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Emerging role of metabolic reprogramming in hyperoxia-associated neonatal diseases

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ABSTRACT

Oxygen therapy is common during the neonatal period to improve survival, but it can increase the risk of oxygen toxicity. Hyperoxia can damage multiple organs and systems in newborns, commonly causing lung conditions such as bronchopulmonary dysplasia and pulmonary hypertension, as well as damage to other organs, including the brain, gut, and eyes. These conditions are collectively referred to as newborn oxygen radical disease to indicate the multi-system damage caused by hyperoxia. Hyperoxia can also lead to changes in metabolic pathways and the production of abnormal metabolites through a process called metabolic reprogramming. Currently, some studies have analyzed the mechanism of metabolic reprogramming induced by hyperoxia. The focus has been on mitochondrial oxidative stress, mitochondrial dynamics, and multi-organ interactions, such as the lung–gut, lung–brain, and brain–gut axes. In this article, we provide an overview of the major metabolic pathway changes reported in hyperoxia-associated neonatal diseases and explore the potential mechanisms of metabolic reprogramming. Metabolic reprogramming induced by hyperoxia can cause multi-organ metabolic disorders in newborns, including abnormal glucose, lipid, and amino acid metabolism. Moreover, abnormal metabolites may predict the occurrence of disease, suggesting their potential as therapeutic targets. Although the mechanism of metabolic reprogramming caused by hyperoxia requires further elucidation, mitochondria and the gut–lung–-brain axis may play a key role in metabolic reprogramming.

1. Introduction

Advances in maternal-fetal medicine and neonatology have increased the survival rate of neonates, especially premature infants, and reduced perinatal mortality by 25% in the last decade [1]. Oxygen therapy is an important therapeutic method for rescuing and maintaining vital signs; however, it also induces oxidative stress by increasing the levels of reactive oxygen species (ROS) associated with many neonatal diseases. Even in full-term infants, sudden hyperoxia over a short period can overwhelm antioxidant defenses, leading to potential free radical-related damage. The most common diseases caused by hyperoxia in the neonatal period are bronchopulmonary dysplasia (BPD), also known as chronic lung disease of prematurity, and retinopathy of prematurity (ROP) caused by long-term oxygen therapy [2,3]. Recent studies have shown that hyperoxia can affect development and cause damage in multiple organs, including the brain, gut, and heart [4–6]. Oxidative stress can regulate a variety of signaling pathways and transcription factors, and participate in multiple biological processes such as inflammation, immunity, and cell proliferation. Recent studies have also shown that abnormal metabolic regulation can affect the occurrence and development of hyperoxia-induced neonatal diseases, including abnormal glucose, lipid, and amino acid metabolism, namely metabolic reprogramming [7,8].

Under normal aerobic conditions, glycolysis initially occurs in the cytoplasm to obtain energy. Subsequently, the mitochondria begin oxidative phosphorylation to obtain energy. Conversely, under hypoxic conditions, cells provide energy primarily through the glycolytic pathway rather than through oxygen-consuming mitochondrial metabolism. However, under certain disease conditions, the metabolic pattern of cells is altered. Warburg first discovered that tumor cells tend

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to undergo glycolysis in the cytoplasm, even under aerobic conditions; this abnormal metabolic phenomenon is known as the "Warburg effect" or "aerobic glycolysis" [9]. In addition to the dysregulation of glucose metabolism, metabolic reprogramming in cells involves aberrant lipid metabolism, amino acid metabolism, and other bioenergetic metabolic pathways. Crosstalk exists among glucose, fatty acids, and amino acids. Pyruvate dehydrogenase (PDH) converts glucose-derived pyruvate to acetyl-CoA, which enters the tricarboxylic acid (TCA) cycle, where it is converted to citrate. Citrate is then exported from the mitochondria to the cytosol and used for de novo fatty acid production [10]. Furthermore, amino acids are involved in regulating glycolytic rate-limiting enzymes such as pyruvate kinase M2 (PKM2) [11]. Here, we provide an overview of glucose, lipid, and amino acid metabolic reprogramming, review abnormal metabolism in neonatal diseases associated with hyperoxia, explore the possible pathogenesis of such diseases based on mitochondrial function and organ interactions, and discuss potential biomarkers and therapeutic targets.

2. Overview of metabolic reprogramming

2.1. Glucose metabolic reprogramming

Glucose is the primary energy source for cells. It enters cells through glucose transporters and is phosphorylated by hexokinase (HK) to form glucose-6-phosphate (G6P). G6P is further metabolized by glycolysis and the pentose phosphate pathway (PPP). G6P is then isomerized into fructose-6-phosphate and metabolized by various glycolytic enzymes into pyruvate, which enters the mitochondria for the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS). This process usually produces 34 adenosine triphosphate (ATP) and other essential metabolites, while glycolysis produces 2 ATP. The main processes involved in glucose metabolism include glycolysis, the TCA cycle, and the PPP [12]. Glycolysis involves multiple steps, including three irreversible reactions controlled by three rate-limiting enzymes: HK, phosphofructokinase, and pyruvate kinase. The PPP is one of the main pathways involved in glucose catabolism. The reducing agent, NADPH, is mainly regulated by G6P dehydrogenase. The activity of G6P dehydrogenase directly reflects the flux of oxidized PPP and determines the distribution of flux between glycolysis and the PPP [13]. Under anoxic conditions, lactic acid, the end product of glycolysis, is formed mainly from pyruvate. Warburg first reported that tumor cells were more likely to obtain energy through aerobic glycolysis (Warburg effect), even under aerobic conditions. Changes in the pattern of glucose metabolism during disease are known as glucose metabolic reprogramming [14].

2.2. Lipid metabolic reprogramming

Lipids are one of three major nutrients. They are closely related to energy supply and storage, and they are also the main building blocks of cell membranes and important molecules in cellular activities. Changes in lipid metabolism can affect a variety of cell functions, such as cell-cell interactions, cell membrane fluidity, and intracellular signal transduction. These changes can also affect downstream signaling pathways related to cell proliferation, adhesion, and movement. Abnormal lipid metabolism includes metabolic reprogramming of fatty acids, cholesterol, and phospholipids, and can cause systemic lipid changes [15].

Fatty acids are major components of triacylglycerols, phospholipids, and other complex lipids. They are components of membranes and a source of energy, and they have biological activities that act to influence cell and tissue metabolism, function, and responsiveness to hormonal and other signals [16]. Sources of fatty acids include endogenous and exogenous fatty acids. Fatty acids can be divided into short-chain, medium-chain, and long-chain fatty acids according to the number of carbon atoms [17]. The uptake of exogenous fatty acids requires specialized transporters to facilitate the effective transmembrane transfer. These transporters include CD36 (also known as fatty acid translocation enzymes), the fatty acid transporter family, and plasma membrane fatty acid binding proteins. In disease states such as tumors, the expression of these genes and proteins increases. This upregulation leads to the increased uptake of exogenous fatty acids, which are stored in lipid droplets. Chylomicrons, droplets of lipids synthesized by the epithelial cells of the intestinal mucosa, including triglyceride, cholesterol, and apolipoprotein, whose primary function is to transport exogenous triglyceride and cholesterol from the intestine to the liver. It can be detected in cord blood before oral feeding begins, and preterm infants had higher cholesterol and lower triglyceride in chylomicrons compared with term infants after oral feeding has been established [18]. Fatty acids are degraded by β-oxidation to produce acyl-CoA. Acyl-CoA then enters the TCA cycle to supply NADH and FADH2 to the electron transport chain. This process results in approximately six times the amount of ATP production during carbohydrate oxidation [19]. De novo lipid synthesis is the process of converting carbohydrates (such as glucose) and amino acids (including glutamine) to fatty acids. This process occurs only in hepatocytes and adipocytes. During the TCA cycle, glucose and glutamine are produced by pyruvate oxidation and reductive carboxylation, respectively. The main substrate for fatty acid synthesis is citrate or acetate, which produces cytoplasmic acyl-CoA. This metabolic pathway can be reactivated in disease states, even in the presence of exogenous lipid sources [20].

Metabolic reprogramming of cholesterol is predominantly characterized by the upregulation of intracellular cholesterol synthesis and the abnormal aggregation of most metabolites. Cholesterol is a crucial lipid that participates in the maintenance of cell membrane homeostasis and is a raw material for synthesizing vitamin D, bile acids, and steroid hormones, which are highly significant for maintaining cell function and metabolic homeostasis. Excess intracellular free cholesterol can lead to endoplasmic reticulum stress (ER stress), which disturbs metabolic homeostasis and induces apoptosis. Therefore, cholesterol can be metabolized in various ways. Intracellular cholesterol homeostasis is precisely regulated by the sterol regulatory element-binding protein (SREBP)-liver X receptor (LXR) axis to avoid cytotoxicity caused by excessive free cholesterol content [21].

2.3. Amino acid metabolic reprogramming

Amino acids are a class of organic compounds containing amino and carboxyl groups that form the basic units of proteins. Amino acids are divided into essential amino acids and non-essential amino acids, both of which are essential for the biosynthesis of nucleotides, glutathione, glucosamine, and polyamines. They also participate as metabolites in the TCA cycle. Amino acid requirements depend on the cell type, metabolic status, and microenvironment. The catabolism of amino acids includes deamination and decarboxylation. Amino acid metabolic reprogramming involves abnormalities in amino acid uptake rate, amino acid metabolic pathways, metabolites, or key metabolic enzymes. In particular, the metabolic reprogramming of glutamine, serine, and glycine has become a key area of research [22]. Glutamate is the most abundant free amino acid, which enters the cytoplasm through the solute carrier family 1 member 5 or alanine-serine-cysteine transporter 2 and is catalyzed by glutaminase to produce glutamate. Glutamate can then be transferred into the mitochondria and converted to alpha-ketoglutaric acid by the oxidative deamination of glutamate dehydrogenase 1, which acts as a TCA cycle intermediate for energy recycling in the mitochondrion (Fig. 1) [23].

3. Metabolic reprogramming in neonatal hyperoxia-associated diseases

3.1. Bronchopulmonary dysplasia

A common respiratory complication correlated with prolonged oxygen inhalation in preterm infants is BPD. The incidence is higher in

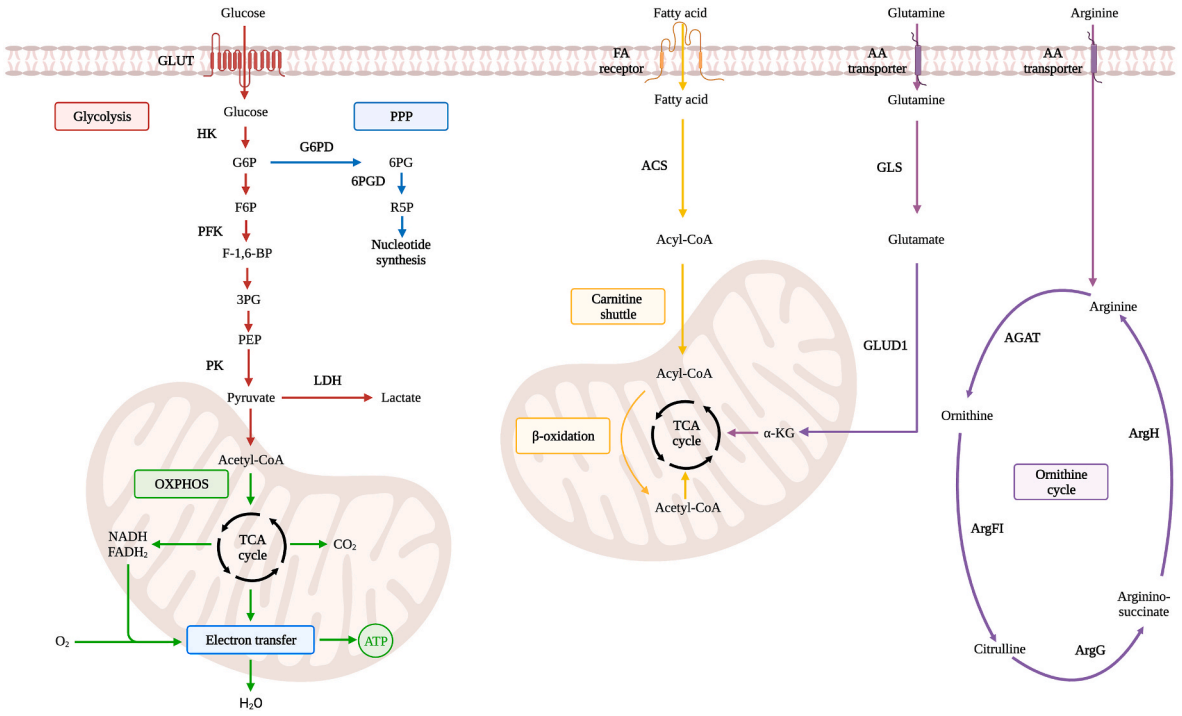

Fig. 1. Catabolism of glucose, fatty acid, and amino acids.
Glucose enters the cell through glucose transporters and is phosphorylated by hexokinase2 (HK2) to form glucose-6-phosphate (G6P). G6P is metabolized by glycolysis and the pentose phosphate pathway (PPP), then isomerized into fructose-6-phosphate and metabolized by various glycolytic enzymes into pyruvate, which enters the mitochondria for the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. The uptake of exogenous fatty acids requires specialized transporters to facilitate effective transmembrane transfer, including CD36. The uptake of exogenous fatty acids increases; these are stored in lipid droplets. Fatty acids are degraded by oxidation to produce acyl-CoA. Acyl-CoA then enters the TCA cycle to supply NADH and FADH2 to the electron transport chain. De novo lipid synthesis describes the process of converting carbohydrates (such as glucose) and amino acids (including glutamine) to fatty acids. The catabolism of amino acids includes deamination and decarboxylation. Glutamine is the most abundant free amino acid, which enters the cytoplasm via the solute carrier family 1 member 5(SLC1A5) or alanine-serine-cysteine transporter 2 (ASCT2), and is catalyzed by glutaminase to glutamate. Glutamate can be transferred into the mitochondria and converted to alpha-ketoglutaric acid by oxidative deamination of glutamate dehydrogenase 1 (GLUD1), which is utilized as a TCA cycle intermediate for energy recycling in the mitochondrion. Image generated using Bio-Render software.

preterm infants with lower birth weight and gestational age, which leads to high mortality rates, long hospital stays, increased social and economic burdens [24], and even long-term adverse outcomes for the respiratory and nervous systems [25]. However, the current therapeutic effects are not ideal, which has prompted a search for effective prevention strategies, treatment methods, and predictive indicators of BPD to reduce its incidence in premature infants and improve poor prognosis. The pathogenesis of BPD is complex and is still being explored, but it includes inflammation, mechanical ventilation, oxidative stress, vascular malformation, malnutrition, and respiratory microecological disorders [26]. Recent studies have shown that abnormal metabolic regulation, including abnormal glucose, lipid, and amino acid metabolism, can affect the occurrence and development of BPD (Table 1).

3.1.1. *Dysregulated glucose metabolism in BPD*

Clinical studies have shown that the basal and maximal oxygen consumption rates of human umbilical vein endothelial cells are lower in infants with BPD than in healthy infants after exposure to hyperoxia, indicating increased glycolysis [27]. Moreover, the urinary metabolomics of infants with BPD at birth exhibit increased lactate levels in the urine and reduced gluconate, suggesting the involvement of anaerobic respiration [28]. Gong et al. reported a significant increase in the expression of phosphogluconate dehydrogenase, the second enzyme in the oxidative arm of the PPP, in the lungs of premature infants requiring mechanical ventilation. They also observed that hyperoxic exposure increased glycolysis and the PPP of endothelial cells in neonatal mice and MFLM-91U cells [29]. Das et al. also observed changes in glucose metabolism both in vivo and in vitro. Hyperoxia reduced glycolytic capacity, glycolytic reserve, and oxidative phosphorylation in MLE-12 cells, and inhibited the function of complex I and II, but not that of complex IV, in isolated mouse lung mitochondria, thereby limiting the energy supply [30]. Furthermore, Ratner et al. reported a reduction in complex I level in a mouse model [31]. In vitro hyperoxia increased glycolysis in cultured MLE-12 cells [32]. Short-term (4 h) exposure to hyperoxia can also influence and reduce OXPHOS and respiratory complex I and IV activities in epithelial cells [33].

3.1.2. *Dysregulated lipid metabolism in BPD*

According to clinical studies, BPD groups exhibit high levels of certain carnitines in the blood, including C0, C2, and C6:1, suggesting enhanced β-oxidation and further oxidative phosphorylation [34]. Martin et al. observed a sharp decrease in docosahexaenoic acid (DHA) and long-chain polyunsaturated fatty acid levels in the first postnatal week, accompanied by an increase in linoleic acid levels. Moreover, the risk of chronic lung disease of prematurity was higher when DHA levels were lower [35]. In human BPD sections of the peribronchial blood vessels, the density of fatty acid binding protein 4 (FABP4)-positive cells was increased. FABP4 is an intracellular lipid-binding protein, and FABPs bind to various hydrophobic ligands, including retinoic acid and long-chain fatty acids, and are associated with regulating important biological processes such as lipid and glucose homeostasis [36]. An in vivo study showed that suppressed FABP4 expression alleviated alveolar developmental impairment and pulmonary fibrosis caused by hyperoxia [37].

The tracheal aspirates of infants with BPD exhibit reduced contents of pulmonary surfactant, which predominantly comprises dipalmitoyl

Table 1
Metabolic reprogramming in hyperoxia-associated neonatal diseases.

Hyperoxia-associated neonatal diseases	Metabolism	Metabolic changes	Reference
BPD			
Infants	Glucose	Reduced basal and maximal oxygen consumption rates of human umbilical vein endothelial cells	[27]
		Reduced gluconate and increased lactate levels in urine	[28]
		Increased phosphogluconate dehydrogenase in the lungs of premature infants requiring mechanical ventilation	[29]
	Lipid	Increased certain carnitines in the blood	[34]
		Reduced DHA and long-chain polyunsaturated fatty acid and increased linoleic acid in blood	[35]
		Increased FABP4 in sections of the peribronchial blood vessels	[36]
		Reduced pulmonary surfactant in tracheal aspirates	[38]
		Increased airway sphingolipids, including ceramides, monohexosylceramide, and sphingomyelin	[39,40]
		Increased unsaturated hydroxy fatty acids, oxy fatty acids, and sulfated steroids in amniotic fluids	[41]
		Increased oxylipins in the umbilical cord blood	[42]
	Amino acid	Increased phenylalanine and methionine, reduced citrulline, glutamate, alanine, and tyrosine in blood	[49]
		Increased glutamic acid, histidine, citrulline, asparagine, glycine, and isoleucine in BPD tracheal aspirates	[50]
		Reduced threonine, arginine, methionine, and glutamine in blood	[34]
		Reduced S-adenosyl methionine in amniotic fluid	[41]
		Reduced taurine in both tracheal aspirates and urine	[28]
In vivo model	Glucose	Increased glycolysis and the PPP of endothelial cells in neonatal mice	[29]
		Inhibited function of complex I and II in isolated mouse lung mitochondria	[30,31]
	Lipid	Increased sphingolipid, glycerophospholipid, and glycerolipid species in the lung tissue of neonatal mice	[44]
		Increased ceramides and sphingolipids in bronchoalveolar lavage fluid	[45]
		Reduced Cpt1a in neonatal mice	[47,48]
	Amino acid	Reduced l-citrulline and l-arginine in rat blood	[51]
In vitro model	Glucose	Increased glycolysis and the PPP in MFLM-91U cells	[29]
		Reduced glycolytic capacity, glycolytic reserve, and oxidative phosphorylation in MLE-12 cells	[30]
		Increased glycolysis in cultured MLE-12 cells	[32]
BPD-associated PH			
Infants	Glucose	Increased G6P and phosphoenolpyruvate in umbilical cord blood	[42]
	Lipid	Reduced sphingomyelins and phosphatidylcholines, increased levels of nonadecanoic acid in the umbilical cord blood	[42]
	Amino acid	Reduced lysine, ornithine, and phenylalanine, and increased asparagine and creatinine	[42]
In vivo model	Glucose	Increased glycogen synthase kinase-3b in neonatal mice	[58]
	Lipid	Reduced total triacylglycerides, lysophosphatidylcholines, cholesterol esters, plasmalogen-phosphatidylcholines, and plasmalogen-phosphatidylethanolamines in rats	[59]
		Increased intermediate of β-oxidation and TCA cycle, and oxylipins in rats	[60]
Hyperoxia-associated brain injury			
Infants	Glucose	Reduced cerebral glucose metabolism	[63]
In vivo model	Amino acid	Accumulated glutamate in brains of rat pups	[8]
		Increased glutamate transporters in the rat brain	[65]
Hyperoxia-associated gut injury			
In vivo and in vitro model	Glucose	Increased lactate dehydrogenase activity in neonatal mice	[76]
		Increased d-lactic acid in intestinal tissues of rat and normal human colon mucosal epithelial cells	[71]
	Lipid	Increased intestinal fatty acid binding protein in intestinal tissues of rat and normal human colon mucosal epithelial cells	[71]
ROP			
Infants	Glucose	Increased glycolytic enzymes in photoreceptors	[79]
		Increased expression of glycolytic intermediates, and decreased metabolites of the TCA cycle in blood	[83,84]
	Lipid	Reduced DHA and arachidonic acid in blood	[81,82]
	Amino acid	Increased glycine in blood	[83,84]
Hyperoxia-associated cardiac injury			
In vivo model	Glucose	Decreased oxidative phosphorylation and increased markers of glycolysis in the rats' muscle tissue of the left ventricle	[85]
	Lipid	Reduced fatty acid synthesis in atrial cardiomyocytes of neonatal mice	[86]

lecithin [38], and elevated airway sphingolipids, including ceramides, monohexosylceramide, and sphingomyelin [39,40]. In addition to abnormal metabolism after birth, unsaturated hydroxy fatty acids, oxy fatty acids, and sulfated steroids are higher in the amniotic fluids of premature infants who developed BPD than in those of preterm infants with no BPD [41]. Moreover, Frano et al. reported elevated levels of oxylipins in the umbilical cord blood of BPD infants [42]. These observations suggest that dysregulation of lipid metabolism may begin during the fetal period. Furthermore, Carraro et al. reported that adolescents with BPD exhibit an altered complex lipid profile in their exhaled breath condensate, suggesting that long-term metabolic abnormalities may persist far beyond infancy [43].

In vivo studies of neonatal mice, hyperoxia altered the lung lipidome and elevated sphingolipid, glycerophospholipid, and glycerolipid species in the lung tissue, which may lead to alveolar simplification and dysregulated vascular development [44]. Tibboel et al. also reported a significant increase in multiple ceramides and sphingolipids in bronchoalveolar lavage fluid after exposure to hyperoxia [45]. Abnormal lipid metabolism may be associated with reduced adiponectin levels,

which modulate fatty acid oxidation. In a study by Shah et al., the addition of recombinant adiponectin to neonatal mice with BPD attenuated pulmonary vascular injury and improved pulmonary alveolarization and function [46]. Furthermore, Chang et al. found reduced levels of Cpt1a, known as a rate-limiting enzyme in the carnitine shuttle, in hyperoxia. Furthermore, upregulating the expression of Cpt1a using baicalin or L-carnitine ameliorated the BPD phenotype [47]. Yao et al. also observed reduced Cpt1a concentrations in endothelial cells of lung exposed to hyperoxia, accompanied by a decrease in fatty acid oxidation, which may be modulated by Cpt1a [48].

3.1.3. Dysregulated amino acid metabolism in BPD

BPD can lead to the dysregulation of amino acid metabolism; however, the specific changes and trends are still debated and require further research. In infants with BPD, Ye et al. observed upregulated phenylalanine and methionine but downregulated citrulline, glutamate, alanine, and tyrosine in blood samples throughout the early days of life [49]. However, Piersigilli et al. showed that glutamic acid, histidine, citrulline, asparagine, glycine, and isoleucine levels were higher in tracheal aspirates of BPD group [50]. Wang et al. observed decreased threonine, arginine, methionine, and glutamine levels in dried blood spots of BPD group [34]. Baraldi et al. found that S-adenosyl methionine, a precursor of the antioxidant glutathione and a methyl donor for biochemical methylation reactions, was lower in amniotic fluid in infants with BPD than in infants with on BPD [41]. In animal studies, L-citrulline and L-arginine levels were decreased in blood in rat exposed to hyperoxia [51]. The contrasting results among the studies may associated with the sample size, source, and basic neonatal conditions. Additionally, taurine was reduced in both the tracheal aspirates and urine samples of infants with BPD, indicating its potential as a new biomarker of BPD [28]. Urine metabolomics is becoming an increasingly popular research method because it is non-invasive and easy to perform.

3.2. Pulmonary hypertension

Pulmonary hypertension (PH) is a common complication of chronic respiratory diseases, including BPD, in premature infants. Here, we will only discuss the metabolic disorders associated with BPD-associated PH. BPD-associated PH often occurs in very low or extremely low-birth-weight infants who are chronically ventilator- or oxygen-dependent. It is characterized by a progressively greater need for respiratory support that is disproportionate to lung disease [52]. Moreover, PH can worsen the clinical course, morbidity, and mortality of BPD, resulting in a poor prognosis. The pathogenesis of BPD-associated PH may be related to alveolar dysplasia and an enhanced pulmonary vasoconstriction response. However, an important characteristic of PH is nitric oxide (NO), which plays a role in regulating pulmonary artery pressure. The conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) is decreased, and the activation of guanylate cyclase in vascular smooth muscle cells is reduced [53]. Neonates with PH typically require exogenous supplemental oxygen to maintain appropriate peripheral saturation of pulse oxygen; however, high oxygen exposure should be avoided. Exposure to hyperoxia affects the normal function of the NO-cGMP signaling pathway, leading to pulmonary vascular dysfunction, thereby exacerbating PH [54].

3.2.1. Dysregulated glucose metabolism in BPD-associated PH

Frano et al. reported increased levels of G6P and phosphoenolpyruvate in umbilical cord blood in the BPD-associated PH group, indicating enhanced glycolysis [42]. In vivo experiments, decreased levels of guanylate cyclase and cGMP were observed in a model of BPD-associated PH, which could be attributed to an increase in phosphodiesterase-5, a major cGMP-hydrolytic phosphodiesterase, and a reduction of cGMP. These changes were associated with glycogenolysis [55,56]. Additionally, aberrant cGMP signaling may persist even during recovery in mice with oxygen-induced PH [57]. Hummler et al. reported increased levels of glycogen synthase kinase-3b, which is associated with glycogen metabolism, in neonatal mice with BPD-associated PH [58].

3.2.2. Dysregulated lipid metabolism in BPD-associated PH

In clinical study, Frano et al. also observed a decrease in sphingomyelins and phosphatidylcholines in the umbilical cord blood of infants with BPD-associated PH, indicating altered phospholipid metabolism. They also reported increased levels of nonadecanoic acid, a saturated fatty acid with 19 carbons [42]. In vivo animal experiments, Frano et al. observed that total triacylglycerides, lysophosphatidylcholines, cholesterol esters, plasmalogen-phosphatidylcholines, and plasmalogen-phosphatidylethanolamines are reduced in rats under the condition of hyperoxia-induced PH [59]. Additionally, intermediate levels are increased in β-oxidation and the TCA cycle, and oxylipins are increased in rats during hyperoxia-induced PH. Oxylipins are metabolites of fatty acids generated through the oxygenation of polyunsaturated fatty acids [60].

3.2.3. Dysregulated amino acids metabolism in BPD-associated PH

In the cord blood of BPD-associated PH infants, there was a reduced in the levels of lysine, ornithine, and phenylalanine, while the levels of asparagine and creatinine increased [42]. In the plasma of newborns with persistent PH, concentrations of arginine, citrulline, and NO metabolites were low [61]. In vivo experiments, supplementation with L-citrulline was shown to prevent hyperoxia-induced PH in newborn rats through the L-citrulline-NO pathway, which represents a potential therapeutic target for protecting the lungs from impaired alveolar development [51]. Currently, there are limited studies analyzing changes in amino acid metabolism in BPD-associated PH, and further research is required to elucidate the alterations in amino acids under BPD-PH conditions.

3.3. Hyperoxia-associated brain injury

In addition to lung damage, hyperoxia can also cause brain damage. The extent of damage may be influenced by factors such as the duration of hyperoxia exposure after birth, brain maturity, and other factors. Hyperoxia-associated brain injury in preterm infants, especially very low and extremely low-birth-weight infants, can lead to permanent dysfunction of the nervous system and requires careful attention. Metabolism is crucial for providing energy to support the various cellular processes necessary for brain function and development. Ketone bodies and glucose are essential substrates that meet the metabolic and energetic demands of the immature and developing brain [62]. In a clinical study, Park et al. found that the regional cerebral glucose metabolic ratio was significantly lower in the right central region and right lateral temporal lobe of preterm infants receiving oxygen therapy [63]. Currently, there are limited studies investigating changes in neonatal brain metabolism under hyperoxia. In an adult study, it was observed that hyperoxia slightly reduced lactate levels in the brain tissue of patients with severe head injuries, suggesting that hyperoxia did not improve glucose oxidation and glycolysis likely remained the dominant pathway [64]. Animal studies have indicated that hyperoxia leads to glutamate accumulation in the brains of rat pups, potentially caused by increased oxidative stress and decreased levels of glutamate transporters [8]. Bigdeli et al. also reported that hyperoxia upregulates glutamate transporters in the rat brain, including excitatory amino acid transporter (EAAT)1, 2, and 3, as well as vesicular glutamate transporter (VGLUT) 1 and 2 [65]. Glutamate excitotoxicity is a primary cause of brain damage associated with premature birth. Additionally, glutamate is involved in synaptic formation and dissolution, neuronal migration, proliferation, and survival, all of which are crucial for brain development [66].

Microglia, which are intrinsic immune effector cells in the central nervous system, play a role in immune surveillance. Overactivation of microglia, as the main source of inflammatory factors, is central to the

occurrence of various nervous system diseases. Activated microglia can be categorized into M1 and M2 phenotypes, with M1 playing a pro-inflammatory role and M2 playing an anti-inflammatory role [67]. Hyperoxia-induced upregulation of ROS leads to the activation of M1 in microglia [68]. Inflammation exposure shifts metabolism from oxidative metabolism to aerobic glycolysis. It also increases the levels of G6P, promotes the PPP to produce amino acids and proteins, and inhibits the TCA cycle [69]. Currently, there are limited studies analyzing changes in the metabolism of neonates with hyperoxia-induced brain injury. Further research is necessary to clarify the specific changes and mechanisms involved.

3.4. Hyperoxia-associated gut injury

The gut is an anaerobic environment where the microbiota are susceptible to destruction by hyperoxia. The microbiota play a crucial role in producing various bioactive compounds, such as vitamins, amino acids, short-chain fatty acids, and metabolites. These compounds are essential for interconnected pathways involved in glycolysis, the TCA cycle, OXPHOS, as well as amino acid and fatty acid metabolism [70]. Upregulation of ROS also triggers inflammation and injury through different pathways, potentially leading to gut disorders such as necrotizing enterocolitis (NEC) [71]. Hyperoxia can disrupt the intestinal barrier, impair intestinal function, increase ileal mucosa thickness, and decrease the number of Paneth cells, goblet cells, and villi in the intestinal epithelium. It can also cause dislocation and dilation of the basal lateral epithelial space in newborn rats, significantly increase epithelial cell apoptosis, and result in increased mortality. The small intestine of newborns is particularly sensitive to excessive oxygen. Thus, exposure to postnatal hyperoxia in neonatal rats leads to damage to the small intestine and disruption of the intestinal barrier, indicating dysfunction of intestinal tight junctions. Damage to the intestinal barrier allows for lipopolysaccharide absorption and exacerbates bacterial invasion [72,73].

Currently, there is a lack of large-scale clinical studies investigating gut metabolism under hyperoxia. However, Li et al. observed that neonatal mice treated in vivo with DHA or arginyl-glutamine dipeptide exhibited less intestinal injury compared to a group with hyperoxia-induced intestinal injury. This finding suggests a metabolic disturbance of amino acids and fatty acids. Arginine reduces inflammation, enhances mucosal integrity, and promotes gut repair. Glutamine, by protecting the actin cytoskeleton, maintains intestinal barrier function and intercellular connections. Moreover, glutamine is synthesized from arginine, which serves as a precursor for other amino acids. The addition of arginine and glutamine can reduce the risk of NEC and alleviate intestinal damage [74,75]. Li et al. also noted a significant increase in lactate dehydrogenase activity in the hyperoxia group, indicating enhanced glycolysis [76]. Additionally, Liu et al. reported that hyperoxia caused injury to the rat intestinal mucosa and significantly increased the expression of d-lactic acid and intestinal fatty acid binding protein in intestinal tissues and normal human colon mucosal epithelial cells. Intestinal fatty acid binding protein controls lipid availability for specific metabolic processes and participates in most lipid-related biological activities [71].

3.5. Others

In addition to the nervous, respiratory, and digestive systems, retinal vascular development is highly vulnerable to hyperoxia, which can result in a high incidence of ROP in preterm infants. This condition is often complicated by oxygen therapy for respiratory diseases [77]. Recent studies have identified metabolic abnormalities in the occurrence and progression of ROP [78]. Despite the existence of many mitochondria, photoreceptors, which are a crucial component of the outer retina, primarily rely on aerobic glycolysis rather than OXPHOS for metabolism. Photoreceptors exhibit high levels of glycolytic enzymes that promote lactate production [79]. Deficiencies in lipids, including short- and long-chain fatty acids, can also contribute to retinal degeneration and abnormal retinal vascular development [80]. Hellström et al. observed a correlation between high serum DHA levels and less severe ROP in preterm infants [81]. Löfqvist et al. reported low levels of arachidonic acid in preterm infants with ROP [82]. Yang et al. discovered increased expression of glycolytic intermediates such as pyruvate and lactate in an ROP group, along with decreased metabolites of the TCA cycle, such as citrate, aconitate, and succinylcarnitine, and increased levels of glycine and malonylcarnitine [83,84].

Hyperoxia can also induce cardiac injury. Rats exposed to hyperoxia exhibit decreased oxidative phosphorylation and increased markers of glycolysis in the muscle tissue of the left ventricle [85]. Cohen et al. found that hyperoxia reduced fatty acid synthesis in atrial cardiomyocytes, leading to inhibited cell proliferation and survival [86]. However, there are limited studies analyzing abnormal lipid metabolism in the liver and kidneys [87]. In conclusion, the multi-system damage caused by hyperoxia in neonates can result in metabolic abnormalities across multiple systems. Therefore, regulating metabolism may be a potential target for future treatments (Fig. 2).

4. Potential pathogenesis of metabolic reprogramming in hyperoxia-associated neonatal diseases

4.1. Role of mitochondria in metabolic reprogramming

4.1.1. Role of mitochondrial ROS

Hyperoxia increases the generation of reactive oxygen species (ROS) [88], which are produced in various cellular structures, including mitochondria, endoplasmic reticulum, plasma membrane, and peroxisomes. While other sources of ROS should not be disregarded, mitochondria-generated ROS are the primary contributors and have been shown to play a significant role in both cell signaling and detrimental processes, particularly under conditions such as hyperoxia [89]. Three decades ago, Saugstad introduced the concept of newborn oxygen radical diseases or neonatal oxidative stress diseases (NOSDs) [90]. This term does not refer to a single disease like ROP, brain injury, BPD, or NEC, but encompasses different manifestations of a single disease in which organs suffer severe injury from the common pathogenic mechanism of oxygen free radicals. Subsequently, extensive research has focused on neonatal diseases and mitochondrial ROS (mtROS) [91].

mtROS can upregulate the expression of hypoxia-inducible factor 1α (HIF-1α) [92,93]. HIFs are transcription factors that respond to changes in cellular oxygen levels and play a crucial role in cellular oxygen balance. HIF-1α is the most significant member of the HIF family and regulates the biological functions of various cells in hypoxic environments. In cancer, HIF-1α can modulate glucose metabolic reprogramming through glucose transporters (GLUT1 and GLUT3), glycolytic enzymes (e.g., HK1, HK2, Eno1, and PKM2), and lactate dehydrogenase (LDHA) [94]. HIF-1α can also promotes lung development in immature fetuses [95]. Although HIF-1α is necessary for lung development, excessive HIF-1α can have counterproductive effects. Animal studies have demonstrated increased HIF-1α levels in BPD models [96]. Furthermore, mtROS can activate NOX1 in BPD mice [97]. NOX1 is an NADPH oxidase associated with glucose metabolism, and its inhibitors significantly suppress aerobic glycolysis [98]. Similar findings have been reported in ROP [99]. Another study indicated that nuclear factor erythroid 2-related factor 2 (Nrf2), which participates in the regulation of glycolysis, fatty acid, glutamine, and glutathione metabolism, can be activated by mtROS in lung and brain injuries induced by hyperoxia. This factor also promotes the expression of the glucose transporter GLUT1 and enhances glucose uptake [100,101].

In hyperoxia-associated brain injury, mtROS can downregulate silent information regulator family protein 1(Sirt1), a highly conserved protein that controls cellular processes related to metabolism and longevity [102]. Loss of Sirt1 enhances glycolytic capacity [103]. In

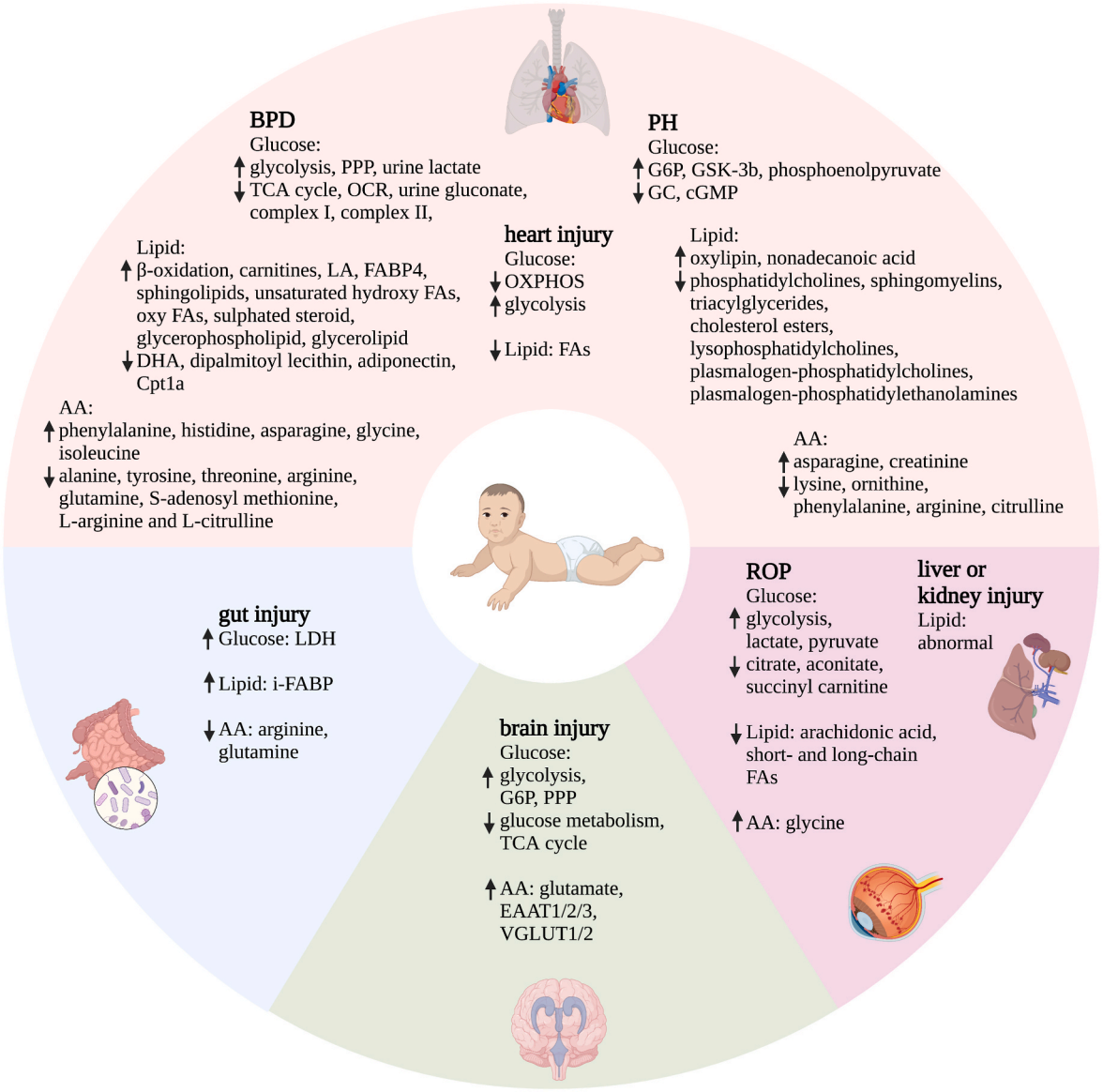

Fig. 2. Metabolic dysregulation in hyperoxia-associated neonatal diseases.
In the glucose metabolism of bronchopulmonary dysplasia (BPD), glycolysis, PPP, and urine lactate are increased, whereas in the TCA cycle, oxygen consumption rates, complex I, complex II, and urine gluconate are decreased. In the lipid metabolism of BPD, β-oxidation, carnitines, linoleic acid (LA), fatty acid binding protein 4 (FABP4), sphingolipids, unsaturated hydroxy fatty acids, oxy fatty acids, sulfated steroid, glycerophospholipid, and glycerolipid are increased, whereas docosahexaenoic acid, dipalmitoyl lecithin, adiponectin, and Cpt1a are decreased. In the amino acid metabolism of BPD, phenylalanine, histidine, asparagine, glycine, and isoleucine are increased, whereas alanine, tyrosine, threonine, arginine, glutamine, S-adenosyl methionine, L-citrulline, and L-arginine are decreased. In the glucose metabolism of BPD-associated pulmonary hypertension (PH), G6P, phosphoenolpyruvate, and glycogen synthase kinase-3b (GSK-3b) are increased, whereas guanylate cyclase and cGMP are decreased. In the lipid metabolism of BPD-associated PH, nonadecanoic acid and oxylipin are increased, whereas phosphatidylcholines, sphingomyelins, cholesterol esters, lysophosphatidylcholines, triacylglycerides, plasmalogen-phosphatidylcholines, and plasmalogen-phosphatidylethanolamines are decreased. In the amino acid metabolism of BPD-associated PH, asparagine and creatinine are increased, whereas lysine, ornithine, phenylalanine, arginine, and citrulline are decreased. In the glucose metabolism of hyperoxia-associated brain injury, glycolysis, G6P, and PPP are increased, whereas glucose metabolism and the TCA cycle are decreased. In the amino acid metabolism of hyperoxia-associated brain injury, glutamate, excitatory amino acid transporter (EAAT) 1, 2, and 3, and vesicular glutamate transporter (VGLUT) 1 and 2 are increased. In the glucose metabolism of hyperoxia-associated gut injury, lactate dehydrogenase (LDH) is increased. In the lipid metabolism of hyperoxia-associated gut injury, the intestinal fatty acid binding protein (i-FABP) is increased. In the amino acid metabolism of hyperoxia-associated gut injury, arginine and glutamine are decreased. In the glucose metabolism of retinopathy of prematurity (ROP), glycolysis, lactate, and pyruvate are increased, whereas citrate, aconitate, and succinyl carnitine are decreased. In the lipid metabolism of ROP, arachidonic acid and short- and long-chain fatty acids are decreased. In the amino acid metabolism of ROP, glycine is increased. Hyperoxia also causes heart, liver, and kidney injury by metabolic reprogramming, although few studies have analyzed this mechanism. Image generated using Bio-Render software.

hyperoxia-associated gut injury, excessive mtROS activates nuclear factor- κB (NF- κB) and tumor necrosis factor (TNF) pathways, which are associated with inflammation, promote inflammatory cascades, and cause mucosal damage [72]. NF-κB and TNF pathways can also regulate aerobic glycolysis [104,105]. Additionally, mtROS can directly interact with glycolytic enzymes, such as HK2, PDH, and α-KGDH [106]. Enzymes involved in lipid metabolism, including fatty acid synthase and hydroxymethylglutaryl-CoA (HMG-CoA) synthase, are downregulated [107,108]. Similarly, enzymes related to amino acid metabolism, such as glutamate dehydrogenase and aspartate aminotransferas, are

influenced by mtROS, and glutamate dehydrogenase is upregulated and aspartate aminotransferase is downregulated [109,110]. mtROS represents one of the most significant mechanisms of metabolic reprogramming in neonatal diseases induced by hyperoxia.

4.1.2. Role of mitochondria dynamics

Mitochondria, which are crucial organelles involved in biosynthesis, energy metabolism, and signal transduction, rely on mitochondrial dynamics for their functional state. This includes the generation of new mitochondria, the dynamic equilibrium between fusion and division, and the degradation of damaged mitochondria through mitophagy. Disruptions in mitochondrial dynamics can lead to disease, and alterations in mitochondrial dynamics play a significant role in the occurrence and development of neonatal diseases [111,112]. Mitochondria regulate the size, quantity, and morphology of mitochondria by continuously fusing and dividing, facilitating the exchange of mitochondrial DNA, proteins, lipids, and metabolites to convey information [113]. The fusion process involves merging the mitochondrial outer and inner membranes due to the bilayer membrane structure of mitochondria [114]. The fusion of the inner mitochondrial membrane is mediated by the dynamin-related GTPase Optic Atrophy 1 (OPA1), which regulates mitochondrial dynamics, energetics, mitochondrial DNA maintenance, and cristae integrity [115]. On the other hand, the fusion of the outer mitochondrial membranes is mediated by the dynamin-like GTPases Mitofusin 1 and Mitofusin 2 (Mfn-1 and Mfn-2), which share high degrees of homology and similar structural organization [116]. In hyperoxic cell models, it has been observed that hyperoxia significantly decreases the expression of Mfn-1 and Mfn-2, while increasing the expression of dynamin-related protein-1 (DRP1) in RLE-6TN cells compared to normoxia [117]. In vivo and in vitro studies of hyperoxia-induced acute lung injury, upregulation of Mfn-1 and Mfn-2 has been shown to aggravate lung damage and cell apoptosis [118]. Additionally, Mfn-1, Mfn-2, and OPA1 have been implicated in the regulation of glucose metabolic reprogramming [119–121].

During mitochondrial fission, a single mitochondrion divides into two smaller mitochondria, which undergo mitophagy [122]. This process helps prevent ROS overproduction and cell stress caused by the accumulation of damaged mitochondria. Mitochondrial fission involves multiple steps, including the marking of a fission site, the assembly of DRP1 dimers and oligomers into a helical structure, GTP hydrolysis, and constriction of the DRP1 helix. The cytosolic GTPase DRP1 is the primary initiator of mitochondrial fission [123], playing a crucial role in regulating cell proliferation, ROS production, and mitochondrial quality control through mitophagy and apoptosis [124]. Unlike conventional dynamins, DRP1 lacks the pleckstrin homology domain that interacts with lipids. Consequently, it can only attach to the mitochondrial membrane by forming a functional complex with its receptor, which is later converted into a larger oligomer and transported to fission sites [125]. Fission 1 (FIS1), mitochondrial fission factor (MFF), and the mitochondrial dynamic proteins of 49 kDa and 51 kDa (MiD49 and MiD51) are the four receptors and/or adapters located on the mitochondrial outer membrane that recruit DRP1 to the outer mitochondrial membranes [126]. Therefore, DRP1 represents a promising therapeutic target. In animal models of BPD induced by high oxygen levels (80–85% O2), during the crucial phase of alveolar formation, DRP1 expression and phosphorylation increased in lung tissues of newborn rats. Small pulmonary artery formation was improved and pulmonary hypertension was reduced with the addition of a mitochondrial division inhibitor-1 (Mdivi-1) [127]. In an in vitro study, pulmonary endothelial cells exhibited increased mitochondrial fragmentation under hyperoxic conditions, along with increased DRP1 phosphorylation and total DRP1 expression, and decreased Mfn1 expression. Additionally, hyperoxia increased OPA1 expression, which could be a compensatory mechanism to prevent mitochondrial fragmentation [128]. Several studies have demonstrated that DRP1 regulates metabolic reprogramming of glucose, lipids, and amino acids [129–131].

Mitophagy, also known as mitochondrial autophagy, is responsible for the selective removal of mitochondria damaged by ROS, cell aging, nutrient deficiency, and other factors. It serves as a crucial mechanism for maintaining mitochondrial and cellular homeostasis by controlling mitochondrial quality [132]. Current research proposes two main mechanisms of mitophagy: ubiquitin (Ub)-dependent and Ub-independent pathways. Among the Ub-dependent pathways, the PTEN-induced putative kinase 1 (PINK1)/Parkin pathway has been extensively studied [133]. The Ub-independent pathways involve several mitochondrial autophagic receptors that directly interact with the autophagosome membrane protein LC3 and microtubule-associated protein 1 light chain 3 via LC3 interaction region motifs, inducing mitophagy without significantly increasing ubiquitination [134]. These receptors mainly include NIX/BNIP3L, BNIP3, and FUNDC1 receptors in mammals [135,136]. The Ub-dependent and independent pathways can also interact with each other [137]. Wu et al. observed higher levels of PINK1, Parkin, BNIP3L/NIX, and LC3B in the lung tissue of newborn rats exposed to hyperoxia compared to normoxic rats [138]. Previous in vitro and in vivo studies have shown that hyperoxia in BPD animal models and RLE-6TN cells leads to a decrease in mitochondrial membrane potential, an increase in autophagosomes, and an upregulation of PINK1, Parkin, and LC3B expression [139,140]. PINK1, Parkin, BNIP3L, and NIX are also associated with glucose metabolic reprogramming, and PINK1 is involved in lipid metabolic reprogramming [140–142].

Currently, research on the relationship between mitochondrial dynamics and metabolic reprogramming mainly focuses on tumors, with limited studies conducted on neonatal diseases. Therefore, the distinct changes in these markers occurring in different diseases remain unclear and require further exploration (Fig. 3).

4.2. Cross talk of organs: potential role of the gut–lung–brain axis

Hyperoxia can damage multiple organs in newborns, especially the brain, lungs, and gut. In addition to direct damage, hyperoxia may also be related to the interaction between organs, including the regulation between microbiota and the immune network. Therefore, we suggest that a “gut–lung–brain” axis may exist in neonatal oxidative stress diseases.

Existing studies have focused on the role of the gut–lung axis in hyperoxia-associated lung injury. Hyperoxia can alter both lung and gut microbiota, leading to oxygen-induced lung injury [143]. Fan et al. observed that BPD mice exhibit gut microbiota disorders. Differential gene enrichment analysis showed that glycan biosynthesis and metabolism were among the top three metabolic pathways with significant differences [144]. Chen et al. reported that intestinal bacteria were present in the lungs of hyperoxia-induced neonatal mice, suggesting that hyperoxia could alter the microbiota of the intestine and lungs and promote bacterial translocation from the intestine to the lungs [145]. Moreover, Wedgwood et al. showed that hyperoxia-induced PH exhibits intestinal dysbiosis and can be attenuated by the administration of *Lactobacillus* [146]. In addition to the imbalance of microbiota, they also found that intestinal dysbiosis affects the developing lung through activation of the Toll-like receptor 4 pathway, suggesting that this pathway may be a key mechanism in the gut–lung axis [147]. Zhang et al. reported that a metabolite of gut microbiota, acetate, reduces inflammatory reactions and lung injury in BPD mice by inhibiting the upregulation of NACHT, LRR, and PYD domain-containing protein 3 (NLRP3) [148]. Ahn et al. observed that the intratracheal transplantation of mesenchymal stem cells in newborn rats reduced hyperoxia-associated lung injury and microbiota disturbance of the gut, lungs, and brain. The relative abundance of *Proteobacteria* increased whereas *Firmicutes* decreased in the brain, lungs, and gut of neonatal rats; these changes were significantly alleviated after treatment. The expression of interleukin-6 levels in the lungs was also positively correlated with the abundance of *Proteobacteria* in the gut, lungs, and brain, but negatively related to the abundance of *Bacteroidetes* in the

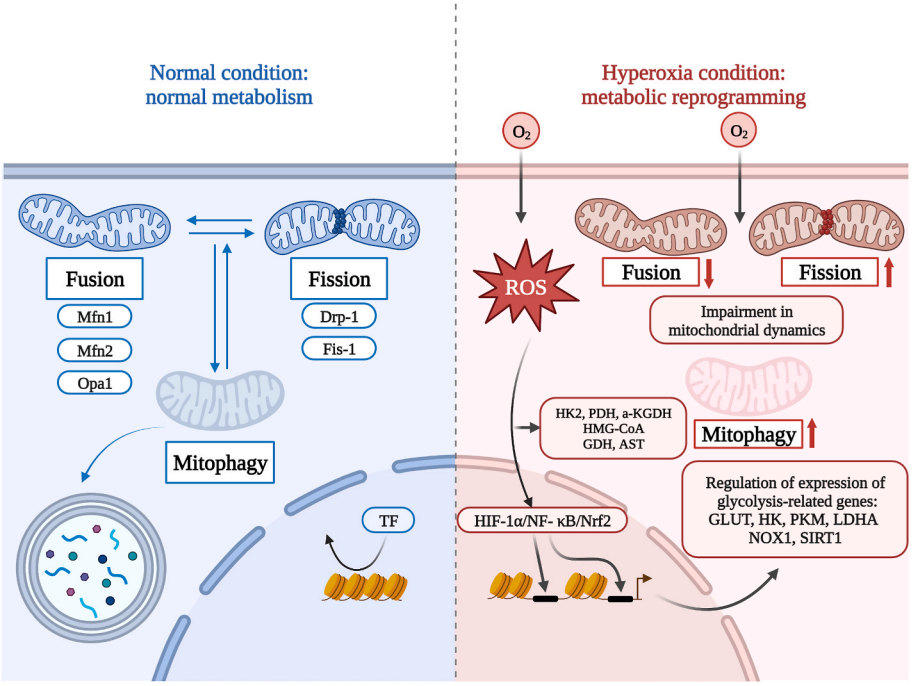

Fig. 3. Potential role of mitochondria in the metabolic reprogramming of hyperoxia-induced neonatal diseases. Hyperoxia increases the formation of mtROS, which can upregulate the expression of HIF-1α, which then regulates glucose metabolic reprogramming such as glucose transporters (GLUT1 and GLUT3), glycolytic enzymes (e.g., HK1, HK2, Eno1, PKM2), and lactate dehydrogenase (LDH). mtROS can also activate NOX1, nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor-κB (NF- κB), silent information regulator family protein 1 (Sirt1), and tumor necrosis factor (TNF) pathways. In addition, mtROS can directly interact with the enzymes of glycolysis, such as HK2, PDH, and α-KGDH, the enzymes of lipid metabolism, such as hydroxymethylglutaryl (HMG)-CoA and fatty acid synthase (FAS), and the enzymes of amino acid metabolism, such as glutamate dehydrogenase (GDH) and aspartate aminotransferase (AST). Hyperoxia will also change mitochondria dynamics; that is, mitochondrial fusion is reduced, whereas mitochondrial fission and mitophagy are enhanced. Image generated using Bio-Render software.

lungs and *Firmicutes* in both gut and lungs. Thus, interleukin-6 may be an important molecule in the regulation of the gut–lung–brain axis [149].

Although relatively rare, some studies have analyzed the role of the lung–brain and gut–brain axes in hyperoxia. Hyperoxia can impair the lungs and brain simultaneously [150]. Preterm infants with BPD typically have poor neurodevelopmental outcomes; however, the mechanistic links remain unclear. According to Kramer et al., decreased bioavailability of insulin-like growth factor (IGF)-1 may impact the lung–brain axis, disrupt the development of lungs and brain, and increase the vulnerability of preterm infants to serious pulmonary and neurocognitive morbidities [151]. Dapaah-Siakwan et al. suggested that the activation of caspase-1, a key component of the inflammasome, aggravates hyperoxia-induced lung and brain injury in neonatal mice, which might be a potential treatment target. After the inhibition of caspase-1, NLRP1 inflammasome activation decreases, and lung and brain injury is attenuated [152]. Neonatal BPD can also cause hippocampus neuronal apoptosis and impaired cognitive function through activation of the HIF-1α and p53 pathways [153]. Research on the neonatal gut–brain axis has focused on NEC, one of the most common gastrointestinal diseases in preterm infants, which is mainly caused by hypoxia. Studies have shown that an imbalance of microbiota in the gut affects the development and function of the brain via the gut–brain axis [154]. Although uncommon, increased ROS levels can lead to NEC. Therefore, the relevant mechanisms need to be elucidated. Therefore, despite the limited number of studies, current research suggests that regulation of the brain–lung–gut axis will be an important future treatment target for neonatal oxidative stress diseases (Fig. 4).

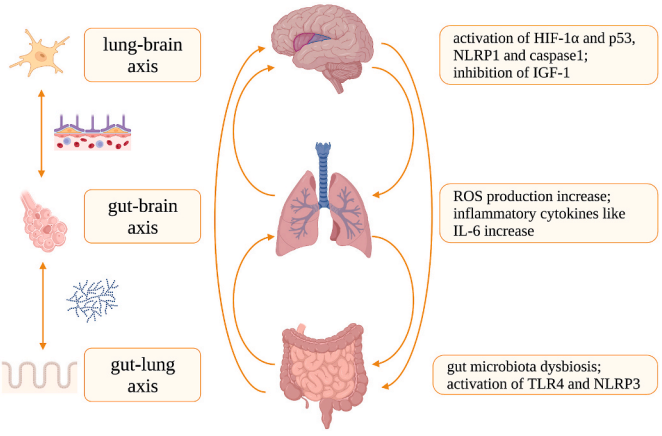

Fig. 4. Potential role of the gut–lung–brain axis in the metabolic reprogramming of hyperoxia-induced neonatal diseases. Hyperoxia can cause multiple-organ injury in neonates, including in the brain, lung, and gut. As well as direct damage, hyperoxia is also associated with the interaction between organs. Hyperoxia can activate the gut–lung axis, lung–brain axis, and gut–brain axis. Therefore, we suggest that a "gut–lung–brain" axis exists in neonatal oxidative stress diseases. Image generated using Bio-Render software.

5. Future research directions of biomarkers and therapeutic targets

Metabolic reprogramming was first proposed for tumors; however, a limited number of studies have reported metabolic reprogramming in neonatal hyperoxia-associated diseases. Changes in the levels and types of metabolites caused by changes in the metabolic pathways and metabolism-related regulatory molecules may be used as potential biomarkers to predict disease progression in hyperoxia-associated diseases. In a study by Kandasamy et al., maximal oxygen consumption rates were a significant predictor of all variables averaged across all feasible logistic regression models related to mortality or BPD. Maximal oxygen consumption of less than 200 pmol/min/3 × 104 cells, gestational age of less than 28 weeks, and birth weight of less than 850 g are all strongly predictive of mortality before discharge or BPD in preterm infants [27]. Moreover, Martin et al. reported that the fatty acid balance is an indicator of chronic lung disease of prematurity, whereby the risk of chronic lung disease of prematurity increased with an increase in the LA/DHA ratio [35]. Many metabolism-related enzymes and metabolites are altered in hyperoxia-associated diseases, as previously mentioned. However, this method has not yet been clinically investigated. Future research should focus on integrating metabolic profiling with multi-omics data, including RNA-seq, genomics, and proteomics, to identify possible biomarkers and treatment targets of newborns with hyperoxia-related injuries. Metabolic flux analysis, single-cell RNA

sequencing, and metabolomics can supply clues regarding metabolism dysregulation during the onset of illnesses. These innovative methods may provide a better understanding of the pathophysiology of disorders associated with hyperoxia.

Vadivel et al. reported that the addition of L-citrulline increased L-arginine and lung arginase activity and prevented hyperoxia-induced lung injury [51]. Treatment with L-carnitine can shorten the duration of mechanical ventilation and reduce the need for surfactants [155]. According to Hummler et al., administration of the glycogen synthase kinase-3b inhibitor can decrease pulmonary vascular remodeling and PH [52]. Tuzun et al. reported that omega-3 fatty acid supplementation improves apoptosis caused by hyperoxia in the developing rat brain [156]. DHA and eicosapentaenoic acid are the two major components of the omega-3 family and are closely associated with neurodevelopment. Zhong et al. reported that supplementation with omega-3 poly-unsaturated fatty acids (PUFA ω-3) effectively protects against infant PH induced by hyperoxia and can improve vascular remodeling and angiogenesis, which are low after birth [157]. However, few relevant studies involve interventions at the animal level; therefore, further research is needed to identify metabolic pathways or targets for preventing and/or treating hyperoxia-associated diseases in neonates.

6. Conclusions

Oxygen is commonly used as respiratory support in neonatal units. However, oxygen treatment presents a double-edged sword. While the goal is to provide sufficient oxygen to tissues without causing oxygen toxicity and oxidative stress, excessive oxygen therapy can lead to multi-system diseases in neonates. Unfortunately, the optimal oxygen levels for newborns and the safety of oxygen therapy remain unknown, necessitating greater attention to oxygen treatment in this population. Recent studies have revealed that hyperoxia can induce metabolic reprogramming, resulting in metabolic disorders across multiple organs in newborns, including disturbances in glucose, lipid, and amino acid metabolism. Abnormal metabolites may serve as biomarkers for predicting disease occurrence and potential targets for therapeutic intervention, indicating promising avenues for further research. Although the precise mechanisms underlying hyperoxia-induced metabolic reprogramming are not yet fully understood, mitochondria and the interplay between the lung, brain, and gut are believed to play significant roles. Extensive research is warranted to elucidate the mechanisms of metabolic reprogramming during hyperoxia and develop strategies for the prevention and treatment of hyperoxia-associated diseases in neonates.

Authors contributions

Jianhua Fu and He Zhang revised the manuscript; Tong Sun and Danni Li searched the literature, screened the studies, and extracted the data; Tong Sun wrote the manuscript; Haiyang Yu prepared the figures.

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Declaration of competing interest

The authors declare that there is no conflct of interest.

Data availability

No data was used for the research described in the article.

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