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Review

Redox System Dysfunction as a Key Mechanism in Autism Spectrum Disorder Pathogenesis

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Abstract

Autism Spectrum Disorder (ASD) is a complex and multifactorial neurodevelopmental condition whose pathogenesis remains only partially elucidated. Earlier accounts of oxidative stress in ASD often relied on the reductive paradigm of an imbalance between oxidants and antioxidants. In contrast, this narrative review, based on a systematic examination of 1102 publications indexed in scientific databases from 2002 to July 2025, reframes the discussion in terms of redox system dysfunction, a broader and more integrative construct. Here, reactive oxidant species, molecular targets, and reducing/antioxidant counterparts are considered elements of a dynamic circuitry whose maladaptation progressively undermines homeostasis. The sequence of events unfolds in three stages. The first is primary redox dysfunction, manifesting as alterations in metabolic, signaling, and defense pathways. From this disturbance, a second stage arises, marked by functional derailment of cellular compartments—from membranes and cytosol to organelles and nuclei—including mitochondrial and peroxisomal deficits. Ultimately, a third stage emerges, defined by neurodevelopmental alterations such as impaired neurotransmission, synaptic dysfunction, abnormal plasticity, morphogenetic defects, neuroinflammation, and gut–brain–microbiota disarrangements. This progression situates the redox system as a central hub at the interface between human cells and the microbiota, resonating with the ecological and evolutionary principles of the holobiont and the One Health framework. By weaving dispersed evidence into a coherent perspective, this review advances beyond previous analyses, offering a unifying paradigm that connects biochemical dysfunction to clinical heterogeneity in ASD and opens new directions for interdisciplinary research.

Keywords: Autism Spectrum Disorder; neuroinflammation; neurodevelopmental vulnerability; redox system; oxidative stress; mitochondrial dysfunction

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1. Introduction

Autism Spectrum Disorder (ASD) is a multifactorial neurodevelopmental condition defined by social-communication deficits and restricted behaviors, with prevalence now estimated at 1 in 36 children in the United States [1–4]. Its etiology involves a complex interplay of genetic, epigenetic, and environmental influences, yet converging evidence highlights a central biochemical vulnerability: redox imbalance [5–7].

More than 1000 genes have been implicated in ASD, many of which affect synaptic function, chromatin remodeling, and developmental signaling, with several intersecting

pathways sensitive to oxidative regulation. On the other hand, epigenetic modifications and environmental factors such as maternal immune activation (MIA) or pollutant exposure further challenge redox homeostasis [5,8]. Therefore, traditionally attributed to disrupted synaptogenesis, connectivity, and neuroinflammation [9,10], ASD is now increasingly framed within a redox-centered model where oxidative stress (OS) integrates diverse pathogenic inputs [11–14].

In our view, OS is not a static imbalance but the dysfunctional output of the redox system—a conserved triad of reactive oxidant species (ROS), molecular targets, and reducing/antioxidant (AOX) agents that normally orchestrates metabolic, signaling, and defensive pathways, through exchange of single electrons [15–18]. In ASD, we hypothesize that this adaptive circuitry collapses into chronic oxidative distress, reshaping neurodevelopmental trajectories [19,20].

To develop this perspective, we conducted a targeted literature search across PubMed, Scopus, ResearchGate, Google Scholar, and Web of Science, identifying 1102 articles published between 2002 and July 2025. Sources were selected to cover genetic, epigenetic, environmental, neurobiological, and biochemical aspects of ASD, with studies limited to biomarkers or nutraceutical interventions intentionally excluded. The goal was not to provide a protocol-driven systematic review but rather a narrative synthesis, integrating heterogeneous findings into an interpretative framework that highlights the centrality of redox system dysfunction in ASD pathogenesis.

Before expanding this hypothesis, we briefly revisit how "oxidative stress" is currently conceptualized in the literature.

2. Reconsidering the Concept of Oxidative Stress: Some Possible Shortcomings

Despite extensive research, the concept of OS in ASD remains ambiguous, limiting data interpretation and clinical translation [19,21,22]. Most studies still rely on Halliwell's classical paradigm—"an imbalance between reactive oxygen species production and antioxidant defenses, disrupting redox signaling and/or causing molecular damage." While historically useful, this model oversimplifies the compartmentalized and heterogeneous redox biology of the brain [23,24]. Crucially, the distinction between oxidative eustress—a physiological adaptive response—and oxidative distress—a maladaptive state—is often overlooked, with ASD research trapped in the oxidant–antioxidant dichotomy [23,25,26].

Critical analysis reveals recurrent misconceptions. A common error is treating the electron as the unit of exchange in redox reactions, rather than the reducing equivalent unit [27]. Similarly, OS is often conflated with all redox reactions, when only single-electron transfer defines the process [28,29]. Reactive oxidant species are usually limited to oxygen- and nitrogen-centered radicals, neglecting carbon-, sulfur-, and chlorine-centered species, which also contribute to ASD pathogenesis [19,20]. Superoxide is frequently mischaracterized as a reactive oxidant species, obscuring the nuanced role of superoxide dismutases (SOD) [25,30]. Free radicals are routinely portrayed as universally "highly reactive oxidants," disregarding their potential to act as oxidants or reductants depending on redox potential, and their variable stability [19,20]. Definitions often exclude biological targets, reducing redox dynamics to a simplistic battle between oxidants and AOX [15,31]. This "good versus bad" dichotomy also blurs the distinction between reducing species and AOX, overlapping but not identical categories [21,22] Compartmentalization across tissues, cell types, and organelles is largely neglected, fostering misleading generalizations [32]. Additional misconceptions concern the nervous system. It is often depicted as strictly aerobic and oxygen-dependent, although neural stem cells thrive in hypoxic niches, challenging traditional assumptions [32–34]. Moreover, the nervous system is usually presented

as a producer of reactive oxidants, with insufficient recognition of its vulnerability as a primary target [35,36].

Altogether, these inaccuracies highlight the urgent need to refine the OS framework in ASD. A revised model must distinguish eustress from distress, acknowledge chemical specificity and spatial compartmentalization, and integrate biological targets [37,38]. Such a framework is essential for clarifying pathogenetic mechanisms, improving diagnostic strategies, and guiding innovative therapeutic approaches [25,37,39,40].

3. Rethinking the Starting Point in ASD Pathophysiology: From Oxidative Stress to Redox System

Understanding OS in ASD requires moving beyond the simplistic imbalance between oxidants and antioxidants, toward a systems-based view of redox biology [15,31,34]. Oxidative stress is now seen as an adaptive response within the redox system, which operates through single reducing-equivalent exchanges involving three interdependent actors: an oxidant species, a molecular target, and a reducing/AOX species [16–18]. This triad regulates metabolism, signaling, and defense under both physiological and pathological conditions, as depicted in Figure 1.

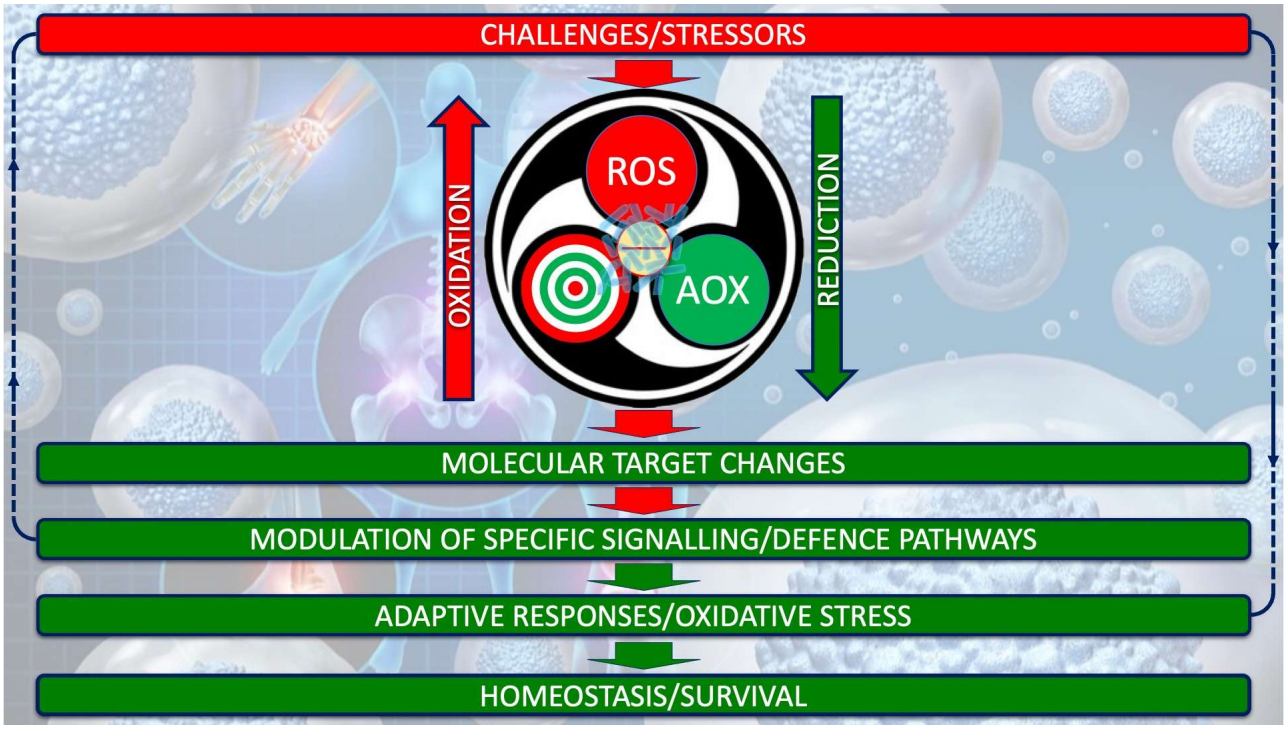


Figure 1. Redox system architecture. The redox system is not a mere oxidant/antioxidant counterbalance but a highly dynamic biochemical network that finely regulates single-electron (the negative electric charge at the center of the system) transfers between reactive oxidant species (ROS), molecular targets, and reducing/AOX agents. This orchestrated exchange interfaced with gut microbiota (superimposed in transparency on the electric charge) underpins the adaptive capacity of cells to sense, process, and resolve oxidative challenges, thereby safeguarding redox homeodynamics.

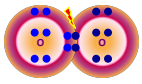
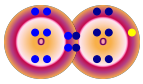
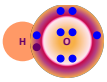
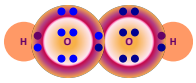
Reactive oxidant species extend beyond oxygen- and nitrogen-centered radicals (reactive nitrogen species, RNS) to include sulfur-, carbon-, and chlorine-centered species, each with distinct reactivities (Table 1) [15,41,42].

Among oxygen-centered species, hydrogen peroxide (H_2O_2), with its longer half-life, often serves as a signaling mediator, whereas hydroxyl radicals or hypochlorite exert immediate destructive effects (Table 2) [41,42].

Table 1. Classification of reactive species involved in redox system.

Chemical Species	Formula	Class	Chemical Species	Formula	Class
Singlet oxygen	$^1O_2$	Non radical	Nitric oxide	$NO^\bullet$	Radical
Superoxide anion (Reducing species)	$O_2^{\bullet-}$	Radical	Nitrous acid	HNO_2	Non radical
Ozone	O_3	Non radical	Nitric tetroxide	N_2O_4	Non radical
Hydroxyl radical	$HO^\bullet$	Radical	Nitric trioxide	N_2O_3	Non radical
Hydrogen peroxide	H_2O_2	Non radical	Peroxynitrite	$ONOO^-$	Non radical
Alkyl radical	$R^\bullet$	Radical	Peroxynitrous acid	ONOOH	Non radical
(Alkyl-)peroxyl radical	$ROO^\bullet$	Radical	Nitronium cation	NO_2^+	Non radical
(Alkyl)hydroperoxide	ROOH	Non radical	(Alkyl)peroxynitrite	$ROONO^-$	Non radical
Semiquinone (from CoQ10)	$Q^\bullet$	Radical	Hypochlorous acid	HClO	Non radical
Tocopheryl (from vit-E)	$E\text{-}O^\bullet$	Radical	Thiyl	$-S^\bullet$	Radical

Table 2. Chemical structure, main sources of production, mean migration distance, half-life ($T_{1/2}$), main molecular targets, and scavenging systems of the most common oxygen-centered reactive oxygen species.

Reactive Oxygen Species	Main Sources of Production	Mean Migration Distance	$T_{1/2}$	Main Molecular Targets	Scavenging Systems
Singlet oxygen 	Plasmamembrane Mitochondria	30 nm	1–4 µs	PUFA double bonds Protein coupled thiol	Carotenoids Tocopherols
Superoxide anion 	Plasmamembrane Mitochondria	30 nm	1–4 µs	Iron-Sulphur clusters	Superoxide dismutases
Hydroxyl radical 	Membranes Mitochondria Cytosol	1 nm	1 µs	Any organic molecule (rapidly reacting with DNA)	Flavonoids
Hydrogen peroxide 	Plasmamembrane Mitochondria Peroxisomes	1 µm	1 ms	Preferably cysteine's moieties	Catalase Glutathione peroxidases

Molecular targets include lipids, proteins, and nucleic acids: polyunsaturated fatty acids (PUFA) are highly susceptible to peroxidation, while protein thiols act as redox switches controlling enzymes and transcription factors [15,43–48].

Reducing agents such as glutathione (GSH), tocopherols, and ascorbate buffer these modifications; reversible changes can be corrected, but irreversible ones, such as lipid hydroperoxides, demand enzymatic detoxification (Figure 2) [49,50].

This architecture sustains both physiological eustress and pathological distress (Figure 3) [34]. In health, eustress underlies essential processes—respiration, motility, immune defense, excitability, and synaptic plasticity—critical for neurodevelopment (Figure 3A) [26,41,46]. When regulation fails, due to genetic predisposition, environmental exposures, or metabolic deficits, the system shifts toward oxidative distress, defined by excess reactive species, insufficient AOX responses, and cumulative molecular damage (Figure 3B) [16–18,23,34,43,51].

The nervous system exemplifies this vulnerability. Despite its small mass, it consumes a disproportionate share of oxygen, predisposing to oxidant overproduction from mitochondria, nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) oxidases, nitric oxide synthases (NOS), and monoamine oxidases (MAO) [35,52–57]. Neural membranes, rich in PUFA, are particularly sensitive, while antioxidant reserves are

modest [58–61]. Moreover, neurons, astrocytes, and microglia possess distinct redox profiles shaped by vascular supply and barrier systems, making the brain both a major generator and a prime target of oxidative imbalance [62–65].

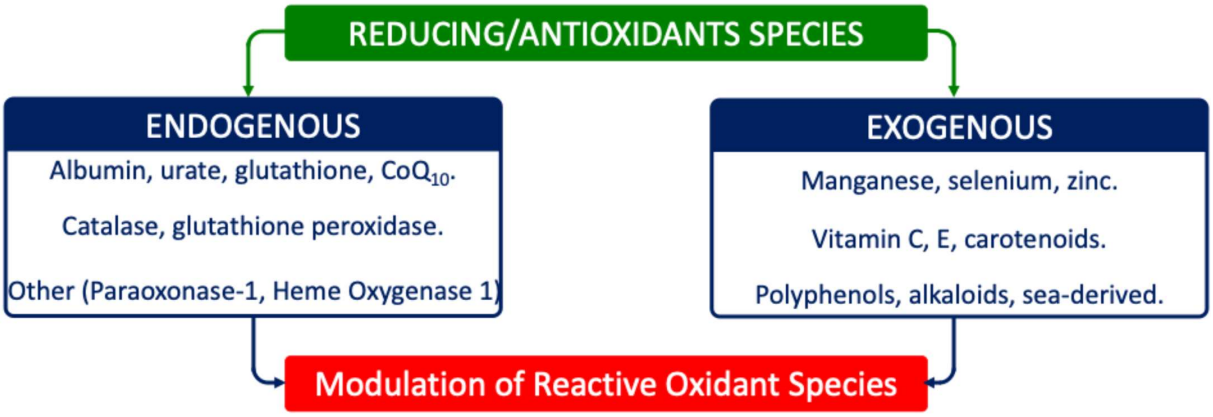


Figure 2. Main reducing/AOX species involved in redox system. Reducing/AOX species include either endogenous or exogenous compounds/enzymes.

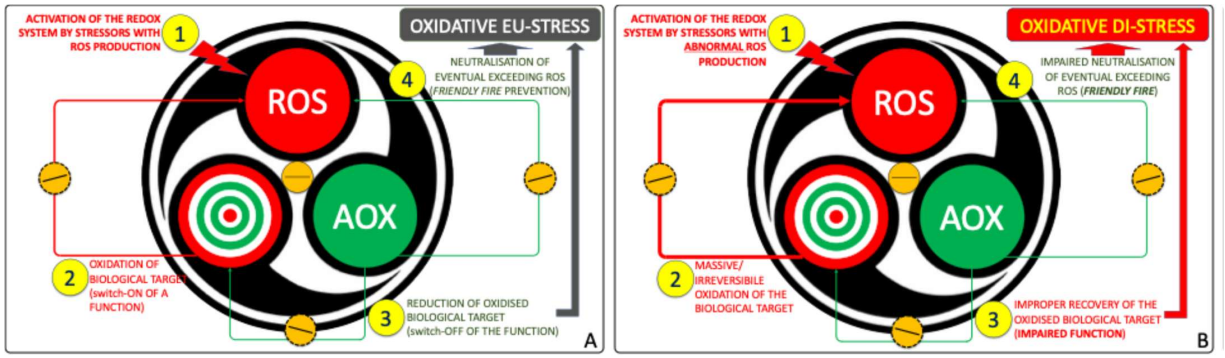


Figure 3. The redox system as manager of OS. (**A**) Under physiological conditions, (1) controlled bursts of Reactive Oxidant Species (ROS) act as signals, (2) transiently oxidizing molecular targets and modulating their function. (3) Antioxidants (AOX) then restore redox balance, while (4) surplus ROS are neutralized, establishing a self-limiting cycle of adaptive oxidative eustress compatible with cellular fitness. (**B**) When this circuitry is dysregulated, (1) ROS production escapes control, (2) causing irreversible oxidation of key and off-target molecules. (3) The antioxidant arm fails to re-establish equilibrium, and (4) the system shifts from eustress to oxidative distress, a hallmark of redox system failure.

Genetic and epigenetic backgrounds further modulate susceptibility, as do environmental agents such as pollutants, drugs, or stress [66–68]. In predisposed contexts, these triggers precipitate collapse into oxidative distress. Within the central nervous system (CNS), this maladaptive state fosters microglial hyperactivation, neuroinflammation, and impaired synaptic morphogenesis, redirecting developmental trajectories toward atypical circuits typical of ASD [69,70].

Thus, OS is indispensable for physiology but becomes pathogenic when unresolved. Recognizing oxidative distress as a core ASD risk factor underscores the need for biomarkers that capture its spatial and temporal dynamics and supports the hypothesis that redox dysfunction drives neurodevelopmental divergence [37,51,71].

In our hypothesis, depicted in Figure 4, redox system dysfunction in autism arises from excess ROS, genetic–epigenetic vulnerability of molecular targets, and limited antioxidant performances. This imbalance alters signaling, metabolism, and defense pathways, leading

to multiple cell function failure. Feedback loops perpetuate oxidative–nitrosative stress, driving neurodevelopmental abnormalities consistent with ASD.

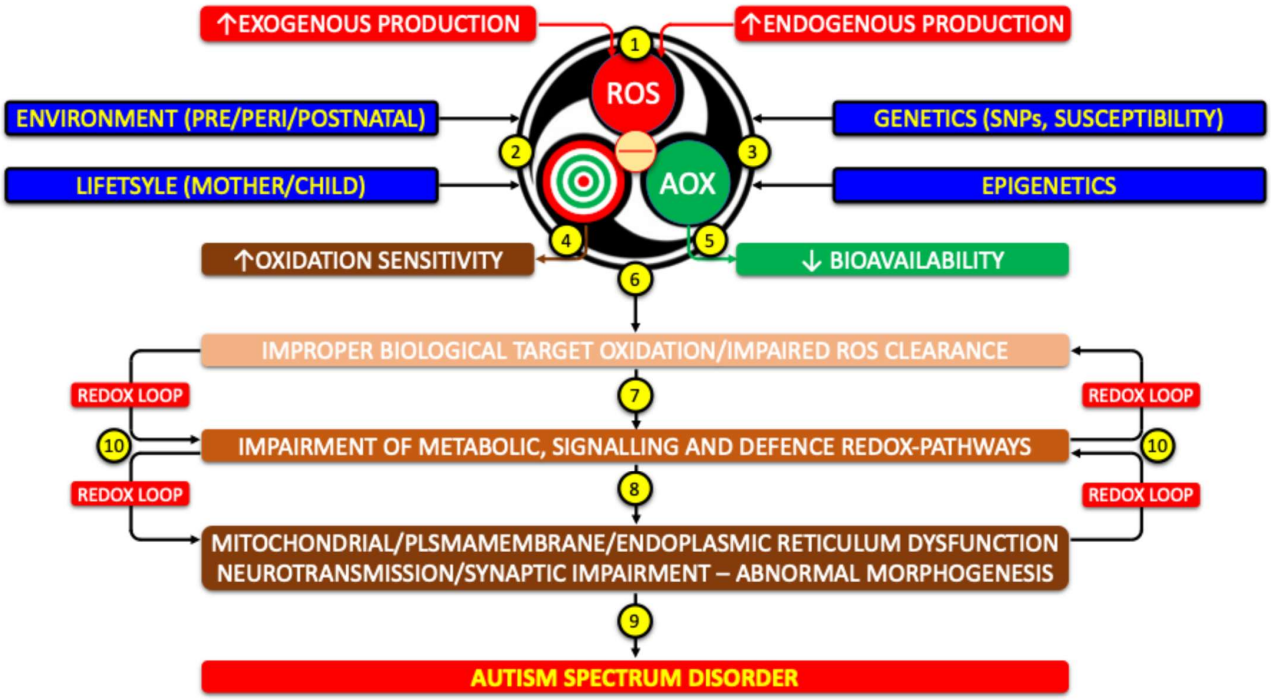


Figure 4. Potential role of redox system dysfunction in the pathogenesis of autism (1) Excess production of ROS, of endogenous or exogenous origin, activates the redox system. (2) Environmental and lifestyle factors and (3) genetic/epigenetic background modulate this response. (4) Increased susceptibility of molecular targets and/or (5) reduced AOX availability trigger (6) a chain reaction. (7) Altered metabolic, signaling, and defense pathways lead to (8) secondary dysfunctions, such as mitochondrial impairment and disruption of the microbiota–gut–brain–mitochondria axis. These changes (9) drive neurodevelopmental alterations consistent with ASD. (10) The process is sustained by self-perpetuating feedback loops of redox dysfunction. (SNPs: Single Nucleotide Polymorphisms).

4. Reactive Oxidant Species Levels Are Increased in ASD

In ASD, ROS arise from both excessive production and insufficient neutralization, driven by environmental insults, metabolic imbalance, dysbiosis, and chronic inflammation [7,11,12,51,72,73]. Their pathogenicity depends not only on the species involved but also on mechanisms of generation and the developmental stage at which they occur, being especially harmful in cortical and cerebellar microenvironments during sensitive windows [62,74–76]. Reactive oxidant species thus act as both initiators and amplifiers of neurobiological dysfunction, reinforcing maladaptive cycles. This evidence positions redox imbalance as a central driver of ASD and underscores the importance of early recognition and personalized strategies to mitigate long-term neurodevelopmental impact [19,37,71].

4.1. Increased Production of ROS by Direct Mechanisms in ASD

Mitochondrial oxidative phosphorylation and dopamine autoxidation are major endogenous ROS sources in ASD [77]. In the respiratory chain, a small fraction of oxygen escapes the four-electron reduction for ATP synthesis, generating superoxide, hydrogen peroxide, and hydroxyl radicals [78,79]. Given that the brain consumes nearly 20% of body oxygen despite its small mass, this leakage has disproportionate consequences, making neural tissue particularly vulnerable (Figure 5) [35,78,79].

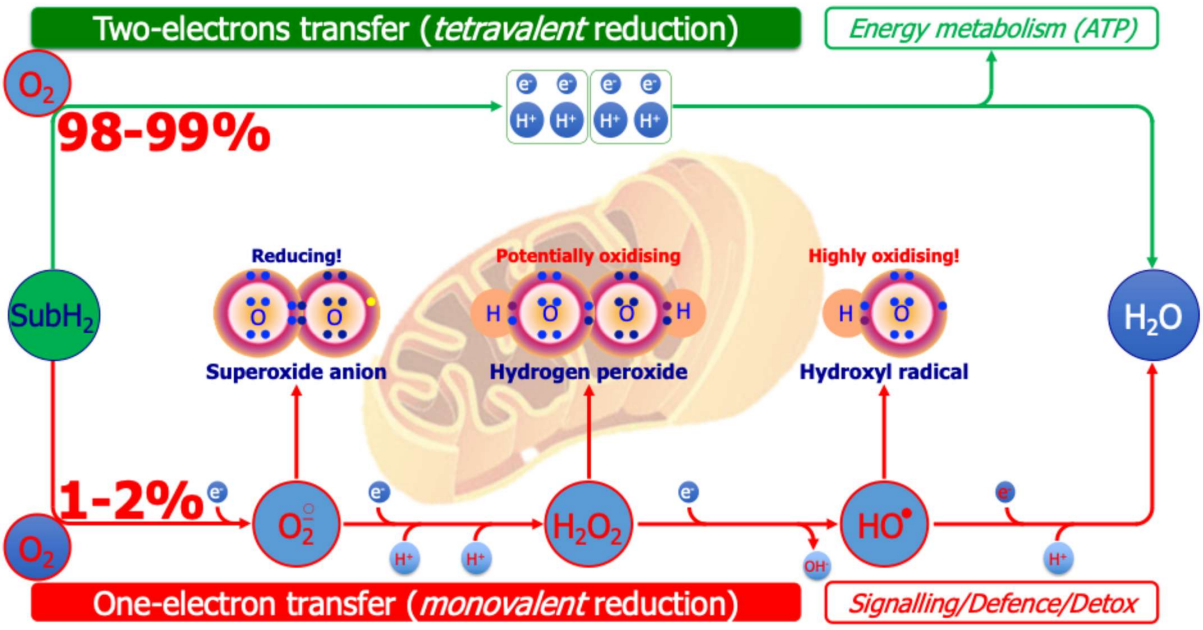


Figure 5. Generation of oxygen-centered reactive species from the mitochondrial respiratory chain. A total of 98–99% of inspired oxygen receives reducing equivalents removed from various metabolic substrates (e.g., fatty acids, glucose) in pairs (tetravalent reduction), generating ATP (top of figure). The remaining 1–2% of inspired oxygen, however, receives reducing equivalents removed from various substrates through one-electron transfer reactions (monovalent reduction), generating oxygen-centered reactive species (bottom of figure), exploited for signaling or defense/detoxification purposes.

Dopamine autoxidation in substantia nigra, striatum, and limbic regions generates quinones and ROS that modify cysteine residues, impair mitochondria, activate microglia, and damage vessels. These events translate into impaired dopaminergic signaling, disruption of synaptic plasticity, and chronic neuroinflammation, contributing to ASD features such as social deficits and stereotypies [78–85].

4.2. Increased Production of ROS by Indirect/Catalytic Mechanisms in ASD

4.2.1. Increased Production of ROS by Inorganic Catalysts

Iron and copper catalyze the conversion of hydrogen peroxide into hydroxyl radicals via Fenton and Haber–Weiss reactions [15,24,86,87]. In ASD, impaired ferritin buffering, neuroinflammation, and mitochondrial dysfunction increase free iron [29], amplifying lipid peroxidation and favoring ferroptosis, which destabilizes membranes and synaptic integrity. Copper-dependent redox cycling may add risk of cuproptosis [88,89]. Genetic and epigenetic alterations in redox-regulating pathways further magnify brain vulnerability to these processes [90–94].

4.2.2. Increased Production of ROS by Enzyme's Dysregulation

Nicotinamide Adenine Dinucleotide Phosphate Oxidases

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX and DUOX isoforms) are membrane-bound oxidoreductases whose sole function is to generate superoxide anion or hydrogen peroxide by transferring electrons from NADPH to oxygen, fueled by the pentose phosphate pathway. In particular, NOX4 and DUOX1/2 generate hydrogen peroxide [52,95,96].

In the CNS, NOX-derived ROS normally contribute to signaling and defense, but in ASD dysregulation become pathogenic. Neuronal and astrocytic NOX4 activity enhances oxidative distress, while microglial NOX2—consistently upregulated in prefrontal

cortex and cerebellum—drives chronic neuroinflammation [53,54]. This hyperactivation destabilizes neuronal and glial membranes via lipid peroxidation, weakens resilience, and promotes ferroptosis or cuproptosis [97–100]. The resulting alterations compromise synaptic integrity and connectivity, linking enzymatic dysregulation directly to neurodevelopmental deficits [101–103].

Myeloperoxidase

Myeloperoxidase (MPO) is a heme-containing peroxidase that uses hydrogen peroxide, largely generated by NADPH oxidases, to oxidize chloride into hypochlorous acid, a highly reactive oxidant that preferentially modifies amino groups [104]. Under neuroinflammatory conditions, microglial MPO amplifies oxidative cascades and becomes a key mediator linking oxidative distress with inflammation, thereby shaping neuro-oxi-inflammation [105–109]. Beyond intracellular activity, MPO has been detected in extracellular vesicles, suggesting it can propagate oxidative signals beyond the producing cell. This extracellular dissemination is increasingly associated with ASD and other CNS disorders, bridging local oxidative damage with systemic inflammatory responses [110,111].

Nitric Oxide Synthases

Nitric oxide synthases—endothelial (eNOS), neuronal (nNOS), inducible (iNOS), and the putative mitochondrial isoform (mitNOS)—are heme–flavoproteins that convert L-arginine into nitric oxide (NO) and L-citrulline [112]. Their activity requires NADPH, flavins, heme, tetrahydrobiopterin (BH_4), calmodulin, and stable dimerization [113]. Endothelial NOS and nNOS are constitutive and Ca^{2+}/calmodulin-dependent, whereas iNOS is transcriptionally induced during inflammation, producing sustained NO fluxes [112]. Mitochondrial NOS may fine-tune oxidative phosphorylation, but excessive activity inhibits cytochrome c oxidase, reducing ATP and increasing ROS [114–116].

As a diffusible messenger, NO regulates cyclic guanyl monophosphate (cGMP) signaling, long-term potentiation and depression, cerebral blood flow, and retrograde synaptic signaling [117]. Yet overproduction in immune or glial cells drives nitrosative stress [118,119]. Under hypoxia or tetrahydrobiopterin deficiency, NOS uncouples, shunting electrons to oxygen and generating superoxide anion [118,119]. Nitric oxide and superoxide anion rapidly combine to form peroxynitrite ($ONOO^-$), a potent oxidant that nitrates tyrosine moieties, oxidizes thiols, damages DNA, and disrupts mitochondria [72,76,117,120–122]. In ASD, NOS variants, iNOS hyperactivation, and nNOS dysregulation foster chronic redox imbalance, mitochondrial dysfunction, and synaptic disorganization [123]. The convergence of NO excess, peroxynitrite, and ROS crosstalk establishes a pathogenic loop of oxidative–nitrosative stress that critically shapes neurodevelopmental vulnerability [124–126].

The Unique Potential Role of Gamma-Glutamyl Transferase/Transpeptidase in ASD

Gamma-glutamyl transferase/transpeptidase (γ-GT) is a plasma-membrane ectoenzyme that catalyzes the transfer of γ-glutamyl groups from GSH to water or amino acids, sustaining GSH turnover and amino acid transport. When γ-GT is overexpressed or mislocalized, extracellular cysteinyl-glycine can reduce ferric to ferrous iron, fueling Fenton chemistry and hydroxyl-radical formation [127,128]. The resulting thiyl-radical environment promotes cis–trans isomerization of fatty acyl chains and accumulation of trans-fatty acids in neuronal membranes (Figure 6) [129,130]. Such structural changes may reduce membrane fluidity, disrupt lipid rafts, and sensitize lipids to peroxidation, thereby amplifying neuro-oxi-inflammation and increasing ferroptotic risk [131,132]. In the CNS, astrocytic and endothelial γ-GT polymorphisms further modulate this vulnerability [133]. From

a translational perspective, γ-GT dysregulation links altered membrane dynamics and synaptic signaling to heightened oxidative burden in ASD [133].

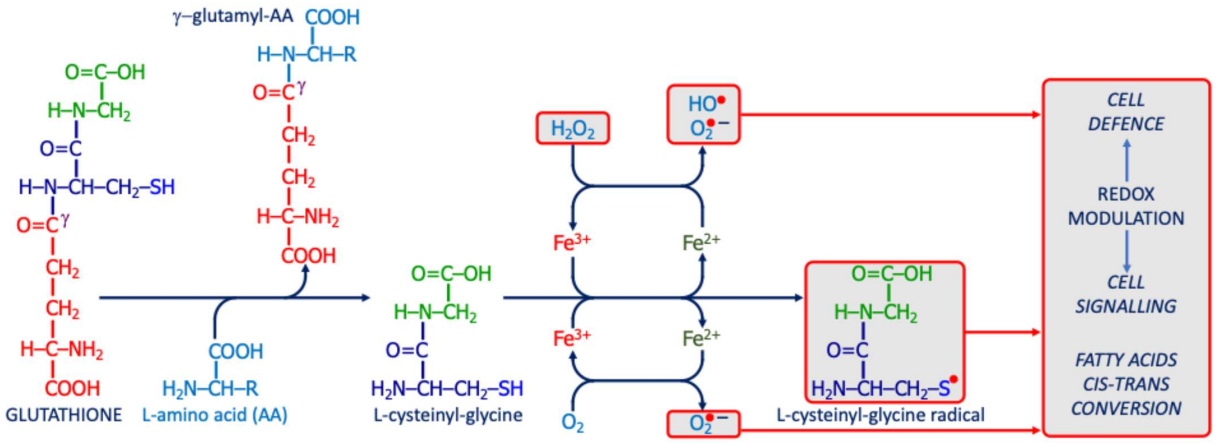


Figure 6. The potential pro-oxidant action of γ-glutamyl-transferase/transpeptidase. The enzyme releases L-cysteinyl-glycine from GSH; this dipeptide can react with iron to generate ROS, producing a radical that modulates redox signaling or disrupts membrane integrity (e.g., via cis–trans isomerization of unsaturated fatty acids).

Mitochondrial Pro-Oxidant Enzymes

α-ketoglutarate dehydrogenase, succinate dehydrogenase, glycerol-3-phosphate dehydrogenase, aconitase, and dihydroorotate dehydrogenase form a pool of pro-oxidant mitochondrial systems that contribute to ROS production [134–138]. In the CNS, where energy demand and mitochondrial density are high, this production is physiologically intense but must remain tightly regulated [139]. When dysregulated, oxidative overload damages macromolecules and fosters conditions that compromise both neurodevelopment and neurodegeneration [139].

On the outer mitochondrial membrane, MAO-A and MAO-B further add to the burden by degrading dopamine, serotonin, and norepinephrine, generating hydrogen peroxide and ammonia [56]. Genetic polymorphisms, such as MAO-A Variable Number Tandem Repeat (VNTR) variants, influence monoaminergic tone and have been linked to ASD-related neurodevelopmental and behavioral phenotypes [140–142]. Monoamine oxidase A predominates in catecholaminergic neurons, whereas MAO-B is enriched in serotonergic neurons and astrocytes, particularly in striatum, substantia nigra, and frontal cortex—regions consistently implicated in ASD. Here, excessive MAO activity or insufficient catalase (CAT) buffering promotes oxidative distress [57,85,143].

From a translational perspective, mitochondrial ROS production and MAO-derived OS directly interfere with neurotransmitter balance, synaptic plasticity, and neuronal survival. This dual impact on energy metabolism and neurotransmission reinforces mitochondria as hubs where biochemical dysregulation translates into ASD neurodevelopmental abnormalities.

Other Pro-Oxidant Enzymes

Very long-chain acyl-CoA oxidase (ACOX) initiates peroxisomal β-oxidation by transferring electrons directly to oxygen, generating hydrogen peroxide, the main peroxisomal ROS. Additional oxidases, including D-amino acid oxidase, also contribute. Normally, CAT detoxifies hydrogen peroxide, but when impaired, hydrogen peroxide accumulation drives oxidative distress [144–146].

Cyclooxygenases (COX) and lipoxygenases (LOX) oxidize arachidonic acid to prostaglandins and leukotrienes, producing reactive metabolites such as lipid hydroperoxides and 4-hydroxynonenal (4-HNE). Elevated COX-2 and LOX expression in ASD correlate

with lipid peroxidation and neuro-oxi-inflammation [58,147]. Fatty-acid desaturases, essential for brain lipid composition, when dysfunctional—often due to Single Nucleotide Polymorphisms (SNPs)—favor ROS production, disrupt lipid metabolism, and contribute to neurodevelopmental deficits [59,148,149].

Cytochrome P_{450} (CYP) enzymes hydroxylate steroids, prostaglandins, leukotrienes, and xenobiotics, generating ROS by-products. Dysregulation alters neurosteroid and eicosanoid balance, enhances oxidative stress, and promotes synaptic dysfunction. Genetic polymorphisms modulate these outcomes [150–154].

Xanthine oxidase (XO), a pathological variant of xanthine dehydrogenase, participates in purine catabolism but shifts to XO during ischemia, reducing oxygen to superoxide and hydrogen peroxide. Upon reperfusion, XO contributes to neuronal oxidative distress in ASD, consistent with elevated serum activity. Xanthine oxidase also reduces nitrites to NO and is partially inhibited by quercetin [155–158].

The kynurenine pathway has gained prominence. Indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase generate superoxide during tryptophan oxidation, while kynurenine 3-monooxygenase consumes NADPH to form 3-hydroxykynurenine, which auto-oxidizes to radicals and hydrogen peroxide. Quinolinic acid over-activates N-Methyl-D-Aspartate (NMDA) receptors, increasing Ca^{2+}-driven ROS and mitochondrial dysfunction [159–163]. In ASD, these alterations amplify neuro-oxi-inflammation and impair neurodevelopment.

5. Biological Target Accessibility/Vulnerability Is Impaired in ASD

5.1. The Polyunsaturated Fatty Acid Target

Polyunsaturated fatty acids in neuronal and glial membranes are major targets of ROS. In ASD, lipid peroxidation represents a pivotal mechanism linking redox imbalance to neurodevelopmental dysfunction (Figure 7, left side).

Nicotinamide adenine dinucleotide phosphate oxidase hyperactivation is a primary trigger [52]. Increased NOX activity in cerebellum and prefrontal cortex elevates oxidative burden and behavioral abnormalities in BTBR T+ Itpr3tf/J mouse strain (BTBR) mice, while environmental exposures such as phthalates or ethanol intensify these effects [54,164,165]. In ASD children, NOX2 overexpression—partly mediated by toll-like receptor (TLR) 4 signaling—drives neuroinflammation. Crosstalk between NOX and nNOS amplifies ROS/RNS generation, accelerating PUFA oxidation [166].

Peroxidation of PUFA-rich membranes initiates chain reactions producing lipid peroxides. Normally, selenium-dependent glutathione peroxidase (GPx) detoxifies these intermediates, but reduced GPx activity, frequently reported in ASD, allows their accumulation [59,99,100]. Peroxides can react with transition metals, propagating ferroptosis or cuproptosis, or degrade into aldehydes such as malondialdehyde (MDA) and 4-HNE [99,167]. Elevated in ASD plasma and the brain, these aldehydes form adducts with proteins, lipids, and DNA, impairing enzymatic activity and synaptic integrity [59,99,100]. 4-hydroxynonenal also acts as a signaling mediator, activating Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NF-κB), Activator Protein-1 (AP-1), and Mitogen-Activated Protein Kinase (MAPK) cascades, reinforcing neuroinflammation [168].

Ferroptosis, an iron-dependent form of regulated cell death, is increasingly implicated in ASD [101,169]. Glutathione peroxidase 4 deficiency and GSH depletion lower the ferroptotic threshold, while mitochondrial dysfunction and iron dysregulation sustain it [102]. Excess ferroptosis during neurodevelopment disrupts pruning and cortical organization [170,171].

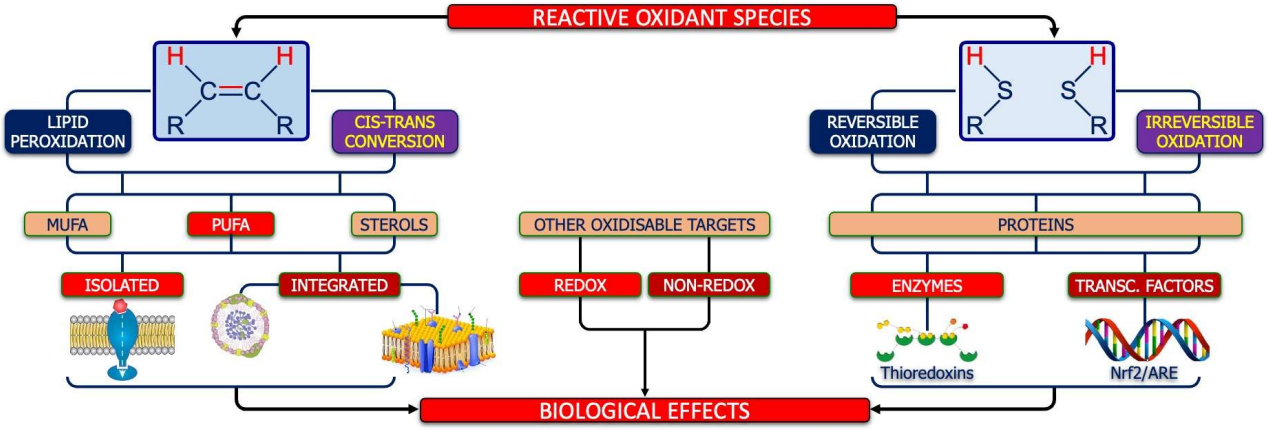


Figure 7. Molecular targets of ROS. As shown on the left side, the first target of ROS is the double bond between carbon atoms, whose oxidation can lead to lipid peroxidation or cis–trans conversion, both affecting monounsaturated fatty acids (MUFA), poly-unsaturated essential fatty acids (PUFA), and sterols. The oxidation of isolated fatty acids (including the PUFA moiety of endocannabinoids) can have an impact on cell reactivity/signaling, while the oxidation of phospholipid-bound fatty acids could have an impact on structure and function of circulating lipo-proteins and/or cell membranes. Globally, lipid peroxidation and/or the isomeric cis–trans conversion can modify the thickness and/or the fluidity of neuronal/glia membranes, with impairment of energetic, metabolic, and signaling flow between the two sides of them. On the other hand, as shown on the right side, ROS can also react, reversibly or irreversibly, with the reduced thiols of cysteine pairs belonging to the same protein (including enzymes, such as thioredoxins, or transcriptional factors such as Nrf2) thus contributing to the adaptative functions of the redox system in nervous system. Finally, as shown in the center of figure, ROS can impact other targets, such as redox-sensitive targets (e.g., oxidants, such as nitric oxide, or antioxidants, such as bilirubin), another adaptative mechanism under the control of the redox system.

Nitric oxide and peroxynitrite also oxidize PUFA, generating nitro-PUFA that, when excessive, compromise membrane fluidity and synaptic signaling [172]. In addition, cis–trans isomerization by thiyl radicals rigidifies membranes, a process worsened by dietary trans-fats [129,173,174]. Such trans-fats may enter via unhealthy diets—whose consumption has been linked to ASD severity—or be produced endogenously under oxidative distress. Lipidomic studies in ASD confirm altered fatty acid composition and increased trans-fat levels [175–177].

Altogether, PUFA peroxidation, aldehyde toxicity, ferroptosis, nitro-PUFA accumulation, and trans-fat incorporation converge as key pathogenic drivers, bridging redox imbalance, mitochondrial dysfunction, and neuroinflammation in ASD.

5.2. The Thiol Proteins' Molecular Target

Protein thiol groups are primary targets of reactive oxidants such as hydrogen peroxide and NO [46,178–180] (Figure 7, right side). In ASD, mitochondrial dysfunction, NADPH oxidase hyperactivation, and chronic neuroinflammation increase ROS, amplifying thiol oxidation and nitrosylation with major effects on neuronal physiology [54,164,181–183].

Under physiological conditions, NO from neuronal and inducible NOS regulates neurogenesis and plasticity through cGMP signaling and controlled S-nitrosylation [55,112]. In ASD, persistent iNOS over-activation drives nitrosative stress and peroxynitrite formation; elevated iNOS and nitrosative lesions in Purkinje cells highlight cerebellar vulnerability [118,120,123].

Hydrogen peroxide-mediated thiol oxidation (sulfenylation, disulfides, glutathionylation, and overoxidation) alters enzyme activity and protein interactions [178–180]. Redox-sensitive proteins—including glutamate receptors, ion channels, tubulin, and actin—

malfunction, leading to impaired neurotransmission, cytoskeletal collapse, and synaptic disorganization; severe oxidation may trigger disulfidoptosis, a thiol-dependent cell death linked to mitochondrial dysfunction [184–186].

Aberrant nitrosylation adds disruption: NMDA subunits and scaffolds undergo excessive S-nitrosylation, disturbing the excitatory/inhibitory balance [187]. In SH3 and Multiple Ankyrin Repeat Domains 3 (SHANK3)-deficient mice, widespread hypernitrosylation correlates with defective trafficking, impaired glutamatergic signaling, and ASD-like behaviors [95,188]. Peroxynitrite irreversibly nitrates tyrosines (3-nitrotyrosine), a consistent ASD marker, while NO-mediated modification of mitochondrial proteins undermines oxidative phosphorylation [72].

Nitrosative stress also reprograms transcription by oxidizing Kelch-like ECH-associated protein 1 (KEAP1), aberrantly activating Nuclear Factor erythroid 2–related Factor 2 (Nrf2), and nitrosylating mechanistic target of rapamycin (mTOR) or glyceraldehyde-3-phosphate dehydrogenase (GAPDH) [189,190]. These changes promote apoptosis, impair neurogenesis, and affect vascular regulation; systemically, thiol modifications compromise differentiation, axonal guidance, and synaptic stability, mirrored by elevated plasma nitrotyrosine/nitrates and reduced thiols [72,117,125]. Tetrahydrobiopterin deficiency, by uncoupling NOS, further distorts NO metabolism [113,191].

In summary, chronic nitrosative stress integrates oxidative distress, excitotoxicity, and maladaptive plasticity, consolidating thiol oxidation, nitrosylation, and disulfidoptosis as key mechanisms linking redox imbalance to abnormal neurodevelopment in ASD [124–126].

5.3. Other Molecular Targets

Protein carbonylation—irreversible ROS-driven addition of carbonyl groups—causes loss of function and resistance to proteasomal degradation, promoting accumulation and damage. Elevated carbonyls in the plasma and brain of ASD patients support their dual value as biomarkers and effectors [192].

Mitochondrial DNA (mtDNA), lacking histones and with limited repair, is highly vulnerable: superoxide and hydroxyl radicals induce 8-oxo-2′-deoxyguanosine, strand breaks, and deletions that impair oxidative phosphorylation and further raise ROS [193–195]. Accumulated mtDNA damage in frontal cortex and cerebellum underscores mitochondrial fragility in ASD [193–195].

At the nuclear level, oxidative stress perturbs Cytosine-phosphate-Guanine (CpG) methylation and histone marks, altering programs crucial for synaptogenesis, neurogenesis, and immune regulation [196,197]. These changes link oxidative injury to altered development and immune dysregulation in ASD [196,197].

Translationally, the convergence of protein carbonylation, mtDNA injury, and epigenetic shifts shows how oxidative stress reshapes cellular integrity and gene control, disturbing neurodevelopmental timing and immune homeostasis within ASD's multifactorial pathology [12,62–65].

5.4. Redox-Sensitive Molecular Pathways' Targets

In ASD, whole metabolic/signaling pathways are reprogrammed by redox imbalance [12,48,76]. Central is the thiol pathway: thiol–disulfide exchanges govern redox sensing [15,46,47]. A consistent hallmark is reduced plasma thiols with increased disulfides, indicating a systemic oxidative shift that compromises synaptogenesis, plasticity, and neuroimmune regulation; aberrant disulfide bonding favors misfolding, axonal impairment, and disulfidoptosis-driven vulnerability [184–186,198].

One-carbon metabolism, essential for methyl transfer and epigenetic control, is also impaired: reduced folate, a lower S-adenosylmethionine/S-adenosylhomocysteine (SAM/SAH) ratio, hyperhomocysteinemia, and global hypomethylation affect differentiation, plasticity, and neurotransmission [199,200]. Methylenetetrahydrofolate reductase (MTHFR) variants aggravate these effects, especially with folate deficiency. Metabolomics further links methylation defects with oxidative biomarkers, reinforcing reciprocal redox–epigenetic interactions [199–202].

The endocannabinoid system—anandamide, 2-arachidonoylglycerol (2-AG), cannabinoid (CB) 1/2 receptors, and enzymes—is redox-sensitive and modulates excitatory/inhibitory balance through retrograde control of glutamate and gamma-aminobutyric acid (GABA) release [203,204]. In ASD, oxidative distress reduces arachidonic acid pools, alters receptor expression, and impairs MAPK and PI3K (Phosphoinositide 3-kinase) Protein kinase B (PI3K–Akt) signaling; clinically, decreased anandamide and CB1 correlate with social deficits and oxidative imbalance [205–207].

Transcriptional programs are compromised: NRF2 is underexpressed, limiting induction of heme oxygenase-1 (HO-1), γ-glutamyl-cysteine ligase (GGL), and GPx, thereby undermining GSH homeostasis, lowering the ferroptotic threshold, and sustaining neuroinflammation [48,103,190,208–212]. Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), crucial for mitochondrial biogenesis, is impaired by epigenetic changes and mtDNA damage, leading to energy deficits and heightened oxidative sensitivity [213–216].

Gasotransmitters add fragility. Reduced carbon monoxide (CO) impairs cGMP signaling and associates with severity/autoimmunity [209,217]. Carbon dioxide dysregulation perturbs pH, excitability, and neurovascular coupling [218,219]. Excess hydrogen sulfide (H_2S) can induce oxidative damage and mitochondrial dysfunction [220,221].

Overall, ASD reflects systemic reprogramming of thiol biology, one-carbon metabolism, endocannabinoid tone, transcriptional networks, and gasotransmitter signaling—converging on impaired bioenergetics, maladaptive plasticity, and aberrant epigenetic programming.

6. Decreased Bioavailability/Activity of Reducing/Antioxidant Systems in ASD

6.1. The Neglected Role of Glucose-6-P-Dehydrogenase

Redox dysfunction in ASD is mirrored by altered antioxidant levels/activities across biofluids and tissues [71,222–224]. Central is glucose-6-phosphate dehydrogenase (G6PD), which generates NADPH via the pentose phosphate pathway—the main reservoir of cellular reducing power [225]. Nicotinamide adenine dinucleotide phosphate sustains reductive biosynthesis (cholesterol, membrane fatty acids), fuels NADPH oxidases, and recycles oxidized components such as GSH [226].

Glucose-6-phosphate dehydrogenase deficiency, reported in ASD, reduces NADPH and disrupts the redox network, fostering neuro-oxi-inflammatory cascades [227–229]. Experimental data show that low NADPH impairs synaptogenesis and alters folate metabolism, with adverse effects on myelination and synaptic performance [225].

Translationally, G6PD deficiency represents a pivotal metabolic vulnerability: by weakening systemic antioxidant defenses, it links cellular redox imbalance to disrupted maturation and connectivity, contributing to the neurodevelopmental phenotype of ASD [225,227].

6.2. Glutathione Pathway

In ASD, redox dysfunction is closely tied to impaired GSH metabolism [230]. As the most abundant low-molecular-weight thiol, GSH is vital in the CNS, where high oxidative metabolism constantly challenges redox balance. Beyond its antioxidant role, it regulates detoxification, thiol homeostasis, signaling, and epigenetic programming [11,13,170].

Evidence shows systemic GSH depletion in plasma, lymphocytes, and brain regions such as cerebellum, prefrontal cortex, and hippocampus [231–233]. Environmental toxicants like mercury and lead aggravate this decline, particularly with low sulfur amino acid intake [234,235]. Glutathione biosynthesis depends on GCL, under NRF2 control [236]. In ASD, attenuated NRF2 responses reduce GCL and GPx expression, forming a dysfunctional Nrf2–GSH loop [236,237].

Polymorphisms in GPX1 and glutathione-S-transferases (GSTM1, GSTT1, GSTP1) further weaken defenses [94,238]. This sustains lipid peroxidation and lowers the ratio between reduced and oxidized glutathione (GSH/GSSG ratio)—a robust ASD biomarker —correlating with impaired energy metabolism, synaptic plasticity, and epigenetic regulation [99,231,232].

Functionally, reduced GSH lowers GPx activity, enabling lipid peroxide accumulation, ferroptotic vulnerability, and reactive aldehyde formation (4-HNE, MDA), which form covalent adducts with macromolecules and amplify microglial inflammation [59,99,100]. Chronic dysregulation perpetuates oxidative distress, DNA damage, and abnormal neurodevelopment [19,239,240].

Altered GSH metabolism also reduces the SAM/SAH ratio, impairing DNA and histone methylation [241,242], undermining epigenetic control of neuronal differentiation and immune regulation [243,244]. Normally, glutathionylation protects proteins and tunes signaling; in ASD, impaired glutathionylation destabilizes protein function and mitochondrial bioenergetics [243,244].

Within the system, GPx1 is ubiquitous, while GPx4 uniquely reduces lipid hydroperoxides and prevents ferroptosis [245,246]. Glutathione peroxidase 4 deficiency, increasingly linked to ASD, heightens neuronal vulnerability, with variants such as GPX1 Pro198Leu reinforcing risk [230,234].

Astrocyte–neuron coupling adds another dimension: astrocytes synthesize and export GSH for neuronal uptake, normally enhanced by norepinephrine, but disrupted in ASD [247].

Altogether, impaired synthesis, excessive consumption, defective recycling, genetic susceptibility, and disrupted glia–neuron cooperation converge on persistent redox imbalance. This promotes lipid peroxidation, thiol oxidation, ferroptosis, and abnormal protein modifications, culminating in synaptic dysfunction. By impairing pruning, dendritic maturation, and epigenetic regulation, GSH dysfunction emerges as a defining feature of redoxomic dysregulation in ASD [12,48,62–64,76,248].

6.3. Other Relevant Antioxidant Enzymes

Catalase, a peroxisomal enzyme, decomposes hydrogen peroxide into water and oxygen, preventing oxidative “friendly fire”. Abundant in astrocytes and neurons, it helps maintain redox balance [249–251]. Autism Spectrum Disorder studies report inconsistent findings [75]: reduced activity in post-mortem brain tissue versus compensatory increases in others [158,252]. These discrepancies highlight the limitations of isolated biomarkers and the need for integrated redoxomic evaluation [230]. Heme oxygenase-1, another NRF2-inducible enzyme, degrades heme into biliverdin, CO, and iron. Biliverdin is reduced to bilirubin (antioxidant), CO acts as a cytoprotective signal, and free iron induces ferritin. In ASD, serum HO-1 is reduced while KEAP1 and Nrf2 are elevated, suggesting OS with inadequate HO-1 response [48,217,253].

8-Oxoguanine DNA glycosylase-1 (OGG1) repairs mutagenic 8-oxoguanine lesions. Neuronal OGG1 protects genomic stability, but its deficiency leads to lesion accumulation, a condition linked to ASD [254–256].

Paraoxonase-1 (PON1), an HDL-bound enzyme, hydrolyzes organophosphates and lipid hydroperoxides [257,258]. Polymorphisms (Q192R, L55M) modulate activity and ASD risk [259]. Reduced PON1 activity, sometimes uncoupled from oxidative markers, interacts with gene–environment factors such as prenatal pesticide exposure [257,260].

Translationally, these enzymes illustrate how deficits in detoxification, DNA repair, and antioxidant buffering converge to exacerbate oxidative distress in ASD, with genetic and environmental interactions shaping vulnerability and outcomes.

7. The Controversial Role of Superoxide Dismutases in ASD

Superoxide dismutases are central redox enzymes with three isoforms: SOD1 (Cu/Zn-SOD) in cytoplasm and intermembrane space, SOD2 (Mn-SOD) in mitochondria, and SOD3 (EC-SOD) extracellularly. All convert superoxide to oxygen and hydrogen peroxide. Hydrogen peroxide, however, if not neutralized, may promote a condition of oxidative distress, despite the protective action of SOD against the superoxide anion [261].

This duality makes SOD a "biochemical paradox": enzymes considered antioxidant, yet potentially pro-oxidant. In Down syndrome, trisomy 21-driven SOD1 overexpression increases hydrogen peroxide production, aggravating stress [262].

In ASD, results are inconsistent. Most studies report reduced SOD activity in blood or immune cells, correlating with elevated oxidative biomarkers and more severe phenotypes [261,263–265]. A low SOD/CAT ratio reflects poor enzymatic cooperation, favoring lipid and DNA oxidation [252,266]. Conversely, some describe increased SOD activity, which, without efficient detoxification, paradoxically intensifies oxidative distress [267,268]. Variability likely reflects genetic polymorphisms, tissue specificity, and comorbidities [71,269,270].

Overall, in ASD, SOD act as a "double-edged sword": essential for superoxide clearance but pathogenic when hydrogen peroxide removal is inadequate. Translationally, this paradox is critical: SOD and SOD-mimetics are often proposed as antioxidants, yet their efficacy may be limited or harmful without adequate downstream detoxification. In ASD, where redox balance is fragile, such interventions must be approached with caution [158,191,271,272].

8. Impairment of Neurons/Glia Subcellular Compartments in ASD

Redox dysfunction in ASD does not remain an abstract imbalance but materializes within specific subcellular compartments. At the membrane, lipid peroxidation and trans-fat incorporation compromise fluidity and receptor organization. In the cytoplasm and mitochondria, ferroptotic activation and impaired antioxidant buffering undermine bioenergetics, neurotransmission, and protein stability. In the nucleus, oxidative and nitrosative stress damage DNA and reprogram epigenetic landscapes, reshaping developmental trajectories. These effects extend beyond neurons: glial cells, particularly microglia, undergo maladaptive activation and chronic neuroinflammation. Such compartment-specific alterations represent the neurobiological foundation of ASD and are detailed in the following sections [6,7,35,36,48,51,65,71,73,74,239,273,274].

8.1. Mitochondrial Dysfunction and Altered Microbiota–Gut–Brain–Mitochondria Axis

Mitochondrial dysfunction in ASD is often simplified as reduced ATP synthesis with ROS overproduction. While relevant, this view overlooks mitochondria's broader functions in apoptosis, neurotransmitter turnover, redox signaling, and immune control. Alterations here profoundly affect brain development and connectivity, making mitochondria key hubs of ASD pathophysiology [181,274–276].

In ASD, impairment extends beyond oxidative phosphorylation to global metabolic and structural abnormalities. Reduced ATP and ROS excess destabilize the Krebs cycle, β-oxidation, and urea cycle, leading to excitotoxicity and synaptic failure. Disturbed polyamine metabolism and steroidogenesis impair chromatin remodeling, neurosteroid synthesis, and excitatory/inhibitory balance [274–277]. At the outer membrane, MAO activity exacerbates oxidative stress through hydrogen peroxide and aldehydes, altering dopamine and serotonin turnover [181,278,279].

Persistent oxidative injury, coupled with defective mitophagy, favors dysfunctional organelles, apoptosis, and senescence [278–280]. Genetic and epigenetic variants in respiratory chain or redox regulation intensify vulnerability, especially in high-demand areas such as the prefrontal cortex, hippocampus, and cerebellum during early development [181,278].

This fragility is reinforced by the evolutionary reciprocity between mitochondria and gut microbes [281,282]. In ASD, dysbiosis reduces butyrate—an anti-inflammatory PGC-1α activator—while increasing propionate, which impairs respiration, raises ROS, and induces ASD-like behaviors [283,284]. Increased intestinal permeability allows lipopolysaccharides and sulfur metabolites into circulation, sustaining systemic inflammation and oxidative distress [285]. Conversely, mitochondrial dysfunction in enterocytes and neurons undermines colonization by symbiotic microbes, destabilizing holobiont equilibrium [215,286,287].

Clinical evidence shows reduced *Lactobacillus* and *Bifidobacterium* and increased *Clostridia* in ASD [288]. Some *Lactobacillus* strains enhance NRF2-dependent antioxidant defenses, exemplifying host–microbe redox dialogue [236,289]. Polyphenols such as curcumin remodel microbiota and generate metabolites that cross the blood–brain barrier, modulating mitochondria, inflammation, and epigenetic programming [290,291].

Thus, mitochondrial dysfunction and dysbiosis represent interconnected consequences of redox imbalance in ASD. Rooted in evolutionary symbiosis, their disruption links genetic susceptibility, environment, and microbial ecology to impaired neurodevelopment, positioning mitochondria and microbiota as central amplifiers of oxidative distress [283,284,292].

8.2. Redox-Mediated Cell Membrane Dysfunction in ASD

8.2.1. Abnormalities in Neurons: Neurotransmission, Plasticity and Synaptic Functions, Morphogenesis

In ASD, redox dysfunction destabilizes neuronal membranes and synaptic machinery, linking oxidative distress to cognitive and behavioral deficits. Neuronal membranes, rich in PUFA and thiol proteins, are highly vulnerable to oxidative/nitrosative stress. Lipid peroxidation reduces fluidity, disrupts receptor clustering, and alters ion channel conductance, while protein oxidation disturbs excitatory/inhibitory balance [72,293,294].

Dopaminergic pathways are particularly sensitive: dopamine auto-oxidation generates quinones, while MAO produces hydrogen peroxide, damaging membranes and neurotransmitter turnover [85,143]. Tryptophan metabolism is redirected by indoleamine 2,3-dioxygenase toward quinolinic acid, a neurotoxic NMDA agonist, while reducing kynurenic acid, enhancing excitotoxicity [295,296]. Gamma-amino-butyric-ergic tone weakens as glutamate decarboxylase (GAD)65/67 undergoes nitrosylation and downregulation, especially in the cerebellum and parietal cortex [293,294]. Exceeding NO, normally needed for plasticity and oxytocin signaling, instead drives aberrant S-nitrosylation, undermining oxytocin–GABA interactions crucial for social cognition [72].

Synaptic proteins such as Soluble N-ethylmaleimide-Sensitive Factor Attachment Protein Receptor (SNARE) complexes, neuroligins, neurexins, and Shank3 are oxidatively modified, impairing vesicle trafficking and receptor anchoring [12,20,51,297]. Mitochondrial dysfunction compounds these effects by limiting ATP supply and calcium buffering, while microglial hyperactivation replaces physiological pruning with neuro-oxi-inflammation [23,51].

Neuroplasticity is severely impaired. Reduced Brain-Derived Neurotrophic Factor (BDNF) limits dendritic arborization, while oxidative modifications of NMDA receptors compromise long-term depression/long-term potentiation (LTP/LTD). Cytoskeletal destabilization further weakens dendritic dynamics [239,298,299]. Glutathione depletion correlates with oxidative injury in the hippocampus, cerebellum, and temporal cortex, reinforcing excitatory/inhibitory imbalance [239,300].

Clinically, these molecular changes manifest as immature dendritic arborization, defective axonal guidance, inefficient pruning, and aberrant connectivity [299]. Social deficits reflect oxytocin–GABA dysfunction, language impairments stem from temporal–frontal disconnection, and sensory hypersensitivity arises from maladaptive excitatory/inhibitory imbalance [298,299].

Overall, redox-driven membrane fragility, neurotransmitter imbalance, protein oxidation, and impaired plasticity converge into a cascade that reshapes neural circuits into hyperconnected yet inefficient networks, providing a biochemical substrate for ASD phenotypes [299].

8.2.2. Abnormalities in Microglia: Neuro-Oxi-Inflammation

In ASD, neuro-oxi-inflammation arises from the convergence of OS and inflammation into a self-sustaining loop that derails neurodevelopment [300]. Central drivers include NOX enzymes, NOS isoforms, and γ-GT, which generate ROS, NO, and cysteinyl-glycine, fueling Fenton chemistry. These reactions turn membranes into pro-oxidant platforms that sustain maladaptive inflammation [98,120,121,301,302].

Although intertwined, OS and inflammation differ mechanistically: OS is a rapid electron-transfer response producing hydrogen peroxide as a signal, whereas inflammation relies on cytokines and transcriptional programs, slower and more energy-consuming. Oxidative distress can exist without inflammation, but rarely vice versa, underscoring redox imbalance as the primary neural trigger [110,303–305].

Maternal immune activation exemplifies this link. Infections or autoimmunity during pregnancy raise ASD risk, as shown in polyinosinic:polycytidylic acid (poly I:C) and lipopolysaccharide (LPS) models [300,306]. Maternal cytokines, such as 6 and 17A interleukins, and tumor necrosis factor (TNF)-α cross the placenta and immature blood–brain barrier, pushing fetal microglia into pro-inflammatory states [182,307]. These cells, evolutionarily related to macrophages, release cytokines and ROS, impairing pruning and maturation Disruption of C-X3-C motif chemokine ligand 1 (fractalkine)—C-X3-C motif chemokine receptor 1 (CX3CL1–CX3CR1) and Cluster of Differentiation 200—CD200 receptor (CD200–CD200R) signaling destabilizes neuron–microglia crosstalk, perpetuating hyperactivation [308].

Myeloperoxidase further amplifies oxidative cascades, while mitochondrial dysfunction sustains the cycle via ROS overproduction and impaired energy buffering. Post-mortem studies confirm reduced complex activity and oxidative injury [105,107]. Epigenetic reprogramming of microglia by maternal cytokines consolidates these predispositions [309,310].

Ultimately, oxidative distress, inflammation, and mitochondrial dysfunction converge to impair pruning, plasticity, and connectivity. The result is dysconnectivity with local synaptic overgrowth, a hallmark of ASD. Clinically, these processes manifest as deficits in language, social cognition, and sensory integration. From an evolutionary perspective, neuro-oxi-inflammation reflects the maladaptive persistence of an ancient defense system, chronically activated during critical windows and predisposing to later neuro-oxi-inflammaging [311–313].

8.3. Redox-Mediated Lysosome Dysfunction in ASD

Lysosomal dysfunction represents another outcome of redox imbalance, linking oxidative stress, defective clearance, and premature aging. Normally, lysosomes sustain homeostasis through autophagy and mitophagy, eliminating damaged mitochondria [314,315]. In ASD, autophagic flux is impaired, while dysregulated mTOR and PI3K–Akt signaling suppress clearance [316–318]. This failure promotes neuronal and glial senescence; senescent microglia release cytokines and proteases that impair pruning, while neural precursor senescence limits neurogenesis and myelination [316–318]. Clinically, these processes manifest as cortical dysconnectivity and altered dendritic spine density [319–321].

8.4. Redox-Mediated Peroxisomal Dysfunction in ASD

Peroxisomes are central redox regulators. They oxidize very long-chain fatty acids and neutralize hydrogen peroxide via CAT. When detoxification is impaired—by genetic defects or CAT insufficiency—hydrogen peroxide accumulates, generating hydroxyl radicals that drive lipid peroxidation and irreversible injury [322]. In the developing brain, this undermines membrane integrity, plasmalogen metabolism, and white matter connectivity [323]. Evidence in ASD includes abnormal CAT activity, altered lipid profiles, and increased peroxidation [239]. Thus, peroxisomes emerge as metabolic hubs converging with mitochondrial dysfunction and inflammation [239].

8.5. Redox-Mediated Endoplasmic Reticulum Dysfunction in ASD

The endoplasmic reticulum (ER) integrates redox balance, lipid metabolism, and protein folding. Oxidative distress destabilizes these processes, altering membrane composition, receptor activity, and steroid synthesis, thereby fueling neuroinflammation and excitatory/inhibitory imbalance. Misfolded proteins accumulate, triggering ER stress and the unfolded protein response (UPR). Initially adaptive, chronic UPR drives pro-apoptotic, pro-inflammatory, and pro-oxidant cascades. In ASD, sustained ER stress has been observed in the temporal cortex and cerebellum, impairing calcium regulation, mitochondrial function, and neuroimmune signaling, thereby disrupting synaptic maturation [159,324,325].

8.6. Redox-Mediated Cytoskeleton Dysfunction in ASD

Cytoskeletal integrity is highly sensitive to OS as reported in some biological models. Oxidation of tubulin cysteines destabilizes microtubule polymerization, impairing axonal guidance and dendritic arborization [326]. Actin filaments and the acto-myosin system are equally vulnerable: ROS/RNS disrupt filament turnover and growth cone motility, hindering neurite extension [327]. At synapses, oxidative modifications of scaffolding proteins compromise dendritic spine density and morphology, consistently observed in ASD [328]. Redox interference with RAT-Sarcoma (RAS) signaling further disrupts LTP and pruning [329]. Mitochondrial and ER dysfunction exacerbate these effects by limiting ATP and calcium buffering [330]. The outcome is defective neuronal migration, abnormal synaptic maturation, and reduced plasticity, translating molecular stress into disorganized connectivity [331].

8.7. Redox-Mediated Nuclear Dysfunction in ASD

The nucleus is a final target of redox imbalance. Oxidative/nitrosative distress triggers guanine oxidation to 8-hydroxy-2′-deoxyguanosine, impairing replication and transcription [332,333]. In parallel, epigenetic marks are altered: DNA methylation, histone acetylation, and microRNA profiles shift, reshaping gene expression [67]. Redox-sensitive transcription factors such as Nrf2, NF-κB, and hypoxia inducible-factor (HIF) 1α become persistently dysregulated, sustaining pro-oxidant and inflammatory programs [48,316,334].

Enzymes like DNA methyltransferases and histone deacetylases, dependent on reducing equivalents, are impaired, amplifying epigenetic instability [66,68]. In ASD, abnormal methylation of synaptic and neurodevelopmental genes correlates with clinical severity, stabilizing oxidative insults into pathogenic trajectories. Thus, nuclear dysfunction anchors redox imbalance to persistent neurodevelopmental reprogramming, consolidating oxidative stress as a central mechanism of ASD [335–337].

9. Conclusions and Future Perspectives

The pathogenesis of ASD can be conceptualized as a sequence of reverberating waves originating from dysfunction of the redox system.

As depicted in Figure 8, the first wave corresponds to the primary collapse of the redox network, where the physiological equilibrium among oxidants, redox-sensitive targets, and reducing agents is lost. What is normally adaptive redox signaling becomes chronic oxidative distress.

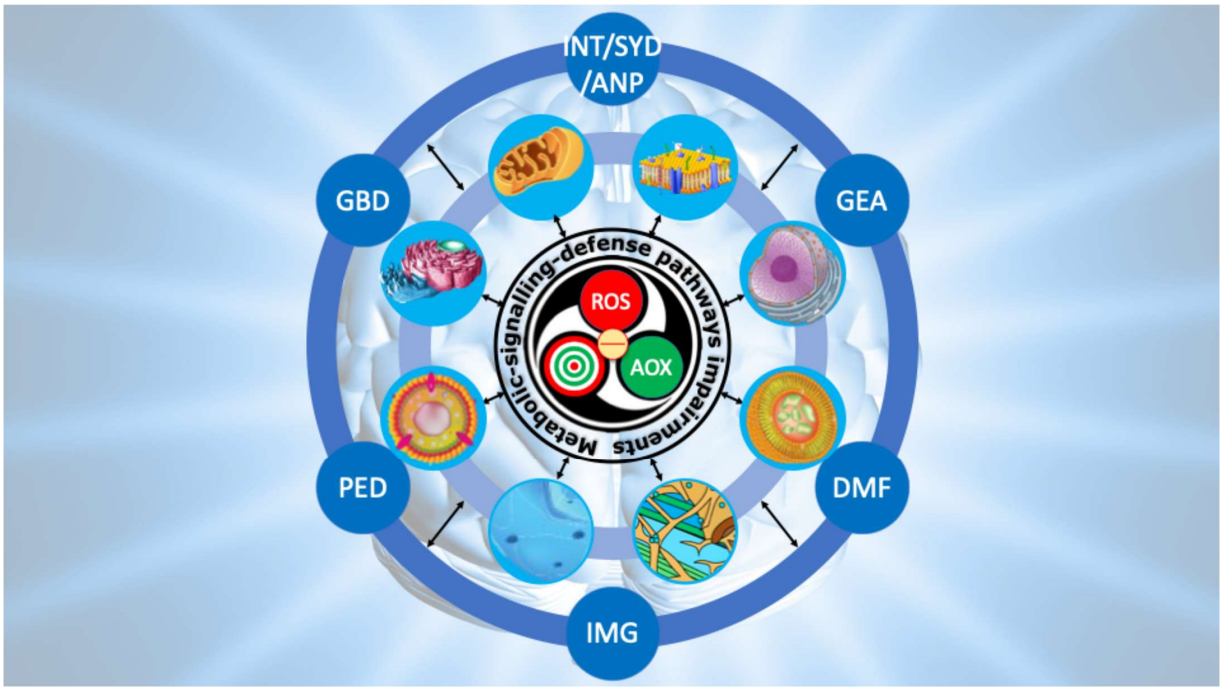


Figure 8. Ripple model to conceptualize the progression from primary redox dysfunction to the clinical phenotype of ASD. The model depicts three interconnected waves linking primary redox dysfunction to the clinical phenotype of ASD. The first wave arises from redox imbalance, which triggers a self-sustaining derailment of metabolic, signaling, and defense pathways. The second wave reflects the progressive collapse of neuronal and glial compartments, extending from the cell membrane to the nucleus. The third wave represents the ultimate neurodevelopmental outcome, characterized by impaired neurotransmission (INT), synaptic dysfunction (SYD), abnormal neuronal plasticity (ANP), genetic and epigenetic alterations (GEA), defective mitophagy (DMF), impaired morphogenesis (IMG), peroxisomal disorders (PED), and gut–brain axis disruption (GBD). Note: the calcium role is not included.

The second wave reflects propagation of this imbalance into redox-dependent pathways, including mitochondrial bioenergetics, neurotransmitter turnover, GSH homeostasis, lipid metabolism, and unfolded protein responses, all critically impaired in ASD.

The third wave encompasses cellular and subcellular consequences: mitochondrial inefficiency, impaired gut–brain dialogue, peroxidized neuronal membranes, defective neurotransmission, maladaptive microglial activation fueling neuro-oxi-inflammation, lysosomal MPO-driven cascades with defective mitophagy and premature senescence, per-

oxisomal insufficiency with unchecked lipid peroxidation, ER stress, cytoskeletal instability, and nuclear genetic–epigenetic reprogramming.

From this third wave emerges the decisive link to neurodevelopmental deviation. When the compartments sustaining synaptic formation, pruning, and plasticity are persistently altered, the developmental trajectory of the brain is redirected. Aberrant connectivity, abnormal spine morphology, disrupted circuit refinement, and faulty integration of sensory, motor, and cognitive networks crystallize into the clinical phenotype of autism. In this sense, the reverberating model explains how an initial molecular imbalance can, through successive layers of perturbation, culminate in the complex manifestations of ASD.

The novelty of this work lies not only in integrating redox dysfunction across multiple biological levels into a unified pathogenetic framework, but also in embedding it in an ecological–evolutionary perspective. Rooting the model in the dual symbiosis that defines eukaryotic life—the ancient endosymbiosis of mitochondria with ancestral bacteria and the dynamic symbiosis with the gut microbiota—frames autism within the broader concept of One Health. Neurodevelopment thus emerges not solely from human genetics or brain-intrinsic processes, but from a continuous biochemical dialogue with microbial partners. Perturbation of these ancient redox-based symbioses reverberates from molecular imbalance to systemic developmental deviation.

Compared with previous literature, this model represents a conceptual advancement. Earlier studies emphasized isolated mechanisms—mitochondrial dysfunction, GSH depletion, neuroinflammation—without fully connecting them within the dynamics of the redox system. By adopting a redoxomic systems biology perspective, we trace the reverberations of imbalance through metabolic pathways, organelle dysfunction, and nuclear reprogramming, bridging molecular pathology with clinical phenotype.

Nonetheless, the model has limitations. It derives from heterogeneous, often cross-sectional data and does not fully capture the temporal sequence from prenatal life to childhood. Bidirectional interactions—between OS and inflammation, or mitochondrial dysfunction and synaptic failure—blur cause and consequence. Patient variability, shaped by genetics, environment, and comorbidities, further challenges universality.

Despite these caveats, the reverberating wave model highlights promising avenues. On the diagnostic side, redox-based biomarkers—enzymatic activities (NADPH oxidases, MAO, MPO), redox couples (GSH/GSSG), lipid peroxidation products, and advanced protein oxidation derivatives—offer dynamic insight into redox performance. Integrated panels, aligned with redoxomic principles, may enable patient stratification, early identification, and real-time monitoring [338]. Beyond classical biomarkers, innovative strategies such as redox imaging, extracellular vesicle analysis, microbiota-derived signals, and genetic/epigenetic redox profiles may expand precision diagnostics [7,121,265,339].

On the therapeutic side, nutraceuticals represent potential tools to modulate redox homeostasis in a personalized way. Bioactive compounds—polyphenols, omega-3 fatty acids, sulfur metabolites, and redox-active vitamins—exert antioxidant effects while influencing signaling, epigenetics, and microbiota composition. Equally promising are novel approaches, including (i) modulation of bitter taste receptors (TAS2Rs) [340], which regulate NO and Ca^{2+} pathways; (ii) control of microbiota-derived redox modulators [341]; and (iii) photobiomodulation [342], which targets mitochondrial chromophores to re-establish redox balance and attenuate microglial activation. These interventions should be viewed not as generic adjuncts but as specific modulators of redox circuits, capable of restoring physiological eustress during critical windows of neurodevelopment.

In conclusion, the reverberating wave model underscores that ASD is best understood as the progressive unfolding of redox system dysfunction across metabolic, cellular, and structural domains, ultimately reshaping neurodevelopment. Embedded within the

ecological–evolutionary framework of One Health, autism reflects not only molecular vulnerability but also the fragility of symbiotic networks sustaining human life. While further longitudinal studies are required, this framework coherently links molecular imbalance to clinical phenotype and supports exploration of redox-based biomarkers, nutraceutical strategies, and theranostic innovations as future pillars of precision medicine in ASD.

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Abbreviations

The following abbreviations are used in this manuscript:

2-AG	2-Arachidonoylglycerol
4-HNE	4-Hydroxynonenal
ACOX	Very-long-chain acyl-CoA oxidase
AOX	Reducing/Antioxidant (species)
AP-1	Activator Protein 1
ASD	Autism Spectrum Disorder
BDNF	Brain-Derived Neurotrophic Factor
BTBR	BTBR T+ Itpr3tf/J mouse strain (ASD model)
CAT	Catalase
CB	Cannabinoid (receptors)
CD200–CD200R	Cluster of Differentiation 200-Cluster of Differentiation 200 Receptor
cGMP	Cyclic Guanosine Monophosphate
CNS	Central Nervous System
CO	Carbon monoxide
COX	Cycloxygenase
CpG	Cytosine-phosphate-Guanine
CX3CL1–CX3CR1	Fractalkine—chemokine receptor 1
CYP	Cytochrome P_{450}
DUOX	Dual Oxidase (NADPH oxidase isoform)
ER	Endoplasmic Reticulum
G6PD	Glucose-6-phosphate dehydrogenase
GABA	Gamma-aminobutyric acid
GAD (GAD65/67)	Glutamate Decarboxylase (65/67)
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
γ-GT	γ-glutamyltransferase/transpeptidase
GPx	Glutathione Peroxidase
GSH	Reduced glutathione/glutathione monomer
GSSG	Oxidized glutathione/glutathione dimer
GSTM	Glutathione S-Transferase Mu class
GSTP	Glutathione S-Transferase Pi class

GSTT	Glutathione S-Transferase Theta class
HIF-1α	Hypoxia-Inducible Factor 1-Alpha
HO-1	Heme Oxygenase 1
KEAP1	Kelch-like ECH-associated protein 1
LOX	Lipoxygenase
LPS	Lipopolysaccharide
LTD	long-term depression
LTP	long-term potentiation
MAO	Monoamine Oxidase
MAPK	Mitogen-Activated Protein Kinase
MDA	malondialdehyde
MIA	Maternal Immune Activation
mitNOS	Mitochondrial Nitric Oxide Synthase (putative)
MPO	myeloperoxidase
mtDNA	mitochondrial DNA
MTHFR	Methylenetetrahydrofolate Reductase
mTOR	Mechanistic Target of Rapamycin
NADPH	Nicotinamide Adenine Dinucleotide Phosphate (reduced form)
NF-κB	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
NMDA	N-Methyl-D-Aspartate
NO	Nitric oxide
NOS	Nitric oxide synthase
nNOS/eNOS/iNOS	Neuronal/Endothelial/Inducible Nitric Oxide Synthase
NOX	NOX NADPH oxidase isoform
NRF2	Nuclear factor erythroid 2–related factor 2 (gene)
Nrf2	Nuclear factor erythroid 2–related factor 2 (gene product)
OGG1	8-oxoguanine DNA glycosylase-1
$ONOO^-$	Peroxynitrite
PGC-1α	Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha
PI3K-Akt	Phosphoinositide 3-Kinase—Protein Kinase B (Akt) (pathway)
poly I:C	Polyinosinic:polycytidylic acid
PON1	Paraoxonase 1
PUFA	Polyunsaturated Fatty Acids
RNS	Reactive Nitrogen Species
ROS	herein Reactive Oxidant Species (not Reactive Oxygen Species)
SAH	S-Adenosylhomocysteine
SAM	S-Adenosylmethionine
SHANK3	SH3 and Multiple Ankyrin Repeat Domains 3 (gene)
Shank3	SH3 and Multiple Ankyrin Repeat Domains 3 (gene product)
SNARE	Soluble N-ethylmaleimide-Sensitive Factor (NSF) Attachment Protein Receptor
SNPs	Single Nucleotide Polymorphisms
SOD	Superoxide Dismutase
TAS2Rs	Taste Receptor Type 2 family (bitter taste receptors)
TLR	Toll-Like Receptors
TNF-α	Tumor Necrosis Factor alpha
UPR	Unfolded protein response
VNTR	Variable Number Tandem Repeat
XO	Xanthine Oxidase

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