatosis	149
	Encephalopathy, myopathy	150
	Hypertrophic cardiomyopathy, hepatomegaly, liver dysfunction and hypotonia, delayed motor development, and mental retardation	151
Complex V	Severe neonatal encephalopathy, neonatal respiratory distress, lactic acidosis, severe peripheral neuropathy, dysmorphism, cataract, arterial pulmonary hypertension, bilateral cataract, and reye-like syndrome	75, 152–156
Combined Class I, II, and III	Steatosis Fibrosis/cirrhosis	149
Fatty acid biosynthesis		
Carnitine palmitoyltransferase I (CPT I)	Hypoketotic hypoglycemia, hyperammonemia, elevated transaminases, and mild metabolic acidosis	157
Carnitine-acylcarnitine translocase (CACT)	Hypoglycemia, seizures, cardiomyopathy, cardiac arrhythmia, and apnea	158
Carnitine palmitoyltransferase II (CPT II)	Nonketotic hypoglycemia, hepatomegaly, encephalopathy, seizures, respiratory distress, and metabolic acidosis. Cardiomyopathy and arrhythmia	159
Very long-chain acyl-coenzyme A dehydrogenase (VLCAD)	Hypertrophic cardiomyopathy and fasting hypoketotic hypoglycemia	160–162
Short-chain acyl-coenzyme A dehydrogenase (SCAD)	Hypotonia, muscle weakness, and seizure	163
Long-chain 3-ketothiolase (LCKAT)	Lactic acidosis, pulmonary edema, and cardiomyopathy	164
Amino acid metabolism		
Phenylalanine hydroxylase	Phenylketonuria	165
Cystathionine synthase	Homocystinuria/homocystinuria	
Branched-chain ketoacid dehydrogenase	Maple syrup urine disease	
Solute carrier family 6 member 19 (SLC6A19)	Hartnup disease	
Pyruvate metabolism		
Pyruvate dehydrogenase E1 subunit alpha 1 (PDHA1)	Lactic acidosis, hypotonia, seizure	166
Pyruvate carboxylase	Hypercitrullinemia and hyperlysinemia	167
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	168
α-KG dehydrogenase	Choreoathetosis, opisthotonos, spasticity, hypertrophic cardiomyopathy, hepatomegaly, and sudden death	169
Fumarase	Lethargy, microcephaly, hypotonia, axial dystonia or opisthotonos, areflexia, or psychomotor retardation	170

75 patients have lethal infantile mitochondrial diseases.[67] In clinic, mutations of mitochondrial complex I lead to Leigh syndrome; lactic acidosis; and renal, cardiac, and hepatic disorders in newborns.[68,69] The mutations of succinate dehydrogenase complex flavoprotein subunit A (SDHA), succinate dehydrogenase complex iron sulfur subunit B (SDHB), and succinate dehydrogenase complex assembly factor 1 (SDHAF1) genes in complex II can cause mitochondrial defects that are associated with neonatal cardiomyopathy and infantile leukodystrophy.[70–72] Mutations in complex III has been reported in one neonate who has severe lactic acidosis associated with hypotonia, irritability, and muscle wasting. Complex III deficiency is mainly caused by mutations in homolog of the S. cerevisiae bcs1 protein, ubiquinol-cytochrome c reductase complex chaperone (BCS1L), ubiquinol-cytochrome C reductase binding protein (UQCRB), ubiquinol-cytochrome C reductase complex III subunit VII (UQCRQ), and mitochondrially encoded cytochrome B (MTCYB) genes, which is passed down maternally. Mutations in complex IV cause neonatal hypertrophic cardiomyopathy, hepatomegaly, liver dysfunction and hypotonia, delayed motor development, mental retardation, encephalopathy, and myopathy.[73] The biogenesis and assembly of cytochrome c oxidase (COX) in complex IV depend on numerous ancillary factors, including copper chaperones, all nuclear encoded. Specifically, disease-causing mutations were found in genes encoding surfeit locus protein 1 (SURF1), essential for the formation of early assembly intermediates; mutation in complex IV is associated with severe neonatal encephalopathy, neonatal respiratory distress, lactic acidosis, severe peripheral neuropathy, dysmorphism, cataract, and arterial pulmonary hypertension.[74] The defects in ATP synthase can cause fatal neonatal mitochondrial encephalopathy.[75]

Pyruvate dehydrogenase complex (PDHc) catalyzes oxidative decarboxylation of pyruvate to produce acetyl CoA and initiates the tricarboxylic acid (TCA) cycle. PDHc deficiency is most often due to mutations in the first component of the enzyme complex, pyruvate dehydrogenase E1α (responsible for 70% of the PDHc deficiencies). There is a spectrum of clinical presentations in E1α mutations. In the most severe form of PDHc mutations, lactic acidosis develops within hours of birth. This is often associated with an altered level of consciousness, profound hypotonia, lethargy, feeding and respiratory difficulties, and coma.[76]

Mitochondrial Transfer from One Cell to Another

Mitochondria and mtDNA can be transferred between cells. It was reported that transient focal cerebral ischemia induced mitochondria release from astrocytes and enter into the adjacent neurons mediated by a calcium-dependent mechanism involving CD38 and cyclic adenosine diphosphate (ADP) ribose signaling.[77] In this way, the survival signal was amplified in cells. In cancer models, mtDNA of host cells in the tumor microenvironment can be horizontally transferred to tumor cells that have a defective respiratory function, leading to the re-establishment of respiration and tumor growth.[78] Mechanisms of horizontal transfer of mitochondria that have been discovered include forming tunneling nanotubes between cancer cells and cells in the tumor microenvironment,[79] packaging mtDNA into extracellular vesicles (EVs)[80] and connexin 43 gap junctions.[81]

A recent study demonstrated that cells from obese mothers may carry fewer mitochondria, which relates to higher levels of triglycerides, free fatty acids, and more lipids. The fewer numbers of mitochondria alter the placental lipid metabolism and transfer of the lipids to the fetus, causing lipid-related diseases such as newborn adiposity.[82] Likewise, reduced mitochondrial function has been found to induce brain injury in newborns. The alteration of cellular oxygen dependency by reduced mitochondrial function that decreased oxygen delivery into the brain causes brain injury and severe encephalopathy.[83] Metabolic shift of fetal/neonatal is important for the function of cardiomyocytes. This metabolic shift is controlled by the mitochondria biogenic surge that involves cardiomyocyte maturation in neonates. Mutation mtDNA and mitochondrial dysfunction leads to dilated cardiomyopathy via mitochondrial transcription factor A (TFAM).[84,85]

Negative Impacts of Inflammation on Mitochondrial Function

Inflammasomes Promote mtDNA Release

Pathogen-associated molecular patterns and damage-associated molecular patterns stimulate the formation of inflammasomes, which bind to apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (CARD) to form a platform for caspase-1 activation and ultimately process pro-interleukin (IL)-1beta and pro-IL-18 to mature IL-1beta and IL-18. Caspase-1 activated by inflammasomes trigger mitochondrial damage including dissipation of mitochondrial membrane potential, mitochondrial permeabilization, and fragmentation of the mitochondrial network. Simultaneously, Caspase-1 inhibits mitophagy leading to the accumulation of defective mitochondria partially mediated by Parkin.[86]

Neutrophils are the first line of defense when external microorganisms attack the human body. It was reported that stimulation with IL-8, or lipopolysaccharide, leads to neutrophils releasing granule proteins and chromatin to form neutrophil extracellular traps (NETs).[87] NETs degrade virulence factors and killing bacteria, in which mtDNA is identified.[88] In systemic lupus erythematosus (SLE), mtDNA in NETs is demonstrated as the interferogenic DNA. Oxidized mtDNA retention in neutrophils and autoantibodies against oxidized mtDNA are observed in SLE patients.[89] In healthy people, neutrophils remove damaged mitochondria by extruding the mitochondrial components including mtDNA devoid of oxidized residues. Once being oxidized, mtDNA is degraded in lysosomes, which requires PKA phosphorylation of the TFAM. In SLE, neutrophils have reduced PKA activation that blocks TFAM phosphorylation.[90] As a result, oxidized mtDNA is accumulated and extruded as interferogenic complexes.

Inflammation Affects Mitochondrial OXPHOS

Mitochondria are the site of OXPHOS in eukaryotes. During OXPHOS, NADH, provided by the TCA cycle, is oxidized and provides electrons to the electron transport chain (ETC) , which consists of complexes I–IV, and ATP synthase. Decreased expression of the mitochondrial respiratory complexes I–V genes was found in patients of Alzheimer's disease that is characterized by progressive neuronal loss and neuroinflammation.[91] In acute inflammation, tumor necrosis factor (TNF) reduces the activity of complexes I, III, and IV in hepatocytes by triggering intracellular signaling cascade, which partially accounts for a shift of energy production from aerobic metabolism to glycolysis.[92] TNF, a proinflammatory cytokine, is elevated in the blood, cerebrospinal fluid (CSF), and striatum region of the brain in patients with Parkinson's disease. TNF upregulates the expression of miRNA targeting mitochondrial complex I, decreasing ATP levels, and increasing ROS production and induces dopaminergic cells death in Parkinson's disease.[93] TNF is also

reported to inhibit OXPHOS via peroxisome proliferator-activated receptor (PPAR)-γ co-activator 1α (PGC-1α), a transcriptional cofactor regulating transcription of ETC genes.[94,95]

Inflammation Affects Mitochondrial Dynamics

Mitochondria are dynamic organelles whose structure, localization, and balance between biogenesis and degradation are under tight control referred to as mitochondrial dynamics. It includes fission and fusion as well as mitochondrial trafficking and mitophagy.[96] In brain slices, proinflammatory stimuli promote mitochondrial fragmentation in astrocytes by triggering phosphorylation of the pro-fission protein dynamin-related protein-1 (Drp-1) and ultimately result in reduced respiratory capacity.[97] TNFα induces mitochondrial fragmentation accompanied with increased mitochondrial fission protein fission-1 and decreased mitochondrial fusion protein optic atrophy protein 1 (Opa1) in adipocytes.[98,99] In a model of dopaminergic neuron degeneration akin to Parkinson's disease, long term and low dose of TNFα exposure induce mitophagy by visualization of the colocalization of the autophagosome marker microtubule-associated protein 1A/1B-light chain 3 (LC3) with mitochondria.[93]

Inflammation Affects Mitochondrial Cell Death Pathways

The proinflammatory cytokine TNFα initiates necroptosis by tumor necrosis factor receptor 1 (TNFR1) signaling under caspase-8-deficient conditions. Receptor-interacting serine/threonine-protein kinase (RIPK)-1 and its downstream RIPK-3 are necessary for necrosome formation. It has been demonstrated that the mitochondrial proteins, PGAM family member 5 (PGAM5), and Drp-1 are downstream of RIPK-3 in the necroptosis pathway.[100] RIPK-3 phosphorylates mixed lineage kinase domain-like (MLKL) and long form of PGAM family member 5 (PGAM5) to activate Drp-1 leading to mitochondrial fission and necroptosis. In the cortical lesions of human samples of multiple sclerosis, TNFα activates necroptosis that is indicated by defective caspase-8 activation, as well as activation of RIPK1, RIPK3, and MLKL.[101]

A consequence of OXPHOS is the production of ROS, which acts as signaling molecules to modulate numerous processes at physiological levels.[102] ROS regulate the activity of phosphatases, which oppose the activity of protein kinases. It has been demonstrated that phosphatases including protein tyrosine phosphatase 1B,[103,104] phosphatase and tensin homolog (PTEN, lipid phosphatase), and mitogen-activated protein kinase ((MAPK)[105–107] are inhibited by ROS under physiological conditions. Mitochondrial ROS regulate TNF-mediated cell death.[108] TNF-induced signaling activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)[109] and pro-apoptotic signaling via c-Jun N-terminal kinase (JNK).[110] ROS promote TNF-induced death and sustained JNK activation by inhibiting MAPK phosphatases.[107] The mitochondrial antioxidant protein superoxide dismutase 2 regulates NF-κB-mediated expression of anti-apoptotic genes.[107]

ROS are necessary signals for self-renewal and cellular differentiation of stem cells. Quiescent stem cells have lower levels of ROS, and mitochondrial ROS promote epidermal differentiation and hair follicle development.[111–113] High expression of pluripotent genes including Nanog, octamer-binding transcription factor 4 (OCT4), and Sox2 reflects the self-renewing ability.[112] In mouse ESCs, knockdown of the mtDNA polymerase DNA polymerase gamma (POLG)[114] or the mitochondrial protein growth factor erv1-like[115] decreases the expression of pluripotent markers including the OCT4, Nanog Homeobox (NANOG), and the putative thiosulfate sulfurtransferase (SSEA). In physiological conditions, mitochondrial H_2O_2 stabilizes the hypoxia-inducible factor proteins,[116] which is indispensable for self-renewal and the pluripotency of mouse and human ESCs.[117]

Mitochondrial Abnormalities and Mitochondrial Diseases in Neonates

Mitochondrial diseases can be described as heterogeneous, progressive, and multisystemic and these characteristics are thought to be due to the early neonatal period when high energy is suddenly demanded from the newborn's organs that can cause the development of significant illnesses such as Leigh syndrome, Alpers syndrome, anemia, seizures (epilepsy), stroke, heart failure, diabetes, and enteropathy.[118,119] Mitochondrial dysfunction in newborns is the result of the mtDNA and nuclear DNA (nDNA).[120] Under dual genetic control, there are approximately 80 subunits of the respiratory chain with 13 of these subunits being encoded by the mtDNA and the remaining 67 subunits are thought to be encoded by the nDNA. There are two groups of mutations classified as originating from the mtDNA that is inherited maternally or from the nDNA.[121] A recent study in pediatrics stated about 36% of cases reveals that the neonatal period produces onset of oxidative phosphorylation disorders.[122,123] In infants and children, other than OXPHOS disorders as affected by mitochondrial dysfunction, mutations and defects in protein importation, mitochondrial dynamics, and mtDNA expression and regulation have been found.[124] However, mutations in the mtDNA have been found to not be primarily responsible for neonatal disease symptoms but rather that mtDNA mutations are consistent with early spontaneous abortions and/or neonatal deaths as revealed by anecdotal experience.[125]

The most common mitochondrial disease in neonates as explained by various larger cohort studies is Leigh syndrome that contains an ATPase6 gene mutation in complex V, m.8993 T >G. Leigh syndrome is the result of at least 26 distinct mtDNA mutations and it is within the first 2 years of life that the child acquires this disease, however, this can present much sooner with most pediatric patients showing symptoms within the first month of life as well as clinical phenotypes such as dystonia, abnormal eye movements, and respiratory abnormalities.[126,127] Another syndrome occurring with neonatal onset is Pearson's syndrome that is characterized by refractory sideroblastic anemia along with vacuolization of bone marrow precursor cells in addition to pancreatic dysfunction. The exocrine pancreas, liver, and kidney also experience dysfunction in this syndrome oftentimes leading to premature death; however, the pediatric patients that do survive acquire Kearns-Sayre syndrome (KSS) in late childhood. Both of these disorders explained (Leigh and Pearson) undergo a large deletion in their mtDNA.[128] Additionally, reversible COX-deficient infantile myopathy is a third syndrome that presents within the neonatal period affecting newborns with hypotonia and severe muscle weakness beginning as early as the life of the first few days to the first few weeks. The underlying mutations of this disease are found in m.14674 T>C of tRNAGlu and often require mechanical ventilation as well as containing severe lactic acidosis. The muscle biopsy material demonstrates absent muscle complex IV or COX activity but patients with these results experience spontaneous improvement between 5 and

20 months of age with a complete reversal to normal COX activity in addition to being phenotypically healthy without any other severe symptoms.[129,130]

These are not the only significant reports of diseases with neonatal onset but rather there are other cases displaying a homoplasmic mutation of m.1624C >T in the $tRNA^{Val}$ gene in a family with six children who fatally died with diagnosed severe lactic acidosis, whereas the seventh had Leigh syndrome.[125] Two of the children in this family with the homoplasmic mutation, m.3303C >T in the $tRNA^{Leu}$ gene died of infantile cardiomyopathy.[131] To further examine infantile and pediatric mitochondrial diseases, a recent study of 262 patients was conducted revealing that approximately 17% of diseases were a result of mtDNA mutations. The majority of mtDNA diseases addressed in this study were "classical" mitochondrial syndromes, including mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), leber hereditary optic neuropathy (LHON), KSS, and myoclonic epilepsy with ragged red fibers (MERRF).[132] Mutations causing MELAS such as the ND1 and ND5 gene mutations are derived from mtDNA-encoded subunits within complex I.[133] Additionally, protein-encoding gene mutations occurring in complex IV and COXIII have been found to induce MELAS.[134] Historically, the first mtDNA point mutation described to give rise to a mitochondrial disease was the m.11778 G >A mutation inducing LHON with more than 95% of patients with LHON containing one of the three following mutations: m.11778 G >A, m.3460 G >A, or m.144484 T >C.[135] One of the progressive myoclonic epilepsies is MERRF and is classified clinically by a set of four constant features: myoclonus, generalized epilepsy, ataxia, and ragged red fibers within muscle tissues. Greater than 80% of patients with MERRF have the mutation of the gene encoding tRNALys at m.8344A >G.[136] Another severe disease that occurs in premature infants is necrotizing enterocolitis (NEC) known as one of the most common gastrointestinal emergencies during the neonatal period due to mitochondrial dysfunction. NEC occurrence is significantly high among infants with very low birth weight (VLBW) with approximately 14% weighing less than 1000 g.[137]

Perspective

This dynamic nature of mitochondria is essential for providing energy and modulating key cellular events. Besides providing energy, mitochondria serve as the other essential cellular functions to support key developmental events of the reproductive process, fertilization, oocyte maturation, and preimplantation embryo development. The highest mtDNA copy number and mass are found in the mature oocyte of any cell. High numbers of mitochondria in oocytes are essential for early embryonic development by providing the capacity for nutrient oxidation.[27] Inhibition on mitochondrial metabolic activity blocks maturation of oocyte and the subsequent embryo development[32,33] as well as fetal and placental growth in animals.[34] After birth, the many functions previously assumed by maternal organs and placenta must be promptly carried by the newborn's organs. A tremendous amount of energy is needed for the newborn to cope with increased energy-demanding physiological processes; thus, the neonates experience a considerable increase in mitochondrial number and function. Neonates' muscles, heart, and brain are mainly dependent on aerobic metabolism that depends on mitochondria function. Disorders of mitochondrial metabolism caused by defects in fatty acid oxidation, pyruvate metabolism, and the respiratory chain, including mitochondrial complexes I, II, III, and IV and ATP synthase, may often present in the neonatal period. Mutations of both nuclear genes and mtDNA can cause mitochondrial dysfunction in neonates since primary and secondary mitochondrial dysfunctions are quite common in neonates.[62–64]

With promising expectations, mitochondrial research is expanding constantly. Finding out more about mitochondrial functions and the underlying mechanisms in the embryonic/neonatal stage in mammals will give us insight on how to develop novel clinical interventions to address mitochondrial dysfunction during this stage. There are still many unknown factors, such as the long-term effects of developmental conditions on mitochondrial function in the early stage, how these observed effects affect health and disease susceptibility during the life cycle, long-term effects of involved molecular mechanisms, and identification of biomarkers that provide information about the mitochondrial function across tissues. A framework for future research is provided by these questions and issues. Additionally, studies using newborn cells offer great promise in terms of understanding mitochondrial function using *ex vivo* experimental challenge paradigms.

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