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Role of Mitochondria in neonatal hypoxic-ischemic encephalopathy

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Role of Mitochondria in Neonatal Hypoxic-Ischemic Encephalopathy

Running title: Mitochondria in HIE

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Abstract

Neonatal hypoxic-ischemic encephalopathy, an important cause of death as well as long-term disability in survivors, is caused by oxygen and glucose deprivation, and limited blood flow. Following hypoxic-ischemic injury in the neonatal brain, three main biochemical damages (excitotoxicity, oxidative stress, and exacerbated inflammation) are triggered. Mitochondria are involved in all three cascades. Mitochondria are the nexus of metabolic pathways to offer most of the energy that our body needs. Hypoxic-ischemic injury affects the characteristics of mitochondria, including dynamics, permeability, and ATP production, which also feed back into the process of neonatal hypoxic-ischemic encephalopathy. Mitochondria can be a cellular hub in inflammation, which is another main response of the injured neonatal brain. Some treatments for neonatal hypoxic-ischemic encephalopathy affect the function of mitochondria or target mitochondria, including therapeutic hypothermia and erythropoietin. This review presents the main roles of mitochondria in neonatal hypoxic-ischemic encephalopathy and discusses some potential treatments directed at mitochondria, which may foster the development of new therapeutic strategies for this encephalopathy.

Keywords: Neonatal hypoxic-ischemic encephalopathy; Mitochondria; HIE;

1. Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE), an important cause of death as well as long-term disability in survivors, is caused by oxygen and glucose deprivation, and limited blood flow (**Fig. 1**) (Verklan et al., 2015). Asphyxia during the perinatal period can induce HIE. The incidence of HIE was estimated as 1.5 (95%CI 1.3 to 1.7) per 1000 live births with population-based results (Kurinczuk et al., 2010). The mortality rate of HIE (deaths/live births) was reported as 0.32% (Velaphi et al., 2007). Queensland Clinical Guidelines updated the clinical guidelines for HIE in 2021, including assessment, diagnosis, and management (Queensland-Clinical-Guidelines, 2021). Hypothermia is currently the only proven therapy for moderate and severe HIE, which improves mortality and long-term outcomes for babies (Wassink et al., 2019; Queensland-Clinical-Guidelines, 2021). In addition to hypothermia, some agents that may be synergistic with hypothermia are proven to relieve patients with HIE at the molecular level (Ruegger et al., 2018; Gou et al., 2020; Wu et al., 2022).

Mitochondria are the nexus of metabolic pathways to offer most of the energy that our body needs. Following hypoxic-ischemic (HI) injury, the characteristics of mitochondria, including dynamics, permeability, and ATP production, are affected. These altered mitochondrial characteristics also feed back into the process of HIE (Thornton et al., 2018; Rodriguez et al., 2020). There are some good review articles about the roles of mitochondria in HIE (Thornton et al., 2018; Ham et al., 2017). Until July 04, 2023, the PubMed database offered 447 articles with two keywords ("hypoxic-ischemic encephalopathy" and mitochondri*), which indicates that researchers are still interested in this content. In this review, mitochondrial roles in HIE were reviewed to offer ideas for potential treatments.

2. Damaged HIE cascades

Following HI injury in the brain, three main damaged cascades (excitotoxicity, oxidative stress, and exacerbated inflammation) were triggered (Pedroza-Garcia et al., 2022). Initially, the adenosine triphosphate (ATP) deficit, caused by lack of blood and oxygen, induces Na^+/K^+ pump failure, causing abnormal intracellular accumulation of sodium, calcium, and water, which will lead to neuronal depolarization and glutamate release. The release of glutamate, an excitatory

neurotransmitter, over activates ionotropic receptors, which will enhance excitotoxicity and aggravate HI brain injury (Iovino et al., 2020).

After HI attack, reactive oxygen species (ROS) production rapidly increases and overwhelms the antioxidant defenses, which are immature in the neonatal brain (Zhao et al., 2016). During reperfusion, increased production of ROS will worsen the situation (Widgerow, 2014).

Inflammation is another main response of the injured brain. Microglia detect changes in the environment and will be activated. Activated microglia migrate to injured sites and produce proinflammatory cytokines, including tumor necrosis factor and chemokines to recruit additional cells and remove pathological agents (Kwon et al., 2020; Rodriguez-Gomez et al., 2020). Similar to microglia, astrocytes have pro-inflammatory and immunoregulatory subpopulations, which are involved in inflammation in HIE (Kwon et al., 2020).

Mitochondria are involved in all three cascades, they offer most of the energy, including ATP, we get to spend. Mitochondria account for the majority of oxygen consumption and are a potential source of ROS (Fuhrmann et al., 2017). Mitochondria can be a cellular hub for infection and inflammation (Andrieux et al., 2021).

3. Oxidative phosphorylation

Under basal physiological conditions, glucose metabolizes into nicotinamide adenine dinucleotide (NADH), ATP, and two molecules of pyruvate, which are oxidized into acetyl CoA and an additional molecule of NADH and carbon dioxide (CO_2). The acetyl CoA is used in the citric acid cycle to offer CO_2, NADH, flavin adenine dinucleotide ($FADH_2$), and ATP. In the mitochondrial inner membrane, NADH and $FADH_2$ are used in oxidative phosphorylation (OXPHOS) to synthesize ATP through an electrochemical transmembrane gradient that is maintained by the electron transfer chain (ETC) (Gilkerson et al., 2003). Electrons are passed to oxygen, the final electron carrier in aerobic cellular respiration, by Complex IV (cytochrome oxidase) through a series of redox reactions. Electrons may be leaked from the ETC to oxygen producing primarily the superoxide anion (O_2•) (Turrens, 2003). Under normal conditions, 50-60% of total O_2 is spent on maintenance of ionic gradients (Erecinska et al., 1989) (**Fig. 2**).

During HI attack, oxygen and glucose deprivation and limited blood flow will induce cells to a

bioenergetic crisis caused by anaerobic metabolism with limited glucose. Aerobic metabolism and anaerobic metabolism produce 32-36 ATP and 2 ATP with a single glucose (Erecinska et al., 1989; Goldhaber, 1997). Lack of oxygen, the final electron carrier in the ETC, blocks the transfer of electrons and reduces ionic gradients, which decreases the production of ATP and causes primary energy failure (**Fig. 2**). Compared with adults, the efficiency of glycolysis in newborns is lower, which leads to more severe primary energy failures. The main reason for this phenomenon is that glucose transporter proteins GLUT1 (glial) and GLUT3 (neuronal) at seven days are expressed at only about 10% of their adult levels (Vannucci et al., 2005).

As the duration of hypoxia increases, ionic gradients imbalance and the ATP decrease will become more severe. Theoretically, the production rate of ROS should decrease with a decrease in oxygen availability. Interestingly, detailed investigations confirmed that the production of ROS showed a burst under conditions of mild hypoxia (1–3% O_2) but not during severe hypoxia or anoxia (Schroedl et al., 2002; Guzy et al., 2006; Hernansanz-Agustin et al., 2014). ROS reduced gradually and disappeared about one hour later, however, these ROS could also damage cells (Hernansanz-Agustin et al., 2014). Deactivation of mitochondrial complex I, switching to a Na^+/H^+ antiporter, is involved in ROS production to face acute hypoxia (Hernansanz-Agustin et al., 2017). In addition to this switching, complex I deactivation presented three functions: 1) reversed the reaction of the tricarboxylic acid cycle dehydrogenases, which are known to produce ROS by this reaction (Tretter et al., 2004); 2) modified ubiquinone pool redox state; and 3) triggered the production of superoxide by complex III (Chandel et al., 1998).

After HI attack, reperfusion and restoration of blood flow send oxygen and glucose back to the neurons. ATP is generated gradually to restore the cell's energy resources. During primary energy failure, cytosolic Ca^{2+} is overloaded, which evokes an increase in intermitochondrial Ca^{2+} to reduce cytosolic Ca^{2+} (Zaidan et al., 1994; Puka-Sundvall et al., 2000). Calcium is an activation signal for mitochondrial phosphatases, which induces dephosphorylation of multiple mitochondrial proteins, including cytochrome c (Cytc) and cytochrome c oxidase (COX), to active their functions (Hopper et al., 2006; Huttemann et al., 2012; Kadenbach, 2020). In addition to the effect on the ETC transfer rate, dephosphorylation of COX also leads to the loss of allosteric inhibition by ATP (Huttemann et al., 2008). Activated oxidative phosphorylation proteins (OxPhos)

could hyperpolarize mitochondrial membrane potential, which could be further exacerbated by the loss of allosteric inhibition by ATP (Huttemann et al., 2008). Hyperpolarization of mitochondrial membrane potential (exceeding 140 mV) causes an exponential increase in ROS generation (Starkov et al., 2003; Liu, 1999, 2010). Accelerated production of ROS overwhelms the antioxidant system, which is immature in neonatal brain (Zhao et al., 2016). Before reperfusion injury becomes obvious, the stage is described as the latent phase (**Fig. 2**).

During primary energy failure, ATP-driven active transport loses its function, which destroys cell homeostasis, induces glutamate-induced excitotoxicity, and leads to the imbalance of Na^{+}, Ca^{2+}, and water (Hasselbach et al., 1962; Mahmoud et al., 2019; Iovino et al., 2020; Chen et al., 2022). Intracellular calcium accumulation generates mitochondrial swelling, which is the major factor leading to mitochondria-mediated cell death (Chapa-Dubocq et al., 2018). Calcium influx also activates nitric oxide synthase (NOS) to synthesize the free radical nitric oxide (•NO), which has high affinity for complex IV (Torres et al., 1998; Cooper et al., 2007). •NO not only inhibits the activity of complex IV to block electron transfer but also reacts with O_2• to produce peroxynitrite (ONOO-), which is a mitochondrial and cellular toxin (Moller et al., 2019; Radi et al., 2002). Exceeding ROS levels are proven to cause significant damage to biological macromolecules, such as protein degeneration, lipid oxidation, and DNA degeneration (Vranic et al., 2018). Thereafter, a phase of secondary energy failure occurs, principally due to mitochondrial dysfunction. In newborn piglets, phosphorus magnetic resonance spectroscopy (^{31}P-MRS) presented progressively declined cerebral bioenergetics and secondary energy failure after a few hours of reperfusion (Lorek et al., 1994).

4. Permeability

Two membranes, inner and outer, separate the mitochondrial matrix from the cytosol, nonetheless, matrix and cytosol can exchange their contents through the mitochondrial permeability transition pore (mPTP). ETC complexes are all in an ion-impermeable inner membrane to maintain membrane potential, which is important for ATP synthesis. Switches of mPTP play an important physiological role, in maintaining healthy mitochondria homeostasis. Although the molecular characterization of the mPTP is not clear, some molecular compositions of mPTP have been

proven, including the adenosine nucleotide translocate (ANT) family of proteins at the inner membrane and the Bcl-2 family of proteins at the outer membrane (Halestrap et al., 1997; Marzo et al., 1998) (**Fig. 3**). In immature rats, data suggested that mPTP opening occurred after HI attack (Puka-Sundvall et al., 2001). mPTP is regulated by many factors, including Ca^{2+}, ROS, and Cyclophilin D (CypD) (Robichaux et al., 2022).

Mitochondrial Ca^{2+} uptake is important for cellular homeostasis. Mitochondrial membrane potential maintained by proton extrusion by ETC is the driving force for Ca^{2+} uptake into the mitochondria. The voltage-dependent anion channel (VDAC) protein family forms the main channel that regulates ions, including Ca^{2+}, and metabolite flux between the outer mitochondrial membrane and the cytosol (Sander et al., 2021). The mitochondrial calcium uniporter (MCU) complex in the mitochondrial inner membrane is identified as the main route for Ca^{2+} uptake from outside the inner membrane to the matrix (Baughman et al., 2011; De Stefani et al., 2011). Cooperation between VDAC and MCU introduces Ca^{2+} into the matrix. Meanwhile, excess intramitochondrial Ca^{2+} plays a crucial role in mPTP opening to maintain the normal level of Ca^{2+} in mitochondria (Haworth et al., 1979). This phenomenon has an interesting name: "Ca^{2+}-induced Ca^{2+} release" (Fabiato et al., 1975). During primary energy failure, abnormal accumulation of cytosolic Ca^{2+} induces Ca^{2+} uptake into the mitochondria by retained mitochondrial membrane potential. Ca^{2+} overload will induce mPTP opening to cause mitochondrial depolarization and swelling of the organelles (Bernardi, 2013). Homo/hetero oligomers formed by BAX and BAK, of the Bcl-2 family containing at least one Bcl-2 homology (BH) domain, may be involved in Ca^{2+}-dependent mPTP opening because mPTP sensitivity to matrix Ca^{2+} is regulated by BH3 mimetic inhibition of the anti-apoptotic Bcl-2 family members localized to mitochondria (Patel et al., 2021). BAX locates to the mitochondrial outer membrane; however, BAX works together with inner membrane proteins, the ANT family, to mediate mPTP opening (Marzo et al., 1998). Independent of Bax and Bak, Ca^{2+} can mediate mitochondrial inner membrane permeabilization to induce cell death, although the exact mechanism is not clear (Quarato et al., 2022).

Analogous to the phenomenon of "Ca^{2+}-induced Ca^{2+} release" is ROS-induced mPTP opening followed by a "burst phase" of ROS generated by the particular mitochondrion and lasting 5-10 s (Zorov et al., 2000). Hicks and Gebicki first established a quantitative relationship between ROS

concentration and rate of lipid peroxidation (Hicks et al., 1978). For the phospholipid bilayer, ROS oxidizes the head groups first, followed by the lipid tails (Yusupov et al., 2017). Oxidation of the lipids alters the structural and dynamic properties of the membrane, which can lead to an increase in the permeability and efflux of contents held within (Chen et al., 1994; Yusupov et al., 2017). ROS not only oxidizes lipids but also targets mPTP regulator proteins via posttranslational modifications (PTMs) to mediate mPTP opening. For example, ROS modified the ANT family and VDAC proteins allowing activation of the mPTP pore with a lower concentration of Ca^{2+} (Chang et al., 2014). ROS can sensitize mitochondria to Ca^{2+}-dependent mPTP opening.

CypD, peptidyl-prolyl cis/trans isomerase, is an activator of mPTP opening because deletion of CypD reduces the sensitivity of mitochondria to Ca^{2+}-dependent mPTP opening (Crompton et al., 1998; Woodfield et al., 1998). Cyclophilin A (CsA) interacts with CypD to inhibit mPTP (Kim et al., 2014; Haleckova et al., 2022). Compared with adult mice, neonatal mice had a considerably higher induction threshold and lower sensitivity to CsA (Wang et al., 2009). CypD-related mPTP opening is critical for the development of brain injury in the adult, whereas in neonatal HI brain injury, mitochondrial permeabilization appears to be primarily Bax-dependent (Wang et al., 2009, 2010). In neuronal mitochondria from postnatal day 1 rat pups, Ca^{2+}-induced mPTP exhibited limited sensitivity to CsA (Brustovetsky et al., 2000).

mPTP opening mainly happens during reperfusion and is a major cause of reperfusion injury (Halestrap, 2009; Morciano et al., 2017). Due to mPTP opening, mitochondria release accumulative ROS and Ca^{2+}, which induce damage in biological macromolecules, excitotoxicity, and inflammatory response. Except for ROS and Ca^{2+}, the efflux of apoptosis-inducing factors, including apoptosis-inducing factor (AIF) and cytochrome c (CytC), will activate apoptosis and cause neuron loss in the immature brain after HI (Kratimenos et al., 2017; Li et al., 2020) (**Fig. 3**).

5. Mitochondrial Dynamics

Mitochondria are highly dynamic organelles that constantly undergo events of fission, fusion, biogenesis, mitophagy, and cytoskeleton-based transport. The master mediator of mitochondrial fission is dynamin-related protein 1 (DRP1) (Mears et al., 2022). The main components involved in mitochondrial fusion are also members of the dynamin-like family of GTPases-Mitofusins 1

and 2 (MFN1/2) in the outer membrane, and optic atrophy 1 (OPA1) protein in the inner membrane (Dorn, 2020). Master regulators of biogenesis are the transcription factors TFAM, NRF1/2, and PGC1α (Ventura-Clapier et al., 2008). PINK1 (PTEN-induced putative kinase 1), PARKIN (Parkin RBR E3 ubiquitin-protein ligase), and FUNDC1 (FUN14 domain containing 1) have important roles in mitophagy (Sica et al., 2016) (**Fig. 4**).

Dynamic regulation helps mitochondria face different environments (Popov, 2020; Yapa et al., 2021). Fusion lets mitochondria share their contents, including mitochondrial DNA (mtDNA), proteins, and lipids. Meanwhile, minor defects caused by low-level mtDNA mutation or accumulating ROS can be fused with more complex mitochondrial networks to correct the defects (Youle et al., 2012). If the area is damaged, fission helps mitochondria clear dysfunctional parts. The fate of mitochondria following fission is based on mitochondrial conditions, including ROS, membrane potential, and mtDNA mutation. Healthy mitochondria act as a "seed", which is used as a substrate for biogenesis. Damaged mitochondria trigger the accumulation and dimerization of PINK1 to initiate mitophagy (Youle et al., 2012; Jones et al., 2022).

In neurons (Baburamani et al., 2015; Li et al., 2016), astrocytes (Quintana et al., 2019), and microglia (Zhou et al., 2019), HI attack can increase mitochondrial fission. Few studies about the mitochondrial morphology of the immature brain after HI *in vivo* have been reported, however, rapid induction of mitochondrial fragmentation after neonatal HI in immature rats was observed (Demarest et al., 2016). HI-induced fragmentation of mitochondria is sex-specific: fission was more prominent in males compared with female ipsilateral sections (Demarest et al., 2016). Consistent with energy failure, fission also presents two phases: primary fission was observed immediately after HI attack, followed by a secondary phase of fission at 24 h following recovery (Nair et al., 2022). Mitophagy also has two phases: it was upregulated immediately after HI followed by a second wave after seven days (Nair et al., 2022). A prospective multicentric study reported that the neonatal plasma level of PARKIN (a protein involved in mitophagy) is related to HI insult and is reliable, also at birth (Tarocco et al., 2022). After lethal oxygen-glucose deprivation, overload of the Ca^{2+}-stimulated activity of calpains mediated the degradation of cytoskeletal protein, causing abnormal mitochondrial distribution (Novorolsky et al., 2020).

6. Discussion

Although HIE is not a mitochondrial disease, the roles of mitochondria should be taken seriously. In this review, mitochondrial roles, including oxidative phosphorylation, mPTP, and dynamics, during and after deprivation of oxygen and glucose were reviewed. Mitochondrial functions are affected and altered by oxygen-glucose deprivation (OGD) after which dysfunctional mitochondria feedback to cells and cause further cell damage.

There are some treatments for HIE with effects on the function of mitochondria or target mitochondria. Moderate-severe HIE in term and near-term infants is treated by therapeutic hypothermia (TH), the only mandated therapy approved for term HIE, to reduce death and improve prognosis (Jacobs et al., 2013; Labat et al., 2022). TH helps cells to restore metabolic and cellular energy state homeostasis, in which mitochondria play an important role. Zhou et al. reported that mild hypothermia alleviates OGD‐induced apoptosis by inhibiting ROS generation and improving mitochondrial dysfunction (Zhou et al., 2022). Sosunov et al. suggested that TH inhibited calcium-induced mitochondrial mPTP to protect neurons and reduce HI-induced injury (Sosunov et al., 2022).

Except for TH, there are no other approved therapies for HIE, however, many drugs have been tried in HIE. These drugs affect mitochondrial functions (Thornton et al., 2018; Rodriguez et al., 2020). Erythropoietin and melatonin can promote mitochondrial biogenesis (Carraway et al., 2010; Niu et al., 2020). Melatonin, a broad-spectrum antioxidant, also restores mitochondrial fusion/fission dynamics affected by OGD and enhances mitophagy (Kang et al., 2016; Nasoni et al., 2021). SkQR1 (Silachev et al., 2018) and MitoSNO (Kim et al., 2018) are other antioxidants that specifically abolish mitochondrial ROS to protect neurons. The rescue of mitochondrial function due to 2-Iminobiotin treatment by inhibition of neuronal and inducible isoforms of NOS is currently under development to reduce brain cell damage after HI injury (Zitta et al., 2017; Albrecht et al., 2019). Thiamine, in particular, has a critical role in oxidative phosphorylation and the TCA cycle in mitochondria; moreover, this micronutrient can regulate mitochondrial transition pore opening (Bâ, 2017; Sechi et al., 2022). An energy source supply alternative to glucose with normalization of aberrant cellular energy metabolism and decreased oxidative stress in ketogenic diets suggests a therapeutic role. Combined treatment with ketone bodies and thiamine may have a

synergistic effect, further fostering the normalization of aberrant cellular energy metabolism (Sechi et al., 2023).

Great efforts provided new visions of mitochondrial functions in HIE. These efforts attracted academic institutions and industries to provide more and more potential therapies for HIE. We will see the approved treatment in the near future.

7. Declarations

7.1 Ethics approval and consent to participate

Not applicable.

7.2 Consent for publication

Not applicable.

7.3 Availability of data and materials

Data from patients are available from the corresponding author after discussion with the Institutional Review Board.

7.4 Competing interests

The authors declare that they have no competing interests.

7.5 Funding

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7.6 Authors' contributions

KWJ collected and analyzed related articles, and then wrote the manuscript. LC collected related articles and drew figures. KWJ supervised data and manuscript. All authors read and approved the final manuscript.

Figure legends

Figure 1. Clinical features of HIE. HIE: Hypoxic-ischemic encephalopathy; RBC: red blood cells; DIC: disseminated intravascular coagulation; NEC: necrotizing enterocolitis.

Figure 2. Changes in the state of ETC during a hypoxic insult. ETC: electron transfer chain.

Figure 3. Factors in regulation of mitochondrial permeability during hypoxic-ischemic attack. AIF: apoptosis-inducing factor. ANT: adenosine nucleotide translocate. BAX: BCL2-associated X. BAK: BCL2 antagonist/killer. BCL2: B-cell lymphoma 2. BCL-xL: B-cell lymphoma-extra-large. CytC: Cytochrome c. ETC: electron transfer chain. MCU: mitochondrial calcium uniporter. ROS: reactive oxygen species. VDAC: Voltage-dependent anion channel.

Figure 4. Dynamics of mitochondria and related factors during a hypoxic insult. AMPK: AMP-activated protein kinase. CaMKKβ: Calmodulin-dependent protein kinase kinase-β. DRP1: Dynamin-related protein 1. FUNDC1: FUN14 domain containing 1. LKB1: Liver kinase B1. MFN1/2: Mitofusins 1 and 2. NRF2: Nuclear factor E2-related factor 2. OPA1: Optic atrophy 1. PARKIN: Parkin RBR E3 ubiquitin-protein ligase. PGC-1α: Peroxisome proliferator-activated receptor-gamma coactivator-1α. PINK1: PTEN-induced putative kinase 1. TFAM: Mitochondrial transcription factor A. Ⓟ: Phosphorylation.

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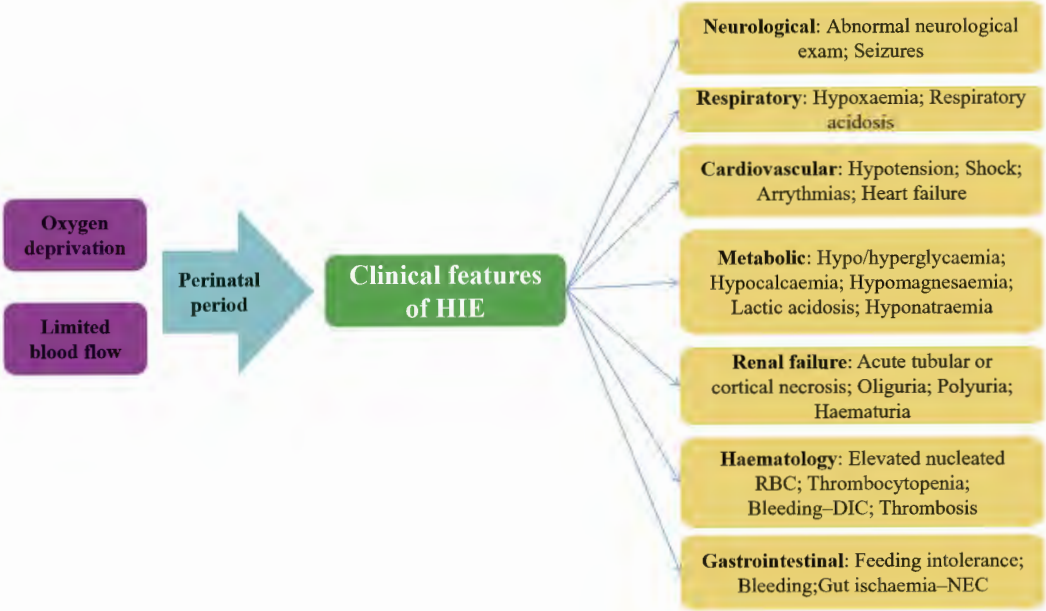
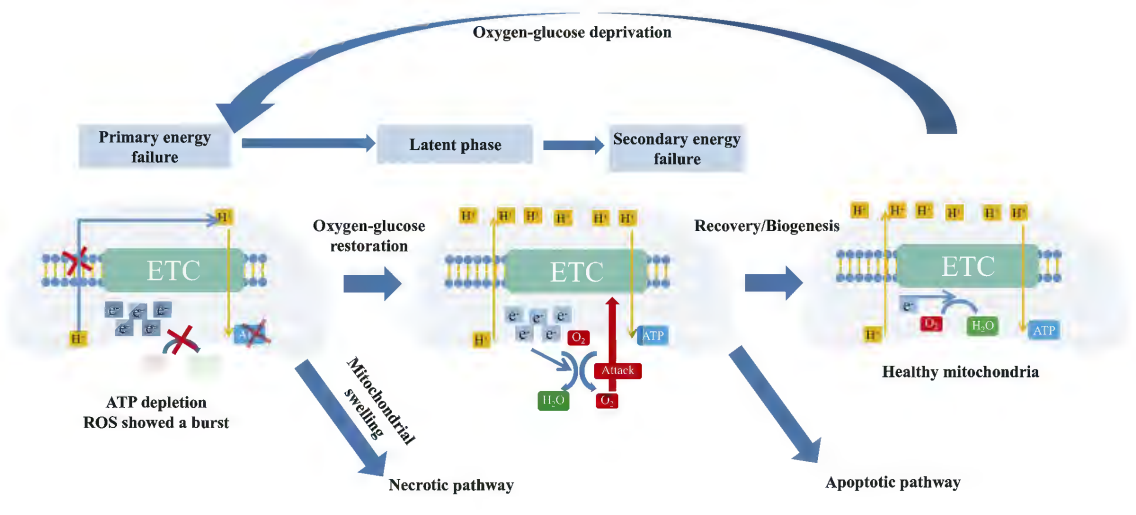
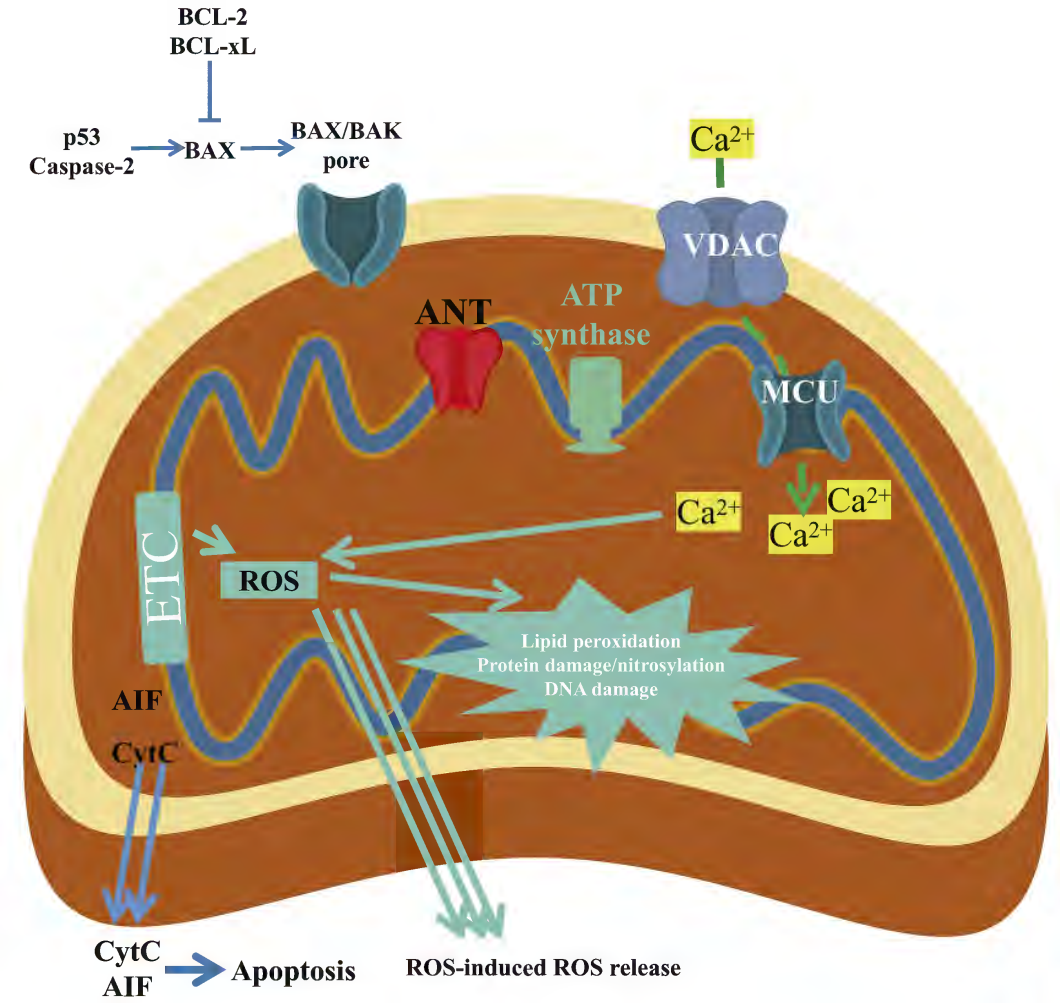

Oxygen deprivation
Limited blood flow
Perinatal period
Clinical features of HIE
Neurological: Abnormal neurological exam; Seizures
Respiratory: Hypoxaemia; Respiratory acidosis
Cardiovascular: Hypotension; Shock; Arrythmias; Heart failure
Metabolic: Hypo/hyperglycaemia; Hypocalcaemia; Hypomagnesaemia; Lactic acidosis; Hyponatraemia
Renal failure: Acute tubular or cortical necrosis; Oliguria; Polyuria; Haematuria
Haematology: Elevated nucleated RBC; Thrombocytopenia; Bleeding–DIC; Thrombosis
Gastrointestinal: Feeding intolerance; Bleeding;Gut ischaemia–NEC


Oxygen-glucose deprivation
Primary energy failure
Latent phase
Secondary energy failure
ETC
ATP depletion
ROS showed a burst
Oxygen-glucose restoration
ETC
ATP
Attack
Mitochondrial swelling
Necrotic pathway
Recovery/Biogenesis
ETC
ATP
Healthy mitochondria
Apoptotic pathway


BCL-2
BCL-xL
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pore
Ca2+
VDAC
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ATP
synthase
MCU
Ca2+
Ca2+
Ca2+
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Protein damage/nitrosylation
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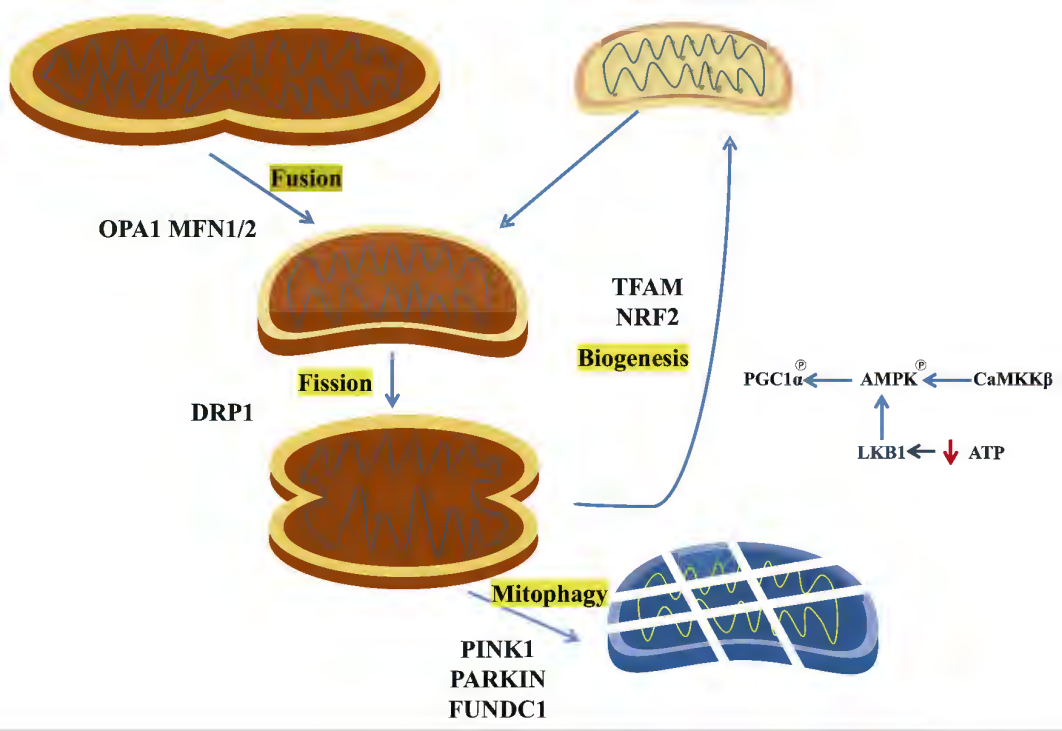
Apoptosis
ROS-induced ROS release


Fusion
OPA1 MFN1/2
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DRP1
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Biogenesis
PGC1α
AMPK
CaMKKβ
LKB1
ATP
Mitophagy
PINK1
PARKIN
FUNDC1