From oxidative stress to epigenetic regulation: Molecular mechanisms of preterm brain injury and neuroprotective strategies (Review)

YUYING LI[1], LING WEI[2], FANG SUN[3], HUIXIA WU[1], XIJUN SUN[4], YIRONG GAN[5] and XIAOHUA KONG[6]

[1]Department of Neonatology, Lanzhou First People's Hospital (Second Clinical Medical College of Gansu University of Chinese Medicine), Lanzhou, Gansu 730000, P.R. China; [2]Nursing Department, Lanzhou First People's Hospital (Second Clinical Medical College of Gansu University of Chinese Medicine), Lanzhou, Gansu 730000, P.R. China; [3]Department of Obstetrics and Gynecology, Lanzhou First People's Hospital (Second Clinical Medical College of Gansu University of Chinese Medicine), Lanzhou, Gansu 730000, P.R. China; [4]Medical Imaging Department, Lanzhou First People's Hospital (Second Clinical Medical College of Gansu University of Chinese Medicine), Lanzhou, Gansu 730000, P.R. China; [5]Cardiovascular Disease Research Institute, Lanzhou First People's Hospital (Second Clinical Medical College of Gansu University of Chinese Medicine), Lanzhou, Gansu 730000, P.R. China; [6]Department of Critical Care Medicine, Lanzhou First People's Hospital (Second Clinical Medical College of Gansu University of Chinese Medicine), Lanzhou, Gansu 730000, P.R. China

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Abstract. Preterm brain injury remains a leading cause of long-term neurodevelopmental impairment despite advances in neonatal care. Oxidative stress (OS), arising from mitochondrial dysfunction, nicotinamide adenine dinucleotide phosphate oxidase activation and iron-mediated Fenton reactions, selectively damages the developing brain because of immature antioxidant defenses and vulnerable oligodendrocyte progenitor cells. Critically, OS triggers enduring epigenetic modifications including DNA methylation alterations, histone acetylation changes and microRNA dysregulation, thereby translating acute perinatal insults into sustained changes in gene expression. The complex cellular interplay involving microglia, astrocytes and the neurovascular unit determines injury progression and repair capacity. Emerging neuroprotective strategies include antioxidant therapies, pathway-targeted agents and cell-based approaches, while artificial intelligence applications show promise for early risk stratification and personalized monitoring, although these tools remain under prospective validation. The present review synthesized current evidence on the pathological cascade from OS to epigenetic dysregulation in preterm brain injury, evaluated the latest advances in neuroprotective interventions and aimed to inform the development of precision-based, developmentally timed interventions that address the multifactorial nature of preterm

Correspondence to: Professor Xiaohua Kong, Department of Critical Care Medicine, Lanzhou First People's Hospital (Second Clinical Medical College of Gansu University of Chinese Medicine), 1 West Wujiayuan Street, Qilihe, Lanzhou, Gansu 730000, P.R. China
E-mail: 15593120923@163.com

Professor Yirong Gan, Cardiovascular Disease Research Institute, Lanzhou First People's Hospital (Second Clinical Medical College of Gansu University of Chinese Medicine), 1 West Wujiayuan Street, Qilihe, Lanzhou, Gansu 730000, P.R. China
E-mail: gyr0080@126.com

Abbreviations: 8-OHdG, 8-hydroxy-2'-deoxyguanosine; aEEG, amplitude-integrated electroencephalography; AI, artificial intelligence; AKT, protein kinase B; EPO, erythropoietin; GABA, γ-aminobutyric acid; HDAC, histone deacetylase; LPS, lipopolysaccharide; MSC, mesenchymal stem cell; NADPH, nicotinamide adenine dinucleotide phosphate; NIRS, near-infrared spectroscopy; NOX, NADPH oxidase; NPBI, non-protein-bound iron; Nrf2, nuclear factor erythroid 2-related factor 2; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; OPC, oligodendrocyte progenitor cell; OS, oxidative stress; PBI, preterm brain injury; PENUT, preterm erythropoietin neuroprotection trial; PPAR-γ, peroxisome proliferator-activated receptor gamma; pre-OL, pre-oligodendrocyte; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; TET, ten-eleven translocation; TGFβ-1, transforming growth factor-beta 1; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-alpha; TORPIDO, targeted oxygen for resuscitation of preterm infants and their developmental outcomes; XO, xanthine oxidase

Key words: preterm brain injury, oxidative stress, epigenetic regulation, neuroprotection, neuroinflammation, artificial intelligence, precision medicine, biomarkers

brain injury and improve long-term neurodevelopmental outcomes.

Contents

1. Introduction

Preterm birth remains a leading cause of neonatal mortality and long-term neurodevelopmental morbidity worldwide. Survival rates have improved substantially, particularly for extremely preterm infants, yet the burden of neurodevelopmental impairment among survivors remains a major public health challenge (1,2). Recent epidemiological data indicate that the prevalence of adverse outcomes, including cerebral palsy, cognitive deficits and behavioral disorders, does not decline commensurately with improved survival, underscoring the critical need for enhanced neuroprotective strategies (3,4).

The conceptual framework for understanding preterm brain injury has evolved considerably in recent decades. Historically, the predominant lesions were characterized as either cystic periventricular leukomalacia or hemorrhagic lesions originating in the germinal matrix. Contemporary neuroimaging and neuropathological studies, however, have revealed a more complex and diffuse pattern of injury. This is now conceptualized as the encephalopathy of prematurity, which encompasses both white matter dysmaturation and gray matter disturbances (5,6). Panfoli *et al* (7) systematically reviewed the role of free radical oxidative damage to the newborn brain and proposed that oxidative stress (OS) constitutes a primary risk factor for preterm brain injury. The authors emphasized the particular maturation-dependent vulnerability of oligodendrocyte precursors. This evolving understanding reveals that the preterm brain possesses unique developmental characteristics that render it selectively vulnerable to injury. Jiang *et al* (8) comprehensively examined the multifaceted aspects of OS in this context. The authors reported that preterm infants are particularly susceptible to inflammation and hypoxia because of their underdeveloped antioxidant systems, high brain metabolic demands in the brain, an immature blood-brain barrier and increased vulnerability to inflammation and hypoxia. Multiple converging pathways, including OS, neuroinflammation, excitotoxicity and cerebrovascular dysregulation, interact to produce the final common pathway of cellular injury and impaired maturation (9,10).

Among these interconnected pathological mechanisms, OS occupies a central position as both an early initiator and an amplifier of injury cascades. The immature brain possesses underdeveloped antioxidant defenses, high metabolic demand and vulnerability to inflammation. These factors converge to create a permissive environment for free radical-mediated damage (5). Critically, the consequences of OS extend beyond immediate macromolecular damage to encompass enduring modifications of the epigenome. Thus, acute perinatal insults are translated into sustained alterations in gene expression and cellular function. Scarpato *et al* (11) provide an overview of how oxidative genome damage can influence DNA methylation, thereby becoming a determinant of pathological conditions in the newborn. This establishes a direct molecular link between OS and epigenetic dysregulation. This conceptual bridge between acute oxidative injury and long-term epigenetic reprogramming offers new insights into the pathogenesis of preterm brain injury and identifies novel targets for intervention (12,13).

Despite the accumulating evidence, several unresolved controversies complicate the translation of these mechanistic insights into clinical practice. Chief among these is the question of causality: Does OS drive epigenetic reprogramming as a primary pathogenic event, or are the observed epigenetic changes predominantly secondary to systemic inflammation, hypoxia and other perinatal insults? The literature contains conflicting findings, with some studies reporting strong associations between oxidative biomarkers and epigenetic modifications, while others suggest that these associations are confounded by gestational age, nutritional status and genetic variability. Furthermore, the extent to which cell-type-specific epigenetic responses, rather than global changes, determine clinical outcomes remains poorly defined. These controversies are not merely academic; they have direct implications for biomarker selection, therapeutic targeting and trial design. The following sections synthesized the available evidence while explicitly highlighting areas of uncertainty and conflicting data.

The present review was organised around a central, unifying thesis: OS is not merely an acute cytotoxic event but a trigger for enduring epigenetic reprogramming that shapes the responses of all cellular players in the preterm brain. Accordingly, the present review proceeded through four interconnected domains. First, the sources and developmental vulnerability of the preterm brain to OS were examined. Second, the molecular mechanisms by which reactive species modify the epigenome, namely DNA methylation, histone modifications and non-coding RNAs, were integrated. Third, the cellular consequences of this OS (OS)-to-epigenetic axis were analysed across the major cell types (oligodendrocyte lineage, astrocytes, microglia, neurons and the neurovascular unit), with the gut-brain axis presented as an emerging systemic modulator. Fourth, neuroprotective strategies were critically evaluated according to which node of the OS epigenetic cascade they target. To guide the reader through this integrated framework, a conceptual diagram (Fig. 1) is provided that illustrates how OS, epigenetic regulation, cellular responses, neuroprotective interventions, AI-based monitoring and systemic modulators (including the gut-brain axis) converge within a unified pathogenic cascade. Within each domain, the discussion prioritized clinically actionable insights, biomarkers with prognostic value, interventions with completed or ongoing clinical trials and AI tools approaching clinical deployment,

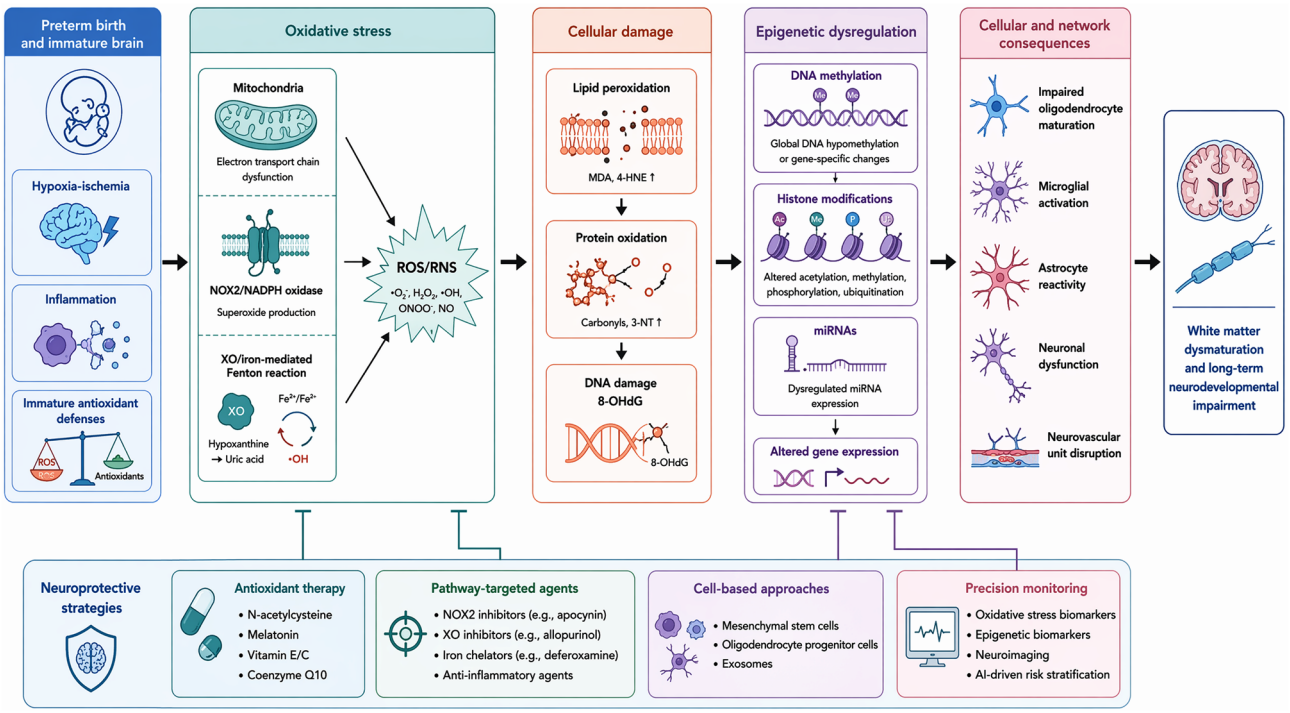

Figure 1. Integrated conceptual framework of preterm brain injury (www.figdraw.com; ID: TIRAT7295f). The diagram illustrates the unifying OS-epigenetic axis connecting OS sources, developmental vulnerabilities, epigenetic modifications, cellular responses, therapeutic interventions targeting specific cascade nodes and AI/monitoring tools within a unified pathogenic cascade. Mechanistic and preclinical findings provide the foundation for future translation, while clinically actionable elements (biomarkers, trialed interventions, validated tools) are prioritized. OS, oxidative stress; AI, artificial intelligence; OPC, oligodendrocyte progenitor cell; ROS, reactive oxygen species; RNS, reactive nitrogen species; NADPH, nicotinamide adenine dinucleotide phosphate; NOX, NADPH oxidase; XO, xanthine oxidase; NPBI, non-protein-bound iron; TET, ten-eleven translocation; HDAC, histone deacetylase; DNMT, DNA methyltransferase; miRNA, microRNA; MSC, mesenchymal stem cell; aEEG, amplitude-integrated electroencephalography; NIRS, near-infrared spectroscopy.

while mechanistic and preclinical findings were presented as the basis for future translation. Throughout the present review, the hierarchy of evidence was observed: clinical findings (from prospective cohorts, randomized controlled trials and meta-analyses) were presented as the strongest evidence; case-control and cross-sectional studies were identified as associative; and preclinical findings (animal models and cell culture) were presented as mechanistic insights that require clinical validation. To enhance transparency, the evidence type (clinical or preclinical) for each study was systematically provided in Tables I-III under the 'Model system' column. In the main text, clinical evidence was signaled by descriptive terms (such as 'clinical cohort', 'randomized controlled trial'), whereas preclinical evidence was identified as 'animal model' or 'mechanistic study'. At the end of each major section, a summary statement highlighted the principal clinical findings and directed the reader to the corresponding tables for detailed source classification.

2. Molecular mechanisms of OS in the preterm brain

The developing brain of preterm infants is particularly susceptible to OS, a condition arising from an imbalance between the production of reactive oxygen and nitrogen species (ROS/RNS) and the capacity of antioxidant defense systems. This vulnerability is not merely a consequence of one single factor but results from a convergence of developmental, physiological and pathological elements that collectively disrupt redox homeostasis. The following sections detailed the primary sources of OS, the inherent vulnerabilities of the preterm brain, the consequential molecular damage and the intricate interplay with other injurious pathways. A summary of the major sources and targets of OS in this context was presented in Fig. 2.

Sources of ROS/RNS. The genesis of OS in the preterm brain is multifactorial, with several key enzymatic and non-enzymatic sources contributing to the ROS/RNS burden. Mitochondria are primary contributors, as electron leakage from the electron transport chain, particularly during the rapid but often inefficient oxidative phosphorylation required for neurodevelopment, generates superoxide anions (14,15). This is compounded by the immature regulation of this process. Beyond mitochondria, the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) family of enzymes plays a significant role. Investigations have shown that NOX enzymes are activated in neuroinflammatory conditions, with neuronal NADPH oxidase 1 contributing to injury in models of cerebral ischemia (16).

Following hypoxia-ischemia, the enzyme xanthine oxidase (XO) is another major source of ROS, generated during the reperfusion phase when molecular oxygen is reintroduced to tissues with accumulated hypoxanthine (17). The phase III ALBINO trial (NCT03162653), an investigator-initiated, randomized, placebo-controlled, double-blinded, multi-national trial, is currently evaluating allopurinol as an adjunct to therapeutic hypothermia for hypoxic-ischemic encephalopathy; the detailed statistical analysis plan has been

Table I. Cell-type specific responses and mechanisms in preterm brain injury.

First author/s, year	Cell type	Model system	Mechanism	Key finding	Outcome	(Refs.)
Srivastava *et al*, 2018	OPC	Mouse model	TLR/AKT/FoxO3 signaling	A TLR/AKT/FoxO3 immune tolerance-like pathway disrupts the repair capacity of OPCs.	Impaired OPC maturation and repair	(66)
Boccazzi *et al*, 2021	Oligodendrocyte	Murine model of PWMI	TLR3 activation	TLR3 activation in oligo-dendrocytes triggers a pro-inflammatory response compromising their survival.	Pro-inflammatory response, reduced survival	(67)
Al-Griw *et al*, 2021	Oligodendrocyte lineage	Ex vivo rat ischemia model	Ionotropic GluR signaling	Inhibition of ionotropic glutamate receptor signaling preserves the oligodendrocyte lineage.	Preservation of oligoden-drocyte lineage and myelination	(68)
Chang *et al*, 2018	OPC	Rat model	IUGR + hyperoxia	Intrauterine growth restriction combined with postnatal hyperoxia induces WMI via OPC disruption.	White matter injury	(69)
Lin *et al*, 2023	Oligodendrocyte lineage	Neonatal rat HI model	Hypoxic-ischemic injury	Characterized dynamic changes in oligodendrogenesis after HI injury, revealing temporal windows of vulnerability.	Limited regenerative capacity, temporal vulnerability	(70)
Parfenova *et al*, 2018	Astrocyte	Newborn pig model	Carbon monoxide production	Astrocyte-produced carbon monoxide protects against cerebrovascular dysfunction after neonatal asphyxia.	Cerebrovascular protection	(71)
Nobuta *et al*, 2012	Astrocyte	Mouse model of neonatal brain injury	STAT3 signaling, TGFβ-1 modulation	STAT3-mediated astrogliosis protects myelin development by modulating microglial TGFβ-1 expression.	Protection of myelin development	(72)
Renz *et al*, 2024	Astrocyte	Perinatal mouse model	Reactive astrogliosis	Neuroinflammatory reactive astrocyte formation correlates with adverse outcomes in perinatal WMI.	Adverse clinical trajectory	(73)
Fang *et al*, 2020	Neurovascular unit (incl. astrocytes)	Neonatal rat HI model	FGF10 signaling	FGF10 protects the neurovascular unit, including astrocytes, in neonatal HI injury.	Neurovascular protection	(74)
Xu *et al*, 2025	Astrocyte	Mouse WMI model	HDAC3 inhibition, iron homeostasis	Targeting HDAC3 suppresses ferroptosis and demyelination partly through restoring astrocytic iron homeostasis.	Reduced ferroptosis and demyelination	(60)

Table I. Continued.

First author/s, year	Cell type	Model system	Mechanism	Key finding	Outcome	(Refs.)
Yang *et al*, 2022	Microglia	Neonatal rat HI model	Microglial polarization (toward anti-inflammatory)	Caffeine treatment reduces HI white matter damage by regulating phenotypic microglial polarization.	Reduced white matter damage	(76)
Charriaut-Marlangue *et al*, 2018	Microglia	Mouse model of neonatal stroke	PARP inhibition, sex-specific responses	Identified sex differences in microglial phenotypes following neonatal stroke.	Differential microglial activation	(77)
Zaghloul *et al*, 2020	Microglia	Rat HI model	NF-κB inhibition	Prophylactic inhibition of NF-κB expression in microglia attenuates HI injury.	Reduced hypoxic-ischemic injury	(78)
Mairesse *et al*, 2019	Microglia	Mouse model of perinatal brain injury	Oxytocin receptor activation	Oxytocin receptor agonist reduces perinatal brain damage by directly targeting microglia.	Reduced brain damage	(79)
Van Steenwinckel *et al*, 2019	Microglia	Developing mouse brain	Wnt/β-catenin signaling	Decreased microglial Wnt/β-catenin signaling drives pro-inflammatory activation in the developing brain.	Pro-inflammatory microglial activation	(80)
Bernis *et al*, 2022	Microglia	Neonatal HI mouse model	Temporal gene expression dynamics	Temporally characterized microglia-associated gene expression in a sensitized HI model.	Inflammatory and anti-inflammatory gene regulation	(81)
Sathyanesan *et al*, 2018	Neuron (Purkinje)	Mouse model of neonatal brain injury	Cerebellar circuit disruption	Neonatal brain injury causes cerebellar learning deficits and Purkinje cell dysfunction.	Learning deficits, Purkinje cell dysfunction	(82)
Sathyanesan *et al*, 2021	Neuron (Purkinje)	Mouse model	Purkinje cell dysfunction	Disruption of neonatal Purkinje cell function underlies injury-related learning deficits.	Learning deficits	(83)
Scheuer *et al*, 2022	Neuron (interneuron)	Mouse model of neonatal hyperoxia	OS	Neonatal OS impairs cortical synapse formation and GABA homeostasis in parvalbumin-expressing interneurons.	Impaired synapse formation, GABA dysregulation	(26)
Lacaille *et al*, 2019	Neuron (interneuron)	Mouse model of neonatal brain injury	Impaired interneuron development	Demonstrated impaired interneuron development in a novel model of neonatal brain injury.	Long-term neuropsychiatric sequelae	(84)
Sheikh *et al*, 2019	Neuron (subplate)	Mouse HI model	Circuit changes in subplate neurons	Neonatal HI causes functional circuit changes in subplate neurons.	Altered cortical development	(85)

Table I. Continued.

First author/s, year	Cell type	Model system	Mechanism	Key finding	Outcome	(Refs.)
Northington *et al*, 2022	Neuron (cholinergic)	Mouse HI model	Cholinergic system damage	Basal forebrain magnocellular cholinergic systems are damaged following neonatal HI in mice.	Long-term cognitive deficits	(86)
Lee *et al*, 2018	Neurovascular unit (endothelial)	*In vitro*/*In vivo* rat HI model	Endothelial resilience	Hypoxia-preconditioned human umbilical vein endothelial cells protect against neurovascular damage after HI.	Neurovascular protection	(87)
Chand *et al*, 2022	Neurovascular unit	Growth-restricted newborn lamb model	Hemodynamic modulation	Neurovascular unit alterations in growth-restricted newborns are improved following ibuprofen treatment.	Improved neurovascular structure	(88)
Fang *et al*, 2023	Neurovascular unit (BBB)	Neonatal rat HI model	BBB protection	Chloroquine protects against neonatal brain injury by mitigating blood-brain barrier disruption.	Reduced brain injury	(89)
Wang *et al*, 2020	Oligovascular unit	Neonatal mouse HI model	PI3K/AKT/mTOR signaling	Oligogenesis in the 'oligovascular unit' involves PI3K/AKT/mTOR signaling.	Oligogenesis	(90)
Seki *et al*, 2021	Gut-brain axis	Human cohort/ preterm neonates	Microbiota-immune-brain axis dysregulation	Aberrant gut-microbiota-immune-brain axis development occurs in premature neonates with brain damage.	Pro-inflammatory tone, brain damage	(91)
Drobyshevsky *et al*, 2024	Gut-brain axis	Mouse HI model	Microbiota modulation	Intestinal microbiota modulates neuroinflammatory response and brain injury after neonatal HI.	Altered neuroinflammation and brain injury	(92)
Liu *et al*, 2023	Gut-brain axis	Human VLBW infant cohort	Microbiota-gut-brain axis dysregulation	Multi-omics analyses reveal aberrant microbiota-gut-brain axis in VLBW infants with white matter injury.	White matter injury	(93)
Vaher *et al*, 2024	Gut-brain axis	Human preterm infant cohort	Microbiota profiles	The neonatal gut microbiota plays a role in the encephalopathy of prematurity.	Adverse neurodevelop-mental outcomes	(94)
Seki *et al*, 2024	Gut-brain axis	Human preterm infant cohort	Microbial genome features	Identified gut microbiota genome features associated with brain injury in extremely premature infants.	Brain injury	(95)

OPC, oligodendrocyte progenitor cell; PWMI, preterm white matter injury; TLR, toll-like receptor; AKT, protein kinase B; FoxO3, forkhead box O3; HI, hypoxia-ischemia; WMI, white matter injury; IUGR, intrauterine growth restriction; STAT3, signal transducer and activator of transcription 3; TGFβ-1, transforming growth factor-beta 1; FGF10, fibroblast growth factor 10; HDAC3, histone deacetylase 3; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PARP, poly (ADP-ribose) polymerase; BBB, blood-brain barrier; VLBW, very low birth weight.

Table II. Summary of neuroprotective strategies for preterm brain injury by mechanism and evidence level.

First author/s, year	Strategy category	Intervention/target	Model/population	Key findings	Evidence level	(Refs.)
Carloni *et al*, 2017	Antioxidant	Melatonin pharmacokinetics	Preterm neonates	Significant interindividual variability in absorption complicates dosing optimization	Clinical pharmacokinetic study	(100)
Domínguez Rubio *et al*, 2017	Antioxidant	Melatonin (maternal administration)	LPS-treated mouse model	Short- and long-term neuroprotective effects in offspring	Preclinical	(101)
Garofoli *et al*, 2024	Antioxidant	Melatonin (oral)	Preterm newborns	Reaches systemic circulation and reduces OS markers	Clinical pilot	(102)
Lee *et al*, 2019	Antioxidant	Melatonin	Mouse model of preterm birth	Prevented preterm birth and associated fetal brain injury	Preclinical	(103)
Ahmed *et al*, 2021	Antioxidant	Melatonin (systematic review)	Neonatal encephalopathy	Safety favorable but evidence insufficient; small samples, heterogeneity	Systematic review	(104)
Favrais *et al*, 2021	Antioxidant	Melatonin	Rat chorioamnionitis model	Partial protective effects only; monotherapy inadequate	Preclinical	(106)
Zmora *et al*, 2021	Antioxidant	N-acetylcysteine (maternal)	Rat NF-κB model	Prevents neonatal brain injury associated with NEC	Preclinical	(107)
Chavez-Valdez *et al*, 2025	Antioxidant	Vitamin C	Neonatal encephalopathy	Shows preclinical promise; clinical translation limited	Commentary/ Review	(108)
Al *et al*, 2020	Antioxidant	Uridine	Neonatal rat hyperoxic brain injury	Antioxidative effects demonstrated	Preclinical	(109)
Chen *et al*, 2024	Antioxidant	Nrf2 induction targeting mitochondria	Experimental models	Protects against preterm birth and fetal brain injury	Preclinical	(110)
Fischer *et al*, 2017	Pathway-targeted	Erythropoietin (meta-analysis)	Preterm infants	Reduces transfusions; neurodevelopmental evidence inconclusive	Meta-analysis	(113)
Juul *et al*, 2020	Pathway-targeted	High-dose erythropoietin	Extremely preterm infants	No significant difference in death or severe neurodevelopmental impairment at 2 years	RCT	(114)
Song *et al*, 2021	Pathway-targeted	Erythropoietin	Preterm infants with IVH	Improved outcomes in IVH subgroup	Clinical cohort	(116)
Jakab *et al*, 2019	Pathway-targeted	Early high-dose erythropoietin	Very preterm infants	Trophic effects on brain connectivity	Neuroimaging study	(117)

Table II. Continued.

First author/s, year	Strategy category	Intervention/target	Model/population	Key findings	Evidence level	(Refs.)
Wassink *et al*, 2017	Pathway-targeted	Prolonged erythropoietin infusion	Preterm fetal sheep (asphyxia)	Partial white and grey matter protection	Preclinical (large animal)	(118)
Ma and Shi, 2022	Pathway-targeted	Erythropoietin (review)	Premature brain injury	Clinical translation requires improved patient stratification	Comprehensive review	(119)
Endesfelder *et al*, 2017	Pathway-targeted	Caffeine	Neonatal rat hyperoxia model	Neuroprotection against hyperoxia-induced injury	Preclinical	(120)
Di Martino *et al*, 2020	Pathway-targeted	Caffeine (therapeutic window)	Neonatal mouse HI model	Early administration critical for efficacy	Preclinical	(121)
Fang *et al*, 2024	Pathway-targeted	PPAR-γ activation	Neonatal mouse HI model	Inhibits microglia-mediated neuroinflammation	Preclinical	(123)
Feng *et al*, 2023	Pathway-targeted	PPAR-γ activation (alpha-asaronol)	OPC culture and animal model	Promotes OPC differentiation and myelination	Preclinical	(124)
Prasad *et al*, 2021	Anti-inflammatory	Various agents (review)	Inflammation-related preterm brain injury	Numerous agents show efficacy; translation limited by complexity	Comprehensive review	(126)
Takahashi *et al*, 2023	Anti-inflammatory	IL-1 receptor blockade	Preterm fetal sheep LPS model	Suppressed neuroinflammation	Preclinical (large animal)	(127)
Bokobza *et al*, 2022	Anti-inflammatory	miR-146b	Perinatal brain injury model	Protects against microglia-induced hypomyelination	Preclinical	(128)
Rantakari *et al*, 2021	Clinical care	Oxygen saturation	Extremely preterm infants	Both low and high saturations associated with adverse outcomes	Clinical cohort	(129)
Oei *et al*, 2026	Clinical care	Targeted oxygen for resuscitation	Preterm infants	No significant difference; highlights complexity of titration	RCT	(130)
Engur *et al*, 2024	Clinical care	Supplemental oxygen	Developing mouse brain	Alters pentose phosphate pathway through SIRT signaling	Preclinical	(131)
Milette *et al*, 2017	Clinical care	Developmental care guidelines	NICU setting	Institutional implementation guidelines	Position statement	(132)
Murthy *et al*, 2020	Clinical care	Neuroprotection care bundle	Preterm infants	Reduced IVH rates following implementation	Quality improvement	(133)
Travis *et al*, 2025	Clinical care	Skin-to-skin holding	Preterm infants	Associated with improved white matter microstructure	Observational	(134)
Belfort and Inder, 2022	Clinical care	Human milk	Preterm infants	Breastfeeding associated with improved brain development	Narrative review	(135)

Table II. Continued.

First author/s, year	Strategy category	Intervention/target	Model/population	Key findings	Evidence level	(Refs.)
Brandt *et al*, 2025	Clinical care	Human milk oligosaccharides	Rat preterm brain injury model	Improve white matter and interneuron development	Preclinical	(136)
Drommelschmidt *et al*, 2017	Cell-based	MSC-derived extracellular vesicles	Inflammation-induced preterm brain injury model	Ameliorate injury	Preclinical	(141)
Thomi *et al*, 2019	Cell-based	MSC-derived exosomes (intranasal)	Perinatal brain injury model	Reduce microglia-mediated neuroinflammation	Preclinical	(142)
Ahn *et al*, 2018	Cell-based	Mesenchymal stem cells	Preterm infants with severe IVH	Phase I: feasibility and safety demonstrated	Phase I clinical trial	(143)
Romantsik *et al*, 2023	Cell-based	Stem cell interventions (Cochrane review)	Preterm infants	Preclinical evidence promising; clinical data insufficient	Systematic review	(144)
Tscherrig *et al*, 2024	Cell-based	miRNAs from MSC extracellular vesicles	White matter injury model	Rescue white matter injury after intranasal administration	Preclinical	(145)
Vaes *et al*, 2024	Cell-based	Modified MSC secretome	Encephalopathy of prematurity model	Prolongs regenerative treatment window	Preclinical	(146)

aEEG, amplitude-integrated electroencephalography; HI, hypoxia-ischemia; IVH, intraventricular hemorrhage; LPS, lipopolysaccharide; MSC, mesenchymal stem cell; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; OPC, oligodendrocyte precursor cell; RCT, randomized controlled trial; SIRT, sirtuin; TNF-α, tumor necrosis factor-alpha.

Table III. AI applications in preterm brain injury: Summary of key studies.

First author/s, year	Application area	AI Method/Model	Data source/ evidence type	Key findings	Primary advantage	(Refs.)
Ahmad *et al*, 2025	Neuroimaging (cranial ultrasound)	Convolutional neural networks (CNN)	Clinical (very preterm infant CUS dataset)	DL models classified CUS images as normal/abnormal in very preterm infants with AUC 0.86; proof-of-concept for computer-aided detection	Automated interpretation of routine screening tool; reduces inter-observer variability	(154)
Chen *et al*, 2024	Neuroimaging (MRI)	nnU-Net (automated segmentation)	Clinical (multi-institutional MRI dataset)	Developed automated neonatal brain MRI extractor trained on multi-institutional dataset; robust generalizability across clinical settings	High-throughput, standardized brain extraction; enables large-scale neuroimaging studies	(155)
Estermann *et al*, 2025	Neuroimaging (cranial ultrasound)	CACTUS multiview classifier	Clinical (CUS volumes)	Detected punctate white matter lesions in CUS volumes; addressed diagnostically challenging task with neuro-developmental implications	Automated detection of subtle pathology; multiview integration improves sensitivity	(156)
Wang *et al*, 2023	Neuromonitoring (aEEG/EEG)	Automated quantitative feature extraction	Clinical (10-year cohort of preterm infants)	Quantitative aEEG features predicted long-term neuro-developmental outcomes in extremely preterm infants; automated extraction matched expert interpretation	Real-time bedside prognostication; reduces need for expert EEG interpretation	(157)
Abbasi *et al*, 2024	Neuromonitoring (EEG)	Deep learning with wavelet-scalogram	Preclinical (fetal sheep HI model)	Developed seizure detection models for post-hypoxic-ischemic EEG in preclinical models	High sensitivity for seizure patterns; generalizable across species	(158)
Roozbehi *et al*, 2024	Neuromonitoring (EEG)	Transformer-based architecture	Preclinical (fetal sheep EEG data)	Refined seizure pattern recognition using transformer models; improved accuracy over conventional deep learning	Captures temporal dependencies in EEG; superior pattern recognition	(159)
Ashoori *et al*, 2023	Neuromonitoring (NIRS)	Machine learning classification	Clinical (preterm infant NIRS data)	Data-driven definitions of prolonged desaturation outperformed threshold-based approaches for IVH detection	Objective, physiology-based risk stratification; identifies subtle hemodynamic instability	(160)

Table III. Continued.

First author/s, year	Application area	AI Method/Model	Data source/ evidence type	Key findings	Primary advantage	(Refs.)
Hibner *et al*, 2026	Multimodal monitoring	Integrated signal analysis (echocardiography, NIRS, electrical cardiometry)	Clinical (preterm infant cohort)	Multimodal approach provided complementary information unavailable from any single modality for IVH prediction	Comprehensive hemodynamic assessment; captures multi-system physiology	(161)
He *et al*, 2025	Predictive modelling (brain injury risk)	CatBoost with SHAP (PBIPred model)	Clinical (prospective cohort of 650 infants)	Developed explainable ML model using 7 clinical features; AUC 0.8229 for PBI prediction; online webserver available	Interpretable predictions at individual patient level; clinically deployable tool	(162)
Yang *et al*, 2024	Predictive modelling (IVH/mortality)	Machine learning (multiple algorithms)	Clinical (nationwide multicenter cohort)	Nationwide multicenter study; robust prediction of early mortality and severe IVH in VLBW infants	Large, representative cohort; generalizable findings	(163)
Han *et al*, 2024	Predictive modelling (IVH)	Time-series machine learning	Clinical (preterm infant physiological data)	Temporal dynamics of physiological data improved IVH prediction compared with static variables alone	Captures evolving physiological instability; dynamic risk assessment	(164)
Song *et al*, 2025	Predictive modelling (WMI)	Ensemble machine learning	Clinical (extremely preterm infant cohort)	Two risk assessment models for WMI in extremely preterm infants; ensemble methods outperformed single algorithms	Robust methodology; comparison of multiple modelling approaches	(165)
Shu *et al*, 2025	Predictive modelling (multimorbidity)	Machine learning (multiple algorithms)	Clinical (VLBW infant dataset)	Predicted mortality and multiple morbidities simultaneously using routinely collected data; comprehensive outcome prediction	Efficient use of existing data; multi-outcome prediction	(166)
Li *et al*, 2025	Prognostication (neurodevelopmental outcomes)	Functional connectivity analysis	Clinical (preterm infant MRI cohort)	Functional connectivity measures predicted outcomes in preterm infants without severe brain injury; identified risk despite normal conventional imaging	Sensitive to subtle network alterations; identifies 'hidden' risk	(167)

Table III. Continued.

First author/s, year	Application area	AI Method/Model	Data source/ evidence type	Key findings	Primary advantage	(Refs.)
Liu *et al*, 2024	Prognostication (brain age)	Graph convolutional neural networks	Clinical (preterm neonatal MRI data)	Predicted brain age; deviations from normative maturation trajectories explained outcomes more accurately than static injury assessments	Dynamic, trajectory-based assessment; captures maturational delay	(168)
Marinelli *et al*, 2024	Prognostication (cerebral palsy)	Machine learning (multiple algorithms)	Clinical (extreme preterm cohort, ages 2 & 10)	Compared predictions at ages 2 and 10 years; early predictions require refinement as children mature	Long-term follow-up; identifies temporal dynamics of prediction accuracy	(169)
Yuan *et al*, 2024	Prognostication (intellectual disability)	Nomogram development	Clinical (children with CP cohort)	Developed practical tool for predicting intellectual disability in children with cerebral palsy; enables early intervention targeting	Clinically applicable tool; user-friendly format	(170)
van Boven *et al*, 2025	Prognostication (neurodevelop-mental outcomes)	Machine learning with oxygenation vital signs	Clinical (preterm infant cohort)	Oxygenation dynamics improved prediction of neurodevelopmental outcomes at ages 2 and 5 years	Incorporates routinely monitored vital signs; long-term outcome prediction	(173)

AI, artificial intelligence; aEEG, amplitude-integrated electroencephalography; AUC, area under the curve; CNN, convolutional neural network; CP, cerebral palsy; CUS, cranial ultrasound; DL, deep learning; EEG, electroencephalography; IVH, intraventricular hemorrhage; ML, machine learning; MRI, magnetic resonance imaging; NIRS, near-infrared spectroscopy; PBI, preterm brain injury; SHAP, Shapley Additive Explanations; VLBW, very low birth weight; WMI, white matter injury.

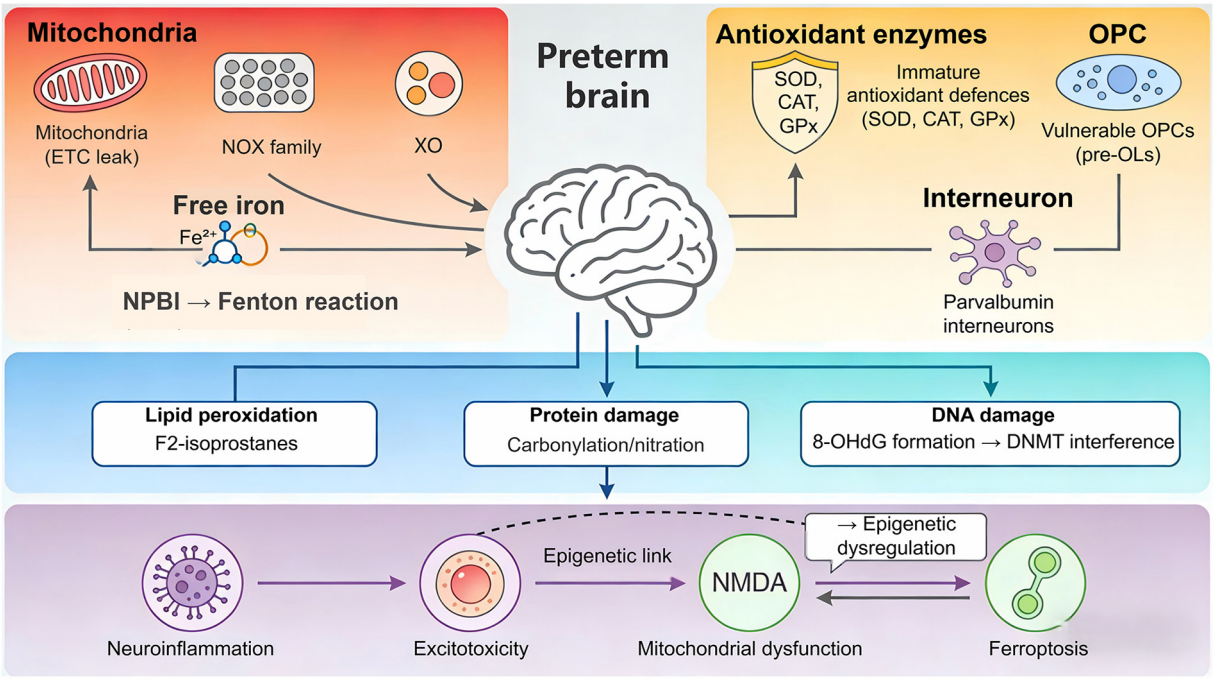

Figure 2. Sources, vulnerability and pathological cascades of OS in preterm brain injury (www.figdraw.com; ID: IWSTO44884). The schematic illustrates major sources of ROS/RNS in the preterm brain, including mitochondrial dysfunction, NOX activation, XO reaction and iron-dependent Fenton reactions. The immature antioxidant system and high susceptibility of OPCs render the preterm brain vulnerable to oxidative damage. OS triggers macromolecular injuries and interacts with neuroinflammation, excitotoxicity and ferroptosis, forming a vicious pathological cascade that exacerbates preterm brain damage. CAT, catalase; DNMT, DNA methyltransferase; ETC, electron transport chain; GPx, glutathione peroxidase; NMDA, N-methyl-D-aspartate; NOX, NADPH oxidase; NPBI, non-protein-bound iron; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; OPC, oligodendrocyte progenitor cell; pre-OL, pre-oligodendrocyte; PV, parvalbumin; ROS, reactive oxygen species; RNS, reactive nitrogen species; SOD, superoxide dismutase; OS, oxidative stress; XO, xanthine oxidase.

published, with the primary endpoint being long-term outcome determined as survival with neurodevelopmental impairment vs. death vs. non-impaired survival at 2 years of age (18). As Martini *et al* (19) and Hu *et al* (20) have detailed, free iron catalyzes the Fenton reaction, converting hydrogen peroxide into the highly toxic hydroxyl radical, thereby amplifying oxidative damage. The convergence of these diverse sources suggests that effective neuroprotection may require a multi-pronged approach rather than targeting any single enzymatic pathway, as the dominant source of ROS likely varies with the phase of injury and individual patient characteristics.

Developmental vulnerability of the preterm brain. The preterm brain possesses an inherent vulnerability to OS that distinguishes it from the mature brain. A critical factor is the underdevelopment of its antioxidant enzyme systems. As Tataranno *et al* (21) and Kletkiewicz *et al* (22) have discussed, the expression and activity of key enzymes such as superoxide dismutase, catalase and glutathione peroxidase are low in the preterm period, limiting the capacity to neutralize ROS. This is further exacerbated by the interruption of the maternal-fetal transfer of essential antioxidant cofactors like selenium, zinc and copper (21).

The cellular composition of the preterm brain also heightens its risk. Oligodendrocyte progenitor cells (pre-OLs), which are abundant in the periventricular white matter during the critical window of 24-32 weeks gestation, are exquisitely sensitive to OS. Pandya *et al* (23) demonstrated that hemoglobin exposure induces OS and mitochondrial dysfunction in these cells, while Sunny *et al* (24) showed that hyperoxia-induced damage in oligodendrocyte progenitor cells (OPCs) is mediated by specific molecular pathways, highlighting their fragility. Wellmann *et al* (25) have explored this concept, framing the vulnerability of white matter as a consequence of either too much or too little oxygen, both of which can disrupt myelination. Even neuronal subpopulations are not spared; Scheuer *et al* (26) provided evidence that neonatal OS, from relative hyperoxia, impairs cortical synapse formation and γ-aminobutyric acid (GABA) homeostasis in parvalbumin-expressing interneurons, potentially explaining long-term neuropsychiatric sequelae. This developmental window of susceptibility underscores that neuroprotective strategies must be timed precisely, as interventions effective in the mature brain may be ineffective or even harmful when applied during this period of unique cellular fragility and ongoing maturation.

Oxidative damage to cellular components. The unmitigated production of ROS and RNS in the vulnerable preterm brain leads to widespread damage to essential cellular macromolecules. Lipid peroxidation is a hallmark of this injury, as the brain's high content of polyunsaturated fatty acids makes it a prime target. The formation of F2-isoprostanes, stable end-products of lipid peroxidation, has been extensively studied. Negro *et al* (27) and Stolwijk *et al* (28) have independently shown that elevated levels of F2-isoprostanes in cord blood or postnatally are predictive of brain damage in term and preterm infants, respectively. Coviello *et al* (29) further linked higher plasma isoprostane levels with decreased functional brain activity on amplitude-integrated electroencephalography

(aEEG) in extremely preterm infants, providing a direct correlation between oxidative injury and early neurophysiological dysfunction.

Proteins are also susceptible, with ROS/RNS causing carbonylation and nitration, which can impair enzyme function and disrupt cellular signaling. Nucleic acids are not immune; the formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG) from DNA damage is a recognized marker of OS and can itself interfere with methyltransferase binding, linking OS directly to epigenetic dysregulation (14). The fact that oxidative damage simultaneously compromises lipids, proteins and DNA suggests that rescue strategies aimed at a single class of macromolecules are unlikely to be sufficient, reinforcing the need for interventions that bolster global cellular resilience rather than targeting isolated downstream effects.

Interplay with other pathological pathways. OS does not occur in isolation; it is intimately interconnected with other major pathological mechanisms of preterm brain injury. A central relationship exists between OS and neuroinflammation. Shin *et al* (30) showed that tumor necrosis factor-α (TNF-α) antagonism attenuates lipopolysaccharide (LPS)-induced white matter injury, underscoring the role of inflammatory cytokines. The interaction of OS with excitotoxicity is also well-established. Overactivation of N-methyl-D-aspartate receptors, as occurs in hypoxia-ischemia, leads to calcium influx and mitochondrial dysfunction, further promoting ROS production (31,32). Mitochondrial dysfunction itself is a critical hub, as highlighted by Odorcyk *et al* (33), who demonstrated age-dependent mitochondrial dysfunction and apoptosis following neonatal hypoxia-ischemia. This bioenergetic failure not only generates more ROS but also compromises cellular repair mechanisms.

Furthermore, OS is a key driver of ferroptosis, an iron-dependent form of regulated cell death, which Chang *et al* (34) reviewed in the context of hypoxia-associated brain injury. The interplay between these pathways creates a vicious cycle where OS amplifies inflammation and excitotoxicity, which in turn exacerbate OS, culminating in cell death and long-term neurodevelopmental impairment (35,36).

In summary, there is broad consensus that mitochondria, NADPH oxidase, xanthine oxidase and iron-mediated Fenton reactions are major sources of OS in the preterm brain and that the developmental vulnerability of OPCs and immature antioxidant defenses are key determinants of injury. However, significant controversies remain. The relative contribution of each OS source likely varies with gestational age, injury phase and clinical context, yet no study has systematically compared these sources across the same cohort. Furthermore, the extent to which OS acts as a primary driver vs. a secondary amplifier of injury, particularly in relation to neuroinflammation and excitotoxicity, remains unresolved. Key unanswered questions include the following: Which OS source is the most tractable therapeutic target; whether antioxidant strategies should be initiated before, during, or after the oxidative burst; and how OS interacts with genetic and epigenetic factors to determine individual susceptibility. Addressing these questions will require integrated multi-omics approaches and longitudinal cohort studies with serial biosampling.

The clinical evidence for oxidative biomarkers (such as F2-isoprostanes, 8-OHdG) and their association with brain injury comes primarily from prospective cohort and case-control studies in preterm infants (27-29), whereas the mechanistic sources of ROS and the developmental vulnerability of OPCs are largely derived from preclinical models (14-16,20,23,26).

3. From OS to epigenetic regulation: The molecular bridge

The previous sections have detailed how OS serves as a central hub of injury in the preterm brain, damaging cellular components and interacting with excitotoxicity and neuroinflammation. However, the effect of OS extends beyond immediate macromolecular damage. A growing body of evidence indicates that OS acts as a potent driver of enduring epigenetic modifications, establishing a molecular bridge that translates acute perinatal insults into sustained changes in gene expression, cellular function and ultimately, long-term neurodevelopmental outcomes. This section explored the epigenetic mechanisms most relevant to neurodevelopment, examined how OS alters the epigenetic landscape and amalgamated the evidence for specific modifications implicated in preterm brain injury. An overview of these key epigenetic changes is presented in Fig. 3.

Introduction to epigenetic mechanisms in neurodevelopment. Epigenetic mechanisms, including DNA methylation, histone modifications and non-coding (nc)RNAs, are fundamental regulators of gene expression that operate without altering the underlying DNA sequence. During brain development, these processes orchestrate critical events such as neural stem cell proliferation, neuronal and glial differentiation, synaptogenesis and the establishment of complex neural circuits (37,38). DNA methylation, the addition of a methyl group to cytosine residues in CpG dinucleotides, is typically associated with transcriptional repression when it occurs in promoter regions and is dynamically regulated by DNA methyltransferases and ten-eleven translocation (TET) demethylases (39). Histone modifications, such as acetylation, methylation and phosphorylation, alter chromatin structure and gene accessibility, with writers, erasers and readers of these marks determining the transcriptional output (40,41). microRNAs (miRNAs) provide an additional layer of post-transcriptional control by degrading or inhibiting the translation of target mRNAs (42,43). The exquisite temporal and spatial control of these processes render the developing brain particularly susceptible to environmental perturbations that can disrupt the normal epigenetic trajectory.

OS as a driver of epigenetic modifications. OS can directly and indirectly influence the establishment and maintenance of epigenetic marks. One primary mechanism involves the modification of enzymes that regulate the epigenome. For instance, the activity of TET enzymes, which catalyze DNA demethylation, is dependent on iron and α-ketoglutarate, making them vulnerable to redox imbalance (44,45). ROS can also cause DNA damage and the repair process itself can lead to the recruitment of DNA methyltransferases to the site of damage, potentially establishing aberrant methylation patterns (11,46).

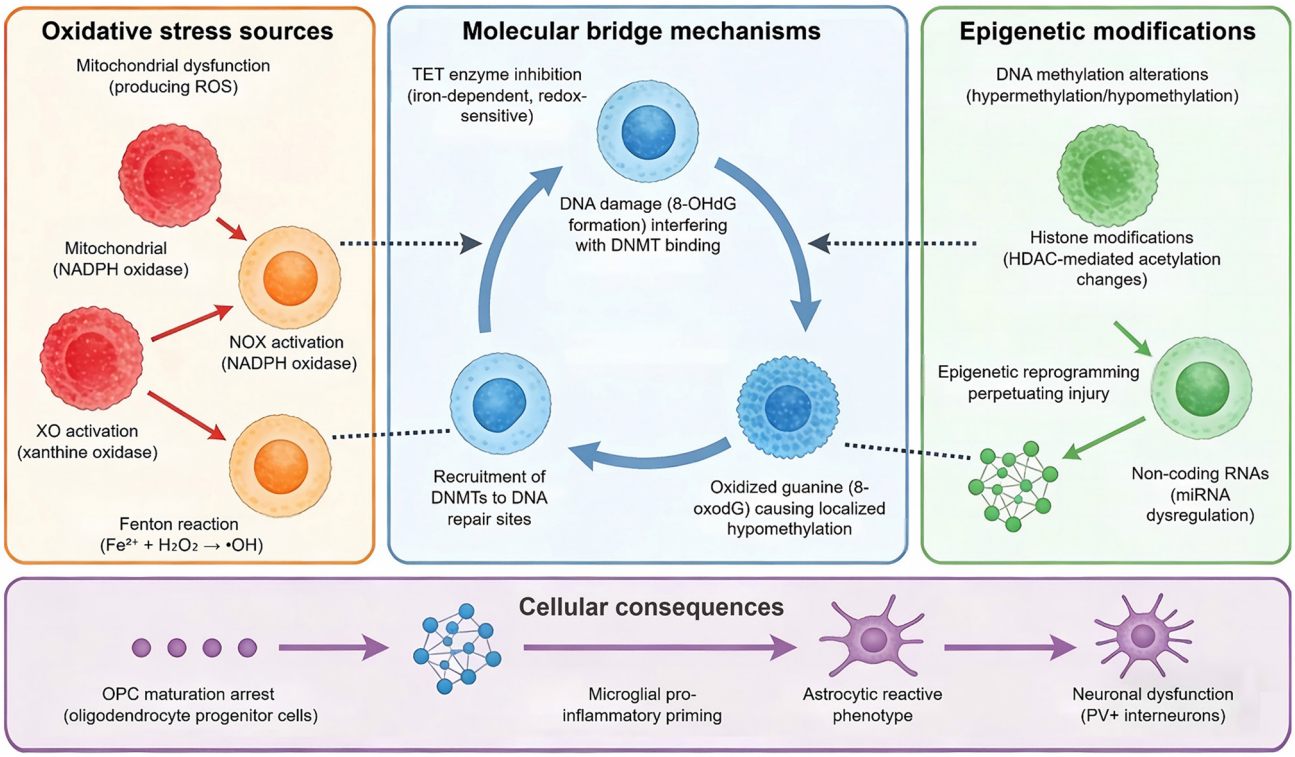

Figure 3. OS-induced epigenetic dysregulation and cellular pathologies in preterm brain injury (www.figdraw.com; ID: WWRAP27077). This diagram shows the molecular linkage between OS and epigenetic modifications in the preterm brain. ROS/RNS disrupts DNA methylation, histone modification and microRNA regulation via altering key epigenetic enzymes. Such persistent epigenetic reprogramming induces abnormal gene expression, triggers cell-specific pathological injuries and ultimately leads to long-term neurodevelopmental deficits in preterm infants. OS, oxidative stress; ROS, reactive oxygen species; RNS, reactive nitrogen species; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; 8-oxodG, 8-oxo-7,8-dihydro-2'-deoxyguanosine; DNMT, DNA methyltransferase; GABA, γ-aminobutyric acid; HAT, histone acetyltransferase; HDAC, histone deacetylase; NOX, NADPH oxidase; NPBI, non-protein-bound iron; OPC, oligodendrocyte progenitor cell; PV, parvalbumin; TET, ten-eleven translocation; XO, xanthine oxidase.

Furthermore, ROS can oxidize guanine bases in DNA to form 8-oxo-7,8-dihydroguanine, which can inhibit the binding of methyltransferases to adjacent CpG sites, leading to localized hypomethylation (47). Scarpato *et al* (11) provided an overview of how oxidative genome damage can be a determinant of pathological conditions in the newborn by influencing DNA methylation. This direct chemical interplay between ROS and the DNA methylation machinery underscores how an acute oxidative burst can have lasting consequences for the epigenome.

A critical question that emerges from these observations is whether the OS-driven epigenetic changes represent a primary pathogenic mechanism or a secondary epiphenomenon. The evidence for causality is strongest for TET enzyme inhibition and 8-oxodG formation, where direct chemical mechanisms have been established *in vitro* and in animal models. For TET enzymes, their dioxygenase activity is iron- and α-ketoglutarate-dependent, rendering them sensitive to redox imbalance. OS has been shown to upregulate TET1 expression and induce active DNA demethylation in human cells (48), while TET2 counteracts aberrant DNA methylation during OS through acetylation-dependent mechanisms (49). For 8-oxodG, this oxidative DNA lesion accumulates in GC-rich promoters and regulatory regions, where it can inhibit DNMT binding to adjacent CpG sites, recruit OGG1 to initiate repair processes and interfere with cytosine methylation. 8-oxodG has also been shown to interplay with histone modifications and DNA methylation through complex regulatory networks (50). However, for most histone modifications and non-coding RNA changes, the causal chain from OS to epigenetic mark to functional outcome remains inferential rather than proven. For histone modifications, OS has been shown to modulate HDAC activity in a context-dependent manner; activated microglia can decrease histone acetylation in astrocytes via increased HDAC activity (51), while specific HDAC isoforms (HDAC1-11) are expressed in glial cells and regulate the neuroinflammatory response. For non-coding RNAs, emerging evidence has revealed complex regulatory networks involving long non-coding (lnc)RNAs, miRNAs and mRNAs that are altered in association with inflammatory and OS markers in neonatal brain injury models, although direct causal relationships remain to be fully elucidated. Specific examples include miR-34c-5p, which attenuates apoptosis and OS following hypoxic-ischemic brain injury in neonatal mice by targeting Arhgap26 (52); miR-210, which promotes microglial pro-inflammatory activation through reprogramming mitochondrial metabolism (53); the lncRNA EVADR, which mitigates neonatal hypoxic-ischemic injury via the miR-145/WNT/β-catenin axis (54); and lncRNA GAS5, which prevents mitochondrial apoptosis through the miR-128-3p/Bax/Akt/GSK-3β axis (55). Circular RNAs (circRNAs) have also been implicated, with distinct expression patterns observed in the brain tissues of neonatal rats with periventricular white matter damage, suggesting that

circRNAs actively respond to hypoxic-ischemic insults (56). Moreover, the temporal relationship between OS exposure and epigenetic modification is rarely examined in human studies; cross-sectional designs cannot distinguish whether methylation changes precede or follow injury. This ambiguity has practical consequences: If epigenetic changes are predominantly secondary to established injury, then targeting them therapeutically may offer limited benefit; if they are primary drivers, they represent compelling intervention targets. Future longitudinal studies with serial sampling from the perinatal period are urgently needed to resolve this question.

Key epigenetic modifications in preterm brain injury. A substantial body of research has now linked specific epigenetic changes to preterm brain injury. DNA methylation is the most extensively studied mark in this context. Lorente-Pozo *et al* (57) delivered a seminal finding by demonstrating that the oxygen load supplied during delivery room stabilization of preterm infants modifies the DNA methylation profile. This work provided direct clinical evidence that a major source of OS, resuscitation with high oxygen, can rapidly alter the neonatal epigenome. Similarly, Rzemieniec *et al* (44) showed that perinatal asphyxia in a rodent model led to hypermethylation of specific genes, an effect that was counteracted by a neuroprotective compound. More recently, Xu *et al* (58) demonstrated that maternal exposure to multiple metals, a known provocation for OS, is associated with an increased risk of spontaneous preterm birth, a relationship potentially mediated by alterations in DNA methylation. Balasubramanian *et al* (46) provided mechanistic depth by showing that traumatic brain injury leads to persistent oxidative damage in the hippocampus via DNA Methyltransferase 3b-mediated DNA methylation and silencing of the antioxidant enzyme superoxide dismutase2. This illustrates a vicious cycle whereby OS-induced methylation can impair endogenous antioxidant defenses, perpetuating oxidative injury.

Histone modifications are also emerging as critical players. The acetylation and deacetylation of histones, controlled by histone acetyltransferases and deacetylases (HDACs), respectively, are sensitive to cellular energy and redox states. Ye *et al* (41), in a comprehensive review, highlighted the potential of HDAC inhibitors as a therapeutic strategy in traumatic brain injury. Experimental studies support this concept. Liu *et al* (59) demonstrated that HDAC2 regulates nuclear factor erythroid 2-related factor 2 (Nrf2) acetylation, influencing neuronal ferroptosis in neonatal rats with hypoxic-ischemic brain injury. Furthermore, Xu *et al* (60) showed that targeting HDAC3 suppresses ferroptosis and demyelination in white matter injury by restoring pyruvate dehydrogenase kinase 4-mediated iron homeostasis. These studies point towards a crucial role for histone deacetylases in orchestrating the cellular response to OS and injury. Beyond acetylation, other histone marks are implicated. For instance, Xiang *et al* (61) found that exposure to fluoride, which can induce OS, exacerbates cognitive deficits in diabetic rats, potentially through mechanisms involving the poly (ADP-ribose) polymerase-1 pathway, a sensor of DNA damage that also modifies chromatin structure.

ncRNAs, particularly miRNAs, add another layer of complexity. These small RNAs can be dysregulated by OS and, in turn, regulate the expression of genes involved in antioxidant defense, inflammation and cell survival. For example, Zhou *et al* (43) demonstrated that suppression of the lncRNA metastasis-associated lung adenocarcinoma transcript 1 alleviated neuronal apoptosis and ROS production through the miR-499-5p/SRY-box transcription factor 6 axis in a model of subarachnoid hemorrhage. Similarly, Chen *et al* (42) reported that depleting SRY-box transcription factor 2 improved ischemic stroke outcomes via the lncRNA plasmacytoma variant translocation 1/microRNA-24-3p/signal transducer and activator of transcription 3 (STAT3) axis. The rapid responsiveness of miRNAs to cellular stress makes them attractive candidates as both early biomarkers and therapeutic targets (62).

Cell-type specific epigenetic responses. It is crucial to recognize that epigenetic responses to OS are not uniform across all brain cell types. The specific vulnerability of OPCs, discussed in the previous section, likely has an epigenetic basis. Kulkarni *et al* (63) demonstrated that brain trauma induces DNA methylation-mediated regulation of the Mitofusin 2 gene, which is critical for mitochondrial dynamics, in the brain, but the cell-specific nature of this regulation requires further elucidation. Astrocytes also undergo significant epigenetic reprogramming in response to injury. Li *et al* (64) showed that alcohol exposure, which induces OS, activates the Nrf2 pathway and influences the expression of genes related to glutathione metabolism in astrocytes, a process with potential epigenetic underpinnings. Microglia, the brain's resident immune cells, are particularly prone to epigenetically mediated priming, where an initial insult leads to a sensitized state and an exaggerated response to a subsequent challenge. Chen *et al* (65) recently reported that HDAC1 dysregulation promotes pro-inflammatory microglial activation and aggravates post-stroke neuroinflammation. This suggests that OS-induced epigenetic changes in microglia could perpetuate a chronic neuroinflammatory state, contributing to ongoing white matter dysmaturation. While much work remains to be conducted, it is evident that the epigenetic landscape of each cell type dictates its unique response to the OS caused by preterm birth. The convergence of evidence from clinical cohorts demonstrating oxygen-induced methylation changes (57) and preclinical models elucidating the pathways of HDAC-mediated ferroptosis (59,60) strongly supports the concept that OS serves as a direct molecular bridge to enduring epigenetic dysregulation. This paradigm shifts from viewing OS as merely an acute insult to recognizing it as a trigger for long-term epigenetic reprogramming opens new avenues for biomarkers and therapies aimed at mitigating the lifelong neurodevelopmental consequences of preterm birth.

The direct clinical evidence linking oxygen exposure to DNA methylation changes in preterm infants is provided by a prospective cohort study (57), while most mechanistic insights into histone modifications and ncRNAs originate from preclinical models (41-44,59-61).

4. Cellular and molecular players in preterm brain injury

The cellular responses that define preterm brain injury, from OPCs vulnerability to microglial activation and astrocyte reactivity, are not independent phenomena. They are unified by a common upstream driver, the OS-epigenetic axis described in the preceding sections. This section therefore examined each major cell type not as an isolated actor but as a node within this integrated pathological network. Understanding how the OS epigenetic cascade manifests in each cell population and how cell-specific responses in turn feedback to amplify or contain the injury, is essential for developing targeted neuroprotective strategies. Table I summarizes current evidence on the roles of oligodendrocyte lineage cells, astrocytes, microglia, neurons and the emerging contribution of the gut-brain axis, providing a cellular framework.

Oligodendrocyte lineage: Primary victims. OPCs represent the most vulnerable cellular population in the preterm brain, with their susceptibility underpinning the predominant white matter injury phenotype. Srivastava *et al* (66) demonstrated that a Toll-like receptor (TLR)/protein kinase B (AKT)/forkhead box O3 immune tolerance-like pathway specifically disrupts the repair capacity of OPCs, providing mechanistic insight into why these cells fail to mature after injury. This maturational arrest is further exacerbated by inflammatory signals; Boccazzi *et al* (67) showed that TLR3 activation in oligodendrocytes triggers a pro-inflammatory response that compromises their survival in a murine model of preterm white matter injury.

The susceptibility extends beyond inflammatory mediators to excitotoxic mechanisms, as Al-Griw *et al* (68) demonstrated that inhibition of ionotropic glutamate receptor signaling preserves the oligodendrocyte lineage in an *ex vivo* model of ischemic injury. Importantly, the fate of OPCs is not uniformly determined. Chang *et al* (69) provided evidence that intrauterine growth restriction combined with postnatal hyperoxia induces white matter injury through mechanisms involving OPCs disruption, while Lin *et al* (70) characterized the dynamic changes in oligodendrogenesis following hypoxic-ischemic injury, revealing temporal windows of vulnerability and limited regenerative capacity. These findings collectively indicate that OPCs injury involves multiple converging pathways and the failure of endogenous repair mechanisms, rather than simply cell death, may be the critical determinant of long-term dysmyelination. The observation that OPCs can survive but fail to mature suggests that therapeutic strategies should target differentiation blockade rather than solely preventing acute cell loss.

Astrocytes: Double-edged players. Astrocytes exhibit context-dependent responses that can either contain injury or amplify damage in the preterm brain. Parfenova *et al* (71) demonstrated a protective role, showing that astrocyte-produced carbon monoxide protects against cerebrovascular dysfunction following neonatal asphyxia. This beneficial capacity is consistent with findings from Nobuta *et al* (72), who reported that STAT3-mediated astrogliosis protects myelin development by modulating microglial transforming growth factor beta-1 (TGFβ-1) expression, thereby preventing impaired oligodendrocyte maturation.

Conversely, astrocytes can adopt pathogenic phenotypes under certain conditions. Renz *et al* (73) demonstrated that neuroinflammatory reactive astrocyte formation correlates with adverse outcomes in perinatal white matter injury, suggesting that the nature of astrocytic reactivity determines clinical trajectory. The signaling pathways governing these divergent responses have been increasingly characterized. Fang *et al* (74) showed that fibroblast growth factor-10 protects the neurovascular unit, including astrocytes, in neonatal hypoxic-ischemic injury, while Xu *et al* (60) demonstrated that targeting HDAC3 suppresses ferroptosis and demyelination partly through restoring PDK4-mediated iron homeostasis. The duality of astrocyte function (protective under some conditions but detrimental under others) highlights the need for nuanced therapeutic approaches that preserve beneficial functions while limiting maladaptive responses. This balance may be particularly critical in the preterm brain, where astrocyte development is ongoing and thus highly susceptible to perturbation.

Microglia: mediators of neuroinflammation. Microglial cells serve as central orchestrators of the neuroinflammatory response, with their activation state critically influencing injury progression and repair (75). Activated microglia produce large quantities of ROS via NADPH oxidase 2 (NOX2), which can in turn perpetuate inflammatory signaling, establishing a feed-forward loop between OS and neuroinflammation (8). Yang *et al* (76) demonstrated that caffeine treatment, initiated before injury, reduces hypoxic-ischemic white matter damage by regulating phenotypic microglial polarization, shifting cells toward a less inflammatory state. This concept of microglial plasticity is supported by Charriaut-Marlangue *et al* (77), who identified sex differences in microglial phenotypes following neonatal stroke, with females showing distinct responses to poly (ADP-ribose) polymerase inhibition compared with males.

The signaling pathways regulating microglial reactivity have been extensively investigated. Zaghloul *et al* (78) reported that prophylactic inhibition of NF-κB expression in microglia attenuates hypoxic-ischemic injury, while Mairesse *et al* (79) showed that oxytocin receptor agonist reduces perinatal brain damage by directly targeting microglia. Van Steenwinckel *et al* (80) provided mechanistic depth by demonstrating that decreased microglial Wnt/β-catenin signaling drives pro-inflammatory activation in the developing brain. The convergence of these studies suggests that microglial responses are not binary but represent a spectrum of activation states and the capacity to modulate these states, either pharmacologically or through endogenous pathways, offers therapeutic potential. Importantly, the work of Bernis *et al* (81), which temporally characterized microglia-associated gene expression in a sensitized hypoxia-ischemia model, emphasizes that the timing of microglial modulation may be as critical as the specific intervention.

Neurons: Targets of injury. Although white matter injury predominates in preterm encephalopathy, neuronal populations are also markedly affected, contributing to long-term

cognitive and motor deficits. Sathyanesan *et al* (82) demonstrated that neonatal brain injury causes cerebellar learning deficits and Purkinje cell dysfunction, revealing that the cerebellum is a previously underappreciated target. This finding aligns with subsequent work from the same group showing that disruption of neonatal Purkinje cell function underlies injury-related learning deficits (83). Cortical neuronal populations are similarly vulnerable. Scheuer *et al* (26) provided evidence that neonatal OS impairs cortical synapse formation and GABA homeostasis in parvalbumin-expressing interneurons, a finding extended by Lacaille *et al* (84) who demonstrated impaired interneuron development in a novel model of neonatal brain injury. Sheikh *et al* (85) showed that neonatal hypoxia-ischemia causes functional circuit changes in subplate neurons, which serve as crucial relay stations during cortical development.

The cholinergic system also appears susceptible; Northington *et al* (86) reported that basal forebrain magnocellular cholinergic systems are damaged following neonatal hypoxia-ischemia in mice. These diverse neuronal vulnerabilities suggest that preterm brain injury represents a multi-system disorder affecting multiple neurotransmitter systems and brain regions. The recognition that interneurons, particularly parvalbumin-positive subtypes, are consistently affected provides a plausible cellular basis for the long-term neuropsychiatric sequelae observed in preterm survivors.

Neurovascular unit. The concept of the neurovascular unit emphasizes that injury to any component (endothelium, pericytes, astrocytes, or neurons) affects the integrity of the whole. Lee *et al* (87) demonstrated that hypoxia-preconditioned human umbilical vein endothelial cells protect against neurovascular damage following hypoxic ischemia, suggesting that enhancing endothelial resilience confers broader neuroprotection. Chand *et al* (88) showed that neurovascular unit alterations in growth-restricted newborns are improved following ibuprofen treatment, linking hemodynamic modulation to structural protection. Fang *et al* (89) provided additional evidence that chloroquine protects against neonatal brain injury by mitigating blood-brain barrier disruption, while Wang *et al* (90) demonstrated that oligogenesis in the 'oligovascular unit' involves PI3K/AKT/mTOR signaling. The interdependence of these cellular components has important therapeutic implications: Interventions targeting a single cell type may fail if other components remain compromised, suggesting that multimodal approaches addressing the entire neurovascular unit may be necessary.

Gut-brain axis in preterm brain injury. Emerging evidence implicates the gut microbiota as a significant modulator of brain injury in preterm infants. Seki *et al* (91) provided seminal findings by demonstrating that aberrant gut-microbiota-immune-brain axis development occurs in premature neonates with brain damage, with *Klebsiella* overgrowth highly predictive of injury and associated with a pro-inflammatory immunological tone. This clinical observation is supported by experimental work from Drobyshevsky *et al* (92), who showed that intestinal microbiota modulates neuroinflammatory response and brain injury following neonatal hypoxia-ischemia. Liu *et al* (93) extended these findings using multi-omics analyses, demonstrating aberrant microbiota-gut-brain axis in very low birth weight infants with white matter injury. Vaher *et al* (94) recently confirmed that the neonatal gut microbiota plays a role in the encephalopathy of prematurity, with specific microbial profiles associated with adverse neurodevelopmental outcomes. Seki *et al* (95) subsequently identified gut microbiota genome features associated with brain injury, suggesting that the mechanistic basis for these associations likely involves microbial metabolites and immune modulation. This evolving field opens novel therapeutic possibilities, including probiotic interventions and dietary modulation, although causal relationships require further validation. The recognition that the gut-brain axis operates during the neonatal period challenges traditional conceptualizations of brain injury as a purely CNS-limited process and suggests that systemic interventions may have central consequences.

The cellular landscape of preterm brain injury reveals a highly interconnected system in which the response of any single cell type influences and is influenced by others. This complexity probably explains why single-target interventions have shown limited clinical success and supports the need for approaches that consider the multicellular nature of injury and repair. Critically, the OS epigenetic axis provides the mechanistic thread that connects these disparate cellular responses: OS modifies the epigenome of each cell type in a context-specific manner and these epigenetic changes, in turn, dictate divergent outcomes ranging from OPCs maturational arrest to astrocyte reactivity and microglial priming. Thus, the cellular diversity of preterm brain injury is not a random assortment of pathologies but a spectrum of cell-type-specific manifestations of a common molecular derangement. However, the cell-type specificity of epigenetic responses also poses a major translational challenge: Interventions that modify the epigenome globally may have unintended consequences in cell types where the same epigenetic mark serves a protective rather than pathogenic function. For example, HDAC inhibition may benefit oligodendrocyte survival while simultaneously promoting astrocyte reactivity or microglial priming, depending on the cellular context and timing of intervention. The responses of astrocytes and microglia to HDAC inhibition are highly context-dependent, varying with the specific HDAC inhibitor used, the cell type and the inflammatory milieu. In pure microglial cultures, HDAC inhibitors such as trichostatin A (TSA) and suberoylanilide hydroxamic acid can potentiate LPS-induced pro-inflammatory cytokine and nitric oxide responses (96). Conversely, in astrocyte-rich cultures exposed to activated microglial factors, TSA and valproic acid restored histone acetylation, upregulated the Nrf2-inducible antioxidant defense and conferred protection against OS (51). In a neonatal rat model of white matter injury, the selective HDAC2/3 inhibitor MI192 administered post-insult markedly reduced oligodendrocyte loss and suppressed microglial activation (97). These findings collectively illustrate that the timing of HDAC inhibition and the specific cell types targeted critically determine therapeutic outcomes, whether the inhibitor is administered prophylactically, immediately after injury, or during the repair phase. This duality underscores the need for cell-type-specific delivery strategies or

interventions targeted to the relevant epigenetic enzymes in a temporally restricted manner. It must be emphasized, however, that the majority of mechanistic insights discussed in this section derive from preclinical models (rodent and *ex vivo* systems). While these findings are invaluable for understanding pathogenesis, their translation to the human preterm brain requires confirmation in clinical cohorts.

Clinical evidence for the gut-brain axis in preterm brain injury comes from prospective cohorts and case-control studies (91,93-95), whereas the majority of cellular response data (oligodendrocyte, astrocyte, microglia, neuron) are derived from animal models. See Table I for full classification.

Intercellular crosstalk in the preterm brain. The pathological responses of individual cell types in preterm brain injury do not occur in isolation; rather, they are shaped by dynamic intercellular communication networks that collectively determine injury progression and repair capacity. Microglia and astrocytes engage in bidirectional crosstalk that profoundly influences the neuroinflammatory milieu. Activated microglia can decrease histone acetylation in astrocytes via increased HDAC activity, thereby impairing astrocytic antioxidant defenses and perpetuating OS (51). Conversely, astrocytes modulate microglial phenotype through STAT3-dependent mechanisms; Nobuta *et al* (72) demonstrated that STAT3-mediated astrogliosis protects myelin development by preventing pathological TGFβ-1 expression in microglia, which would otherwise inhibit oligodendrocyte progenitor maturation. This protective astrocyte-microglia interaction is critical, as TGFβ-1 directly and dose-dependently inhibits the maturation of purified oligodendrocyte progenitors (11).

Astrocytes also exert direct effects on oligodendrocyte lineage cells. Shiow *et al* (98) showed that reactive astrocytes in neonatal white matter injury develop 'A2' reactivity and produce COX2-derived prostaglandin E, which acts directly on oligodendrocyte progenitor cells via the EP1 receptor to block their maturation. *In vivo* inhibition of COX2 rescues hypomyelination and behavioral impairment, demonstrating that astrocyte-derived inflammatory mediators are functionally significant drivers of OPC maturation arrest (98).

Microglia-oligodendrocyte interactions are equally critical. Inflammatory activation of microglia releases cytokines and ROS that directly impair oligodendrocyte survival and maturation (8,30). Conversely, protective microglial phenotypes can support oligodendrocyte development; M2 microglia-derived exosomal miR-144-5p has been shown to promote OPC growth and reduce white matter injury by regulating the PTEN/AKT pathway (99). The work of Bernis *et al* (81) further emphasizes that the temporal dynamics of microglial activation, shifting from pro-inflammatory to anti-inflammatory gene expression over time, determine whether microglia exert harmful or beneficial effects on oligodendrocyte lineage cells.

The neurovascular unit represents another critical interface for intercellular crosstalk. Endothelial cells, pericytes, astrocytes and neurons communicate through reciprocal signaling that maintains blood-brain barrier integrity and regulates cerebral blood flow. Lee *et al* (87) demonstrated that hypoxia-preconditioned endothelial cells confer broader neuroprotection, suggesting that enhancing the resilience of one cellular component benefits the entire unit. Wang *et al* (90) showed that oligogenesis in the 'oligovascular unit' involves PI3K/AKT/mTOR signaling, illustrating how vascular and glial compartments coordinately regulate white matter repair. Collectively, these findings establish that preterm brain injury is not a cell-autonomous process but a network disorder in which the responses of microglia, astrocytes, oligodendrocytes and vascular cells are intimately interconnected through reciprocal signaling pathways. This interconnectedness provides a mechanistic explanation for why single-cell-type interventions have shown limited success and supports the rationale for multimodal therapeutic strategies that target the broader cellular network.

5. Neuroprotective strategies: Current evidence and emerging approaches

The preceding sections have elucidated the complex cascade from OS to epigenetic dysregulation in preterm brain injury, involving multiple cellular populations and interconnected pathological pathways. To impose conceptual order on the diverse array of neuroprotective strategies currently under investigation, this section organised interventions according to which node of the OS epigenetic cascade they target: Prevention of OS generation (antioxidants, oxygen management); blockade of epigenetic modification (HDAC inhibitors, miRNA modulators); or modulation of downstream cellular responses (anti-inflammatory agents, cell-based therapies). This complexity poses significant challenges for neuroprotection, as interventions targeting single mechanisms may prove insufficient. It is important to distinguish between preclinical promise and clinical evidence: while numerous agents demonstrate efficacy in animal models, the number that have been rigorously tested in adequately powered human trials remains small and the translational gap is substantial. The following sections critically evaluate current and emerging neuroprotective strategies, with particular attention to the strength of evidence and areas of ongoing controversy. A summary of these strategies, categorized by mechanism and evidence level, is presented in Table II.

Antioxidant-based strategies. Melatonin has been extensively investigated as an antioxidant neuroprotectant. Carloni *et al* (100) characterized melatonin pharmacokinetics following oral administration in preterm neonates, demonstrating significant interindividual variability that complicates dosing optimization. Domínguez Rubio *et al* (101) reported that maternal melatonin administration exerted both short- and long-term neuroprotective effects in offspring from lipopolysaccharide-treated mice. Garofoli *et al* (102) recently confirmed that orally administered melatonin reaches systemic circulation and reduces OS markers in preterm newborns, although clinical impact on neurodevelopmental outcomes awaits definitive trials. Lee *et al* (103) demonstrated in a mouse model that melatonin administration prevented preterm birth and associated fetal brain injury. However, the systematic review by Ahmed *et al* (104) concluded that while safety appears favorable, evidence for neuroprotection remains insufficient due to small sample sizes and heterogeneity in dosing

and timing. A more recent review by Häusler *et al* (105) systematically examined the pathomechanisms underlying preterm brain injury and correlated them with melatonin's neuroprotective potential, while emphasizing significant pharmacokinetic and pharmacodynamic uncertainties that must be addressed before clinical translation can be realized. Favrais *et al* (106) showed only partial protective effects of melatonin in a rat model of chorioamnionitis, suggesting that monotherapy may be inadequate against multifactorial injury. Other antioxidants, including N-acetylcysteine (107), vitamin C (108) and uridine (109), have shown preclinical promise but limited clinical translation. Chen *et al* (110) recently demonstrated that targeting mitochondrial OS through Nrf2 induction protects against preterm birth and fetal brain injury in experimental models, although clinical validation is awaited. Beyond these agents, emerging preclinical evidence continues to expand the repertoire of potential antioxidant neuroprotectants. Gunduz *et al* (111) recently demonstrated that polydatin, a natural polyphenolic compound, exerts dose-dependent protective effects against sodium fluoride-induced oxidative and inflammatory damage in rats, as evidenced by restored antioxidant enzyme activities (glutathione, catalase, superoxide dismutase), reduced lipid peroxidation (malondialdehyde) and suppressed pro-inflammatory gene expression (TNF-α, NF-κB, IFN-γ). Although this study was conducted in a fluoride-toxicity model rather than a perinatal brain injury context, it reinforces the broader principle that pharmacological agents capable of restoring redox balance and modulating inflammatory pathways hold therapeutic potential for conditions characterized by OS. Importantly, polydatin has also been shown to exert neuroprotective effects in neonatal rat models of hypoxic-ischemic brain injury, improving learning and memory impairments through upregulation of brain-derived neurotrophic factor (112). These findings suggest that polydatin warrants further investigation as a candidate neuroprotective agent in the preterm population, although rigorous preclinical optimization and clinical translation studies are required before any clinical recommendations can be made.

Targeting specific molecular pathways. Erythropoietin (EPO) represents the most extensively studied pathway-targeted agent. Fischer *et al* (113) performed a meta-analysis concluding that while EPO reduces transfusions, evidence for improved neurodevelopmental outcomes was inconclusive. The landmark Preterm Erythropoietin Neuroprotection Trial (PENUT) trial by Juul *et al* (114) randomized 941 extremely preterm infants to high-dose EPO or placebo and found no significant difference in the primary outcome of mortality or severe neurodevelopmental impairment at 2 years between the two groups. Ehrenreich *et al* (115) emphasized that negative findings highlight the importance of patient selection and dosing rather than refuting EPO's potential. By contrast, Song *et al* (116) reported that EPO improved outcomes specifically in preterm infants with intraventricular hemorrhage, suggesting subgroup-specific benefits. Jakab *et al* (117) used network-based statistics to reveal trophic effects of early high-dose EPO on brain connectivity in very preterm infants. Wassink *et al* (118) showed that prolonged EPO infusion provided partial white and grey matter protection after asphyxia in preterm fetal sheep. Ma and Shi (119) comprehensively reviewed cellular mechanisms of EPO neuroprotection, concluding that clinical translation requires improved patient stratification. The discrepancy between the neutral PENUT trial and positive preclinical and subgroup studies likely reflects several factors: The PENUT trial administered EPO at 24 h of life, whereas preclinical data suggest earlier administration (within 6 h) may be more effective; the extremely high baseline rate of favourable outcomes in the control group (79.6% survival without impairment) limited statistical power to detect a benefit; and the trial excluded infants with significant prior brain injury, potentially removing the population most likely to respond (114,119). These observations suggest that EPO may benefit specific subgroups, particularly infants with established injury or those treated earlier, rather than providing universal neuroprotection and that future trials should stratify by injury severity and timing of intervention. The conflicting results between consistently positive preclinical models and largely neutral clinical trials underscore the limitations of animal models and the critical importance of adequately powered trials.

Caffeine has emerged as a candidate neuroprotective agent. Endesfelder *et al* (120) demonstrated that caffeine provides neuroprotection against hyperoxia-induced neonatal brain injury in rats. Yang *et al* (76) showed that caffeine treatment reduced hypoxic-ischemic white matter damage through regulation of phenotypic microglia polarization. Di Martino *et al* (121) defined a therapeutic window for caffeine neuroprotection, showing that early administration is critical for efficacy. A recent network meta-analysis by Wang *et al* (122) comparing caffeine, erythropoietin, magnesium sulfate and thyroxine found that caffeine showed the most promising effect in reducing the risk of neurodevelopmental impairment [relative risk (RR): 0.43, 95% confidence interval (CI): 0.22-0.86] and cerebral palsy (RR: 0.55, 95% CI: 0.43-0.70) in preterm infants. These preclinical data, combined with caffeine's established safety profile, support its continued use, although prospective trials with neurodevelopmental primary outcomes are lacking. Emerging pathway-targeted strategies include HDAC modulation, with Liu *et al* (59) demonstrating that HDAC2 regulates Nrf2 acetylation and thereby influences neuronal ferroptosis. Peroxisome proliferator-activated receptor gamma (PPAR-γ) activation has also been investigated, with Fang *et al* (123) demonstrating inhibition of microglia-mediated neuroinflammation and Feng *et al* (124) showing promotion of oligodendrocyte precursor cell differentiation. All remain at preclinical stages.

Anti-inflammatory strategies. Beyond direct antioxidant and pathway-targeted approaches, modulating the inflammatory cascade itself represents a distinct and complementary therapeutic avenue, given that neuroinflammation both amplifies oxidative injury and operates through partially independent molecular networks (125). Shin *et al* (30) demonstrated that TNF-α antagonist attenuated lipopolysaccharide-induced white matter injury in neonatal rats. Prasad *et al* (126) comprehensively reviewed anti-inflammatory therapies, examining agents including TNF-α antagonists (such as

etanercept), minocycline, COX-2 inhibitors, melatonin and IL-1 receptor antagonists. While numerous agents show preclinical efficacy, clinical translation has been limited by the complexity of the inflammatory cascade and the difficulty of timing interventions appropriately. The inflammatory cascade involves sequential activation of multiple mediators: peripheral immune responses trigger central neuroinflammation characterized by proinflammatory cytokine release (TNF-α, IL-1β, IL-6), microglial activation and reactive gliosis, which in turn activate NADPH oxidase enzymes generating ROS, establishing a feed-forward loop between OS and inflammation (8,30). The temporal heterogeneity of microglial responses, shifting from pro-inflammatory to anti-inflammatory gene expression over time, further complicates therapeutic targeting (80). Different anti-inflammatory agents require distinct therapeutic windows: etanercept administered at three days after hypoxia-ischemia ameliorates white matter injury (30); early postnatal caffeine treatment confers improved neuroprotection than late treatment (76,120,121); minocycline requires early post-insult administration to target secondary neuroinflammation; and dexamethasone exhibits a developmentally sensitive therapeutic window (126). These temporal constraints, combined with the difficulty of predicting the onset and progression of inflammation in individual preterm infants, pose substantial barriers to clinical translation.

IL-1 has emerged as a promising target, with Takahashi *et al* (127) demonstrating that pharmacological IL-1 receptor blockade suppressed lipopolysaccharide-induced neuroinflammation in preterm fetal sheep. Van Steenwinckel *et al* (80) identified decreased microglial Wnt/β-catenin signaling as a driver of pro-inflammatory activation. Bokobza *et al* (128) demonstrated that miR-146b protects against microglia-induced hypomyelination, suggesting that microRNA-based therapies could modulate neuroinflammation more selectively. The temporal heterogeneity of microglial responses, emphasized by Bernis *et al* (81), implies that anti-inflammatory interventions must be precisely timed to avoid interfering with beneficial microglial functions.

Clinical care strategies to reduce OS. Oxygen management is paramount. Rantakari *et al* (129) demonstrated that both low and high oxygen saturations are associated with adverse outcomes. The targeted oxygen for resuscitation of preterm infants and their developmental outcomes (TORPIDO) 30/60 trial randomized 1,469 preterm infants and found no significant association between initial FiO_2 concentration (0.6 vs. 0.3) for resuscitation and death or brain injury at 36 weeks' corrected gestational age (130). Engur *et al* (131) provided mechanistic insight by demonstrating that supplemental oxygen alters the pentose phosphate pathway through sirtuin signaling.

Developmental care practices have been codified into neuroprotective care bundles. Milette *et al* (132) published guidelines for institutional implementation of developmental neuroprotective care. Murthy *et al* (133) evaluated a neuroprotection care bundle, reporting reduced intraventricular hemorrhage rates following implementation. Travis *et al* (134) demonstrated that skin-to-skin holding is associated with improved white matter microstructure. Nutritional strategies have also been investigated. Belfort and Inder (135) reviewed the relationship between human milk and brain development, concluding that breastfeeding is associated with improved outcomes. Brandt *et al* (136) demonstrated that human milk oligosaccharides improve white matter and interneuron development in a rat model. These strategies offer low cost and wide availability, but definitive evidence of neuroprotective efficacy remains limited.

Multimodal neurocritical care. Multimodal neuromonitoring has become a cornerstone of neurocritical care in preterm infants, enabling early detection of physiological instability and evolving brain injury before irreversible damage occurs. El-Dib *et al* (137) provided a comprehensive framework for integrating multiple monitoring modalities, including aEEG, near-infrared spectroscopy (NIRS) and magnetic resonance imaging (MRI), to detect cerebral dysfunction across different physiological domains. Among these, aEEG has emerged as a particularly valuable bedside tool. Variane *et al* (138) demonstrated that early aEEG monitoring effectively identifies neonates at high risk for brain injury, facilitating timely intervention. Griesmaier *et al* (139) further validated the prognostic utility of aEEG by demonstrating significant associations between aEEG patterns and MRI defined injury severity at term equivalent age, establishing a correlation between functional and structural assessments that enhances clinical interpretation. Beyond electrophysiological assessment, Lin *et al* (140) integrated aEEG with General Movements assessment, showing that combining neurophysiological and motor function evaluations provides a more comprehensive prediction of neural recovery than either modality alone. Despite these advances, the clinical value of multimodal monitoring ultimately depends on the availability of effective, evidence-based interventions to act upon the detected abnormalities. The integration of real time neuromonitoring data with AI-driven decision support systems and biomarker panels represents a promising avenue for translating early detection into improved outcomes, although prospective validation in large cohorts is still needed.

Cell-based therapies represent an emerging frontier. Drommelschmidt *et al* (141) demonstrated that mesenchymal stem cell-derived extracellular vesicles ameliorate inflammation-induced preterm brain injury. Thomi *et al* (142) showed that intranasally administered exosomes reduce microglia-mediated neuroinflammation. Ahn *et al* (143) conducted a phase I dose-escalation clinical trial of mesenchymal stem cells for severe intraventricular hemorrhage, demonstrating feasibility and safety. However, the Cochrane systematic review by Romantsik *et al* (144) sought to include randomized controlled trials comparing stem cell-based interventions vs. control for the prevention (in infants <28 weeks' gestation, ≤24 h of age, without ultrasound diagnosis) or treatment (in infants <37 weeks' gestation, with ultrasound-confirmed germinal matrix-intraventricular hemorrhage or encephalopathy of prematurity) of these conditions. However, no completed studies met the inclusion criteria; only three ongoing trials were identified. The authors concluded that no evidence is currently available to evaluate the benefits and harms of stem cell-based interventions for treatment or prevention of these conditions in preterm infants (144). Tscherrig *et al* (145) identified specific miRNAs

from mesenchymal stromal cell extracellular vesicles that rescue white matter injury. Vaes *et al* (146) demonstrated that modifying the secretome prolongs the regenerative treatment window. Despite extensive preclinical literature, the gap between experimental promise and clinical evidence remains substantial, necessitating rigorous trial design before cell-based therapies enter routine practice. Viewed through the OS epigenetic lens, the therapeutic landscape becomes coherent: Antioxidants and oxygen management aim to reduce the upstream trigger; HDAC inhibitors and miRNA-based approaches target the epigenetic machinery that translates oxidative insults into persistent cellular dysfunction; and cell-based therapies seek to modulate the downstream cellular responses that determine repair vs. injury. This conceptual taxonomy underscores that effective neuroprotection will likely require multimodal strategies that address multiple nodes of the integrated OS epigenetic cellular pathway, timed to the developmental window of vulnerability.

In synthesizing the neuroprotective evidence, several points of consensus emerge: Melatonin and erythropoietin have been the most extensively studied agents, both showing favourable safety profiles but inconsistent efficacy; caffeine has a strong preclinical rationale and established clinical safety; and cell-based therapies hold substantial promise but remain experimental. However, major controversies and unresolved questions persist. The most critical is the translational gap between consistently positive preclinical findings and largely neutral or inconclusive clinical trials, a discrepancy that may reflect differences in timing, dosing, patient selection, or the inherent limitations of animal models. There is also no consensus on whether combination therapy (such as antioxidants plus anti-inflammatory agents) is superior to monotherapy, or whether interventions should be targeted to specific injury subtypes. Emerging preclinical evidence has begun to explore multimodal combination strategies. For instance, combination therapy with sulforaphane (an Nrf2 activator with NF-κB inhibitory properties) and deferiprone (an iron chelator) has been shown to mitigate M1 microglial infiltration, suppress inflammation and reduce ferroptosis in a neonatal rabbit model of intraventricular hemorrhage (147). Combined omega-3 polyunsaturated fatty acid and folic acid supplementation has demonstrated enhanced neuroprotection against neonatal hypoxic-ischemic brain injury through synergistic anti-inflammatory and anti-apoptotic mechanisms (148). The combination of erythropoietin and melatonin has shown sustained repair of functional deficits in a rat model of cerebral palsy following preterm brain injury (149), with ongoing clinical trials evaluating the safety of this combinatorial approach in very preterm infants with intraventricular hemorrhage or white matter injury. N-acetylcysteine combined with vitamin D has been shown to decrease OS in plasma and central nervous system and is associated with favorable developmental outcomes in neonatal hypoxic-ischemic encephalopathy models (150). Furthermore, allopurinol (a xanthine oxidase inhibitor) is currently being evaluated in the phase III ALBINO trial as an adjunct to therapeutic hypothermia for hypoxic-ischemic brain injury (17). These emerging combination approaches, although primarily at preclinical or early clinical stages, highlight the potential for multimodal strategies targeting both oxidative and inflammatory pathways to achieve superior neuroprotection compared with monotherapy. Furthermore, the optimal window for intervention, before, during, or after the oxidative insult, has not been established for most agents. Future research must prioritise adequately powered, biomarker-stratified trials with long-term neurodevelopmental follow-up to resolve these uncertainties and translate preclinical promise into clinical reality.

The clinical evidence base for neuroprotective agents is strongest for caffeine [network meta-analysis of randomized controlled trials (RCTs)], erythropoietin (PENUT RCT and cohort studies) and oxygen titration (TORPIDO RCT), whereas melatonin, HDAC inhibitors, PPAR-γ agonists and cell-based therapies remain largely at preclinical or early-phase clinical stages (see Table II for detailed evidence levels and model systems). Several systematic reviews and meta-analyses have amalgamated the evidence for neuroprotective agents in preterm infants (105,122,144). A Cochrane review on stem cell-based interventions concluded that no completed RCTs met inclusion criteria, highlighting the substantial gap between preclinical promise and clinical evidence (144). Network meta-analysis data suggest caffeine may be the most promising agent for reducing neurodevelopmental impairment and cerebral palsy risk (122), although this finding derives from indirect comparisons and requires confirmation in prospective trials. For melatonin, a systematic review consistently identified small sample sizes and dosing heterogeneity as major limitations precluding definitive conclusions (105). Formal guidelines from international bodies provide specific recommendations for neuroprotective interventions. The American Academy of Pediatrics recommends therapeutic hypothermia for neonates with moderate-to-severe hypoxic-ischemic encephalopathy born at ≥36 weeks' gestation, initiated within 6 h of birth and continued for 72 h (151). UK national guidelines recommend antenatal magnesium sulfate for mothers in preterm labour (<30 weeks' gestation) to reduce the risk of cerebral palsy (152). The European Resuscitation Council 2025 guidelines provide evidence-based recommendations for newborn life support, including neuroprotective strategies during transition at birth (153). Additionally, structured neuroprotection care bundles have been shown to markedly reduce death or severe brain injury in extremely preterm infants (133). Despite these established guidelines, formal consensus from the American Academy of Pediatrics or European bodies specifically addressing pharmacological neuroprotection for preterm brain injury beyond therapeutic hypothermia and magnesium sulfate remains limited.

6. Artificial intelligence (AI) in preterm brain injury: Prediction, diagnosis and monitoring

AI has emerged as a transformative tool in neonatal care, offering novel approaches to predict, diagnose and monitor preterm brain injury. As summarised in Table III, AI applications now span neuroimaging analysis, electrophysiological signal processing and multimodal risk stratification, each contributing uniquely to the evolving landscape of neurocritical care.

AI in neuroimaging analysis. AI has substantially enhanced neuroimaging interpretation accuracy and efficiency. Ahmad *et al* (154) demonstrated that deep learning models could classify cranial ultrasound images for brain injury detection in very preterm infants, achieving performance comparable to expert clinicians. Chen *et al* (155) developed an automated neonatal nnU-Net brain MRI extractor trained on a large multi-institutional dataset, showing robust generalizability across different clinical settings. For subtle pathology, Estermann *et al* (156) introduced CACTUS, a multiview classifier for detecting punctate white matter lesions in cranial ultrasound volumes, addressing a diagnostically challenging task with significant neurodevelopmental implications. These advances suggest AI-based image analysis has substantial potential to enhance neuroimaging interpretation, although protocol variability across institutions, limited external validation and the absence of prospective clinical trials remain important barriers to clinical deployment.

AI-enhanced neuromonitoring. Continuous neuromonitoring generates vast physiological data ideally suited for AI-based analysis. Wang *et al* (157) conducted a landmark cohort study demonstrating that quantitative features from early amplitude-integrated electroencephalography predicted long-term neurodevelopmental outcomes in extremely preterm infants, with automated feature extraction performing equivalently to combined qualitative and quantitative assessments. Abbasi *et al* (158) developed deep learning models for seizure detection using wavelet-scalogram approaches in preclinical models, subsequently refined by Roozbehi *et al* (159) using transformer-based architectures. Ashoori *et al* (160) applied machine learning to NIRS signals, demonstrating that data-driven definitions of prolonged desaturation outperformed traditional threshold-based approaches for detecting intraventricular hemorrhage. Hibner *et al* (161) extended this concept by developing a multimodal approach combining echocardiography, NIRS and electrical cardiometry, showing integrated signal analysis provides complementary information unavailable from any single modality.

Predictive modeling for brain injury risk. AI-based predictive models have shown considerable promise for early risk stratification. He *et al* (162) developed PBIPred, an explainable machine learning model using seven clinical features that achieved an area under the curve of 0.8229 for predicting preterm brain injury, with Shapley Additive Explanations rendering predictions interpretable at individual patient level. For intraventricular hemorrhage specifically, Yang *et al* (163) conducted a nationwide multicenter study demonstrating robust prediction using machine learning. Han *et al* (164) incorporated time-series analysis of physiological data, showing that temporal dynamics improve prediction compared with static variables alone. For white matter injury, Song *et al* (165) developed two risk assessment models in extremely preterm infants, demonstrating that ensemble methods may outperform single algorithms. Shu *et al* (166) applied machine learning to predict mortality and multiple morbidities simultaneously, showing comprehensive outcome prediction is feasible using routinely collected data.

AI in prognostication and outcome prediction. Long-term neurodevelopmental prognostication represents the most clinically challenging AI application. Li *et al* (167) demonstrated that functional connectivity measures predict outcomes in preterm infants without severe brain injury, suggesting subtle network alterations captured by AI analysis identify risk even with normal conventional imaging. Liu *et al* (168) used graph convolutional neural networks to predict brain age, showing deviations from normative maturation trajectories explain outcomes more accurately than static injury assessments. For cerebral palsy, Marinelli *et al* (169) compared predictions at ages 2 and 10 years, revealing that early predictions require refinement as children mature. Yuan *et al* (170) developed a nomogram for predicting intellectual disability, providing a practical tool for early intervention targeting. Despite these advances, two recent systematic reviews identify critical limitations in AI applications for neonatal care. Ortega-Leon *et al* (171) reported that >70% of studies lacked a validation procedure, highlighting a critical gap in methodological rigor in their systematic review of machine learning techniques for predicting neurodevelopmental impairments in premature infants. Similarly, Martinez-Millana *et al* (172) found that among AI studies in the neonatal intensive care unit setting, the majority lacked external validation, limiting generalisability to new clinical settings. These limitations suggest that while AI applications have progressed from proof-of-concept to clinical validation, generalisability remains the principal barrier to widespread adoption.

Despite the proliferation of AI studies, several fundamental limitations impede clinical translation. First, external validation, the critical step for demonstrating generalizability, is performed in <30% of published models and performance consistently declines in cross-institutional settings (154,173). Second, heterogeneity in imaging protocols, EEG configurations and clinical data definitions across centers creates substantial challenges for model generalization (155,157). Third, the 'black-box' nature of numerous deep learning algorithms, combined with poor clinical interpretability, undermines clinician trust and hinders bedside adoption (162). Fourth, the absence of prospective impact studies, trials demonstrating that AI-assisted decision-making actually improves patient outcomes rather than merely achieving statistical accuracy, represents the most critical evidence gap (173). These limitations suggest that while AI applications have progressed from proof-of-concept to clinical validation, generalizability and implementation remain the principal barriers to widespread adoption.

7. Integration and future directions

The convergence of mechanistic insights into OS and epigenetic dysregulation with advances in neuroimaging, electrophysiological monitoring and AI heralds a transformative era in the care of preterm infants at risk for brain injury. This convergence is not coincidental but logically coherent: The OS epigenetic axis provides the mechanistic rationale that unifies the diverse cellular pathologies and therapeutic targets discussed in preceding sections, while AI and multimodal monitoring provide the tools to detect, quantify and

track this axis in real time at the bedside. In this framework, molecular pathophysiology supplies the biological targets and explanatory mechanisms; AI-based predictive tools enable early identification of at-risk infants and dynamic risk stratification; and clinical translation operationalizes these insights into preventive and therapeutic strategies. The synergy among these three components, mechanism, prediction and intervention, constitutes the unifying conceptual framework that transforms a descriptive understanding of preterm brain injury into an actionable, precision-based clinical paradigm. Specifically, the OS-epigenetic axis and its cell-type-specific consequences (such as OPC maturational arrest, microglial priming) serve as the core biological targets supplied by molecular pathophysiology; AI tools such as the PBIPred model (CatBoost with SHAP explanations), convolutional neural networks for aEEG maturational age estimation and multimodal monitoring integration (NIRS, aEEG, echocardiography) provide predictive and monitoring capabilities; these have been clinically translated into early risk stratification, personalized bedside monitoring and decision-support tools, although prospective impact validation remains ongoing (162,174). The recognition that early-life perturbations can programme long-term neurological outcomes, potentially extending even to neurodegenerative risk in adulthood, underscores the imperative for precision-based, developmentally timed interventions (175).

AI has emerged as a pivotal tool for synthesizing the high-dimensional data generated by contemporary neonatal intensive care. Mader *et al* (174) demonstrated that convolutional neural networks applied to amplitude-integrated electroencephalography (aEEG) recordings accurately estimate EEG maturational age in preterm infants, with predicted age difference scores correlating markedly with cognitive outcomes at two years. This automated approach enables real-time, bedside tracking of brain maturation and holds promise for early identification of infants requiring targeted neuroprotective interventions. Similarly, He *et al* (162) developed and validated PBIPred, an explainable machine learning model incorporating seven clinical features that achieved robust prediction of preterm brain injury (area under the curve 0.8229) in a prospective cohort of 650 infants, with Shapley Additive Explanations rendering individual-level predictions interpretable for clinical decision-making. These advances align with broader efforts to develop multimodal, AI-driven diagnostic frameworks that integrate imaging, electrophysiological and clinical data.

Parallel progress in neuromonitoring technologies is refining the ability to detect evolving injury before irreversible damage occurs. The integration of cerebral NIRS with aEEG provides complementary information on hemodynamic stability and electrophysiological function. Wang *et al* (157), in a landmark 10-year cohort study, demonstrated that both qualitative and quantitative aEEG features predict long-term neurodevelopmental outcomes in extremely preterm infants, with automated feature extraction achieving accuracy comparable to expert interpretation. Griesmaier *et al* (139) further validated this approach by demonstrating significant associations between aEEG patterns and MRI-defined injury severity at term-equivalent age, reinforcing that functional and structural assessments provide complementary prognostic information. The SafeBoosC-III trial, while not demonstrating a significant reduction in death or severe brain injury with cerebral oximetry monitoring in the primary analysis, has generated important ancillary data and ongoing Bayesian re-analyses that may identify subgroups most likely to benefit (176). The neutral primary outcome of SafeBoosC-III merits critical interpretation. The absence of a significant benefit may reflect the heterogeneous nature of preterm brain injury, the fact that cerebral oximetry provides physiological data but does not itself constitute a therapeutic intervention and the challenge of translating monitoring-derived insights into consistent clinical actions across participating centers (175). Importantly, the trial demonstrated that cerebral oximetry is feasible and safe and ancillary MRI analyses have revealed potential benefits in specific injury patterns, suggesting that the value of such monitoring lies not in universal application but in enabling targeted interventions for physiologically defined subgroups (175). Future trials should integrate cerebral oximetry with other neuromonitoring modalities and biomarker data to identify infants most likely to benefit from physiology-guided care. Emerging technologies such as functional ultrasound imaging offer the potential for non-invasive, bedside assessment of cerebral blood flow and vascular abnormalities, further expanding the multimodal monitoring armamentarium.

Cell-based therapies represent one of the most promising frontiers for neurorepair, moving beyond neuroprotection toward active regeneration. The recently completed PREMSTEM consortium, a six-year multinational effort, systematically evaluated human mesenchymal stem cell (MSC) therapy in preclinical models of perinatal brain injury, establishing that intranasal administration of umbilical cord-derived MSCs yields optimal therapeutic effects when delivered shortly after injury (177). Despite this promising preclinical foundation, it must be acknowledged that cell-based therapies remain experimental in the context of preterm brain injury. The number of treated infants in published trials remains small, long-term safety data are sparse and optimal dosing, timing and cell source have not been established. Thus, while the therapeutic potential is substantial, clinical readiness is not yet achieved and current evidence does not support routine clinical use. This route exploits the olfactory nerve-cerebrospinal fluid pathway, enabling rapid and targeted delivery to injured brain regions while avoiding systemic side effects. Mechanistically, MSCs exert their effects not through direct cellular replacement but via paracrine signaling, releasing anti-inflammatory cytokines (hepatocyte growth factor, IL-1RA) that suppress microglial activation and neurotrophic factors (granulocyte colony-stimulating factor, leukemia inhibitory factor) that promote neurogenesis and oligodendrocyte maturation (177,178). Importantly, combination with therapeutic hypothermia extends the treatment window and produces synergistic neuroprotection, addressing a critical clinical limitation of hypothermia alone (178). Clinical translation is now accelerating, with multiple phase I trials demonstrating feasibility and safety of cord blood-derived cell therapies in extremely preterm infants (179). Zhou *et al* (179) recently reported secondary analyses from the CORD-SaFe trial, showing encouraging early neurodevelopmental outcomes in infants receiving autologous cord blood cell administration,

although larger randomized controlled trials are required to establish efficacy.

A critical limitation of current AI applications, however, is their dissociation from biological mechanism. Predictive models based on clinical or imaging features can identify infants at risk with considerable accuracy, but they do not reveal why those infants are at risk or which molecular pathways are driving the injury. A systematic review of machine learning applications for predicting neurodevelopmental impairments in premature infants (26 studies; 2018-2023) identified that most models rely on clinical and neuroimaging data, while the inclusion of multi-omics or molecular data remains largely absent (171). The present review emphasized that current approaches predominantly utilize static clinical variables without integrating dynamic biological pathway information, limiting their ability to provide mechanistic insights into injury pathogenesis (171). Furthermore, the 'black box' nature of numerous deep learning algorithms, combined with heterogeneity in data sources and imaging protocols across institutions, presents a significant barrier to understanding the biological drivers underlying predictions. This creates a translational bottleneck: risk prediction without mechanistic understanding cannot guide targeted intervention. Conversely, the mechanistic insights reviewed in Sections 2-4, the OS epigenetic axis and its cellular consequences, lack the real-time, individualized assessment that AI can provide. The integration of these two domains, mechanistic biology and computational prediction, represents the next frontier. Emerging evidence supports this integrative paradigm. Pammi *et al* (180) demonstrated that leveraging AI and machine learning tools for the integration of multiomics data (genomics, epigenomics, metabolomics, proteomics) with clinical information enables the development of predictive models that identify risk before the condition is clinically apparent, thereby facilitating early interventions and paving the way for precision medicine in perinatology. Reiss *et al* (181) further proposed that systems biology approaches incorporating ante- and post-natal risk factors and analyzing omic and multiomic data using machine learning are promising methodologies for elucidating the biologic mechanisms of fetal and neonatal brain injury. Collectively, these frameworks illustrate how molecular pathophysiology supplies the biological targets and explanatory mechanisms, AI-based predictive tools enable early identification and dynamic risk stratification and clinical translation operationalizes these insights into preventive and therapeutic strategies. For instance, incorporating epigenetic biomarkers (such as methylation patterns) or metabolomic signatures into AI models could bridge the gap, enabling both accurate risk stratification and biological insight into the underlying pathology. Such integrative approaches remain rare but hold transformative potential.

Looking forward, several interconnected priorities emerge. Foremost among these is the need to translate the OS epigenetic framework from a conceptual model into a clinically actionable paradigm. First, the integration of AI-driven predictive models with real-time neuromonitoring data should enable dynamic, personalized risk stratification that adapts to an infant's evolving clinical trajectory (162). Second, the identification of robust molecular biomarkers, including epigenetic signatures, extracellular vesicle cargo and metabolomic profiles, will facilitate early diagnosis and monitoring of treatment response (175). Third, rigorous preclinical optimization of cell therapy parameters (dose, timing, route and combination with hypothermia) must be followed by adequately powered multicenter trials with long-term neurodevelopmental follow-up (177). Finally, a lifespan perspective acknowledging that early neurodevelopmental disturbances may predispose to later neurodegenerative processes reinforce the need for sustained surveillance and early intervention strategies extending well beyond the neonatal period.

Three priority research areas are identified: i) Prospective validation of epigenetic, OS and miRNA biomarkers for early outcome prediction (57,62); ii) optimization of therapeutic windows for candidate agents through pharmacokinetic studies; and iii) development of integrated multimodal risk prediction algorithms (162). Regarding translational readiness, caffeine is ready for phase III trials with neurodevelopmental primary outcomes (120,122); melatonin and erythropoietin require further dose-optimization and patient-selection studies (114,119); and HDAC inhibitors, miRNA-based approaches and cell-based therapies remain at preclinical stages requiring safety and target-engagement validation (128,144). Future trials should incorporate biomarker-enriched enrolment, adaptive designs, long-term neurodevelopmental follow-up (≥2 years) and biomarkers requiring validation include F2-isoprostanes, 8-OHdG, DNA methylation signatures and circulating miRNAs. The OS epigenetic framework provides a unifying thread that connects these diverse priorities: it offers a mechanistic rationale for biomarker selection, a biological basis for AI-based risk stratification and a molecular target for therapeutic development. The convergence of these diverse but complementary approaches offers genuine hope that the paradigm is shifting from reactive neuroprotection to predictive, personalized neurorestoration for the most vulnerable patients.

8. Conclusions

Preterm brain injury arises from converging mechanisms wherein OS not only causes acute damage but also triggers enduring epigenetic modifications that program long-term neurodevelopmental outcomes. This OS epigenetic axis serves as the common pathogenic denominator that unifies the diverse cellular responses, from OPC maturational arrest to microglial activation and astrocyte reactivity and provides a coherent framework for understanding why single-target interventions have had limited success. The complex cellular interplay involving oligodendrocytes, microglia and astrocytes underpins this pathophysiology. Emerging AI applications now enable early risk stratification and personalized monitoring. Future neuroprotective strategies must integrate multimodal approaches targeting oxidative-epigenetic pathways with precisely timed, cell-specific interventions to translate mechanistic insights into improved clinical outcomes for this vulnerable population.

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YG and XK led the project's conception and critical revision. YL and LW contributed substantially to the design, literature synthesis and drafting of major sections. FS, HW and XS provided specialized comments and suggestions on methodological and technical content. All authors participated in the intellectual development, manuscript revision, final approval and assumes public accountability for their contributions to the present review. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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