

The Trx1–ATM–PPP axis in traumatic brain injury: Redox regulation and neuroprotective perspectives

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Abstract

Traumatic brain injury (TBI) poses a significant global health challenge, where secondary injury processes driven by oxidative stress and metabolic crisis are key determinants of poor neurological outcomes, yet lack effective treatments. This review synthesizes emerging evidence on a novel neuroprotective pathway—the thioredoxin-1 (Trx1)–ataxia-telangiectasia mutated (ATM)–pentose phosphate pathway (PPP) axis. We elaborate on how this axis functions as an integrated redox-metabolic response system: oxidative stress triggers Trx1-dependent activation of ATM, which subsequently enhances PPP flux to boost NADPH production. This cycle creates a feed-forward loop that reinforces cellular antioxidant defenses, sustains redox homeostasis, and promotes neuronal survival. Preclinical findings demonstrate that bolstering this axis mitigates oxidative damage and improves recovery after TBI. Consequently, the Trx1-ATM-PPP axis presents a paradigm-shifting therapeutic target, moving beyond direct antioxidant scavenging towards modulating endogenous resilience networks. Future efforts to develop specific modulators of this pathway hold promise for pioneering new treatments for TBI and other CNS disorders linked to oxidative stress.

Keywords: Traumatic brain injury, Oxidative stress, Redox regulation, Thioredoxin-1, ATM kinase, Pentose phosphate pathway

Abbreviations: 4-HNE: 4-Hydroxynonenal; ASK1: Apoptosis Signal-regulating Kinase 1; ATM: Ataxia-Telangiectasia Mutated; BBB: Blood-Brain Barrier; CNS: Central Nervous System; DDR: DNA Damage Response; G6PD: Glucose-6-Phosphate Dehydrogenase; G6P: Glucose-6-Phosphate; GSH: Glutathione (reduced); GSSG: Glutathione (oxidized); NADPH: Nicotinamide Adenine Dinucleotide Phosphate (reduced); NF-κB: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; PPP: Pentose Phosphate Pathway; ROS: Reactive Oxygen Species; TBI: Traumatic Brain Injury; Trx: Thioredoxin; Trx1: Thioredoxin 1 (cytosolic isoform); TrxR: Thioredoxin Reductase; TrxS: Thioredoxin System

Introduction

Traumatic brain injury (TBI) is a leading cause of mortality and long-term disability worldwide, imposing a substantial burden on individuals and healthcare systems [1–3]. In China, the incidence is especially high, further straining medical resources and families [4]. Despite advances in neurosurgical techniques, intensive care, and rehabilitation, patient outcomes remain unsatisfactory, with persistent mortality, severe disability, and an increased risk of chronic neurodegenerative conditions [5–7].

Research over the past decades has revealed that TBI involves both primary and secondary injury. Primary injury refers to the immediate and irreversible mechanical damage that occurs at the moment of impact. It includes cerebral contusion, vascular disruption, tissue shearing, and diffuse axonal

injury, all of which lead to instantaneous structural destruction of neurons, glial cells, and blood vessels. These biomechanical forces also initiate ionic imbalance and membrane disruption, setting the stage for subsequent metabolic collapse [8,9]. Because primary injury occurs within milliseconds and cannot be reversed, current therapeutic strategies focus primarily on mitigating downstream cascades rather than directly targeting this initial event.

Secondary injury unfolds over minutes to days after TBI and encompasses a multifaceted cascade involving oxidative stress, mitochondrial dysfunction, excitotoxicity, neuroinflammation, and progressive cell death [8,9]. The sustained overproduction of ROS drives lipid peroxidation, protein oxidation, and DNA fragmentation, severely impairing neuronal survival. Astrocyte and microglial activation further amplifies inflammation and oxidative burden [10–12]. These interconnected processes significantly expand the initial lesion and represent the principal therapeutic window in which modulating redox balance and metabolic resilience—such as through the Trx1–ATM–PPP axis—may offer neuroprotection.

The pathophysiology of secondary injury is underpinned by an intricate interplay between neurons and glial cells. Astrocytes, the most abundant glial cells, play a dual role. Under physiological conditions, they provide crucial metabolic support to neurons by delivering antioxidant precursors for glutathione (GSH) synthesis and clearing excess glutamate to prevent excitotoxicity [13,14]. However, after TBI, many astrocytes become reactive, contributing to scar formation and releasing pro-inflammatory factors [12]. Microglia, the resident immune cells of the brain, similarly exhibit a double-edged sword effect. They can adopt a protective M2 phenotype, promoting tissue repair and debris clearance, but often polarize towards a detrimental M1 state, releasing a plethora of pro-inflammatory cytokines and reactive oxygen species (ROS) that exacerbate oxidative stress and neuronal damage [13,14].

Within this hostile microenvironment, neurons are particularly vulnerable. Their high metabolic rate and oxygen consumption render them susceptible to oxidative damage. This vulnerability is compounded by a high content of polyunsaturated fatty acids in their membranes—a prime target for lipid peroxidation—and a relatively limited endogenous antioxidant capacity compared to glial cells [15,16]. The resulting oxidative stress is a hallmark of secondary injury, where excessive ROS trigger lipid peroxidation, protein dysfunction, and DNA damage, amplifying neuronal loss [8,17]. Therefore, a key unresolved issue is how to not only mitigate oxidative stress but also reinforce the intrinsic antioxidant defense system within neurons, while simultaneously modulating the glial response to foster a supportive microenvironment.

Exploring redox-regulating systems and their integration with metabolic pathways may provide such therapeutic opportunities. A promising approach lies in targeting endogenous antioxidant hubs that can directly quench ROS and reprogram cellular metabolism to sustain redox homeostasis.

Oxidative Stress and Mitochondrial Homeostasis in TBI

Oxidative stress constitutes a core mechanism of secondary neuronal injury after TBI. The massive and sustained generation of reactive oxygen species (ROS), including superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and the highly reactive hydroxyl radical ($\bullet OH$), overwhelms cellular antioxidant defenses

[17]. This oxidative assault triggers deleterious cascades, including lipid peroxidation of neuronal membranes, which generates toxic aldehydes like 4-hydroxynonenal (4-HNE) that further propagate damage [18]. Additionally, ROS induce protein carbonylation, nitration, and DNA strand breaks, collectively disrupting essential cellular functions and activating death pathways [19,20].

The primary intracellular source of ROS in neurons is the mitochondrion, an organelle highly vulnerable to mechanical and metabolic stress [21]. The brain's high metabolic demand, reliant on oxidative phosphorylation, results in significant electron leakage from the mitochondrial respiratory chain (particularly Complexes I and III), constituting a basal level of ROS production that is drastically amplified following TBI [22,23]. This disruption of mitochondrial homeostasis is catastrophic: it leads to a precipitous decline in ATP production, impairing energy-dependent processes such as ion pump function and synaptic transmission. Concurrently, damaged mitochondria exhibit impaired calcium buffering capacity, leading to calcium overload which activates calpains and other proteases, and initiates apoptotic cascades through cytochrome c release [24,25].

Beyond mitochondria, enzymatic sources contribute significantly to the oxidative burden. NADPH oxidases (NOXs), especially the microglia-enriched NOX2 isoform, are rapidly activated post-TBI, producing substantial amounts of $O_2^{\bullet-}$ in a process termed “oxidative burst,” which intensifies neuroinflammation and parenchymal damage [26,27].

Despite robust preclinical evidence demonstrating the efficacy of various antioxidant agents (e.g., free radical scavengers, mitochondrial-targeted antioxidants like MitoQ) in improving outcomes in animal models of TBI, their translation into clinical success has been largely disappointing [28,29]. This translational failure can be attributed to several factors: the limited blood-brain barrier (BBB) penetration of many compounds, the challenge of achieving the correct therapeutic timing and dosing in a heterogeneous patient population, and perhaps most critically, the conceptual limitation of merely “scavenging” ROS after their generation without restoring the upstream regulatory nodes that govern redox equilibrium and metabolic adaptation [30,31]. This underscores the pressing need for novel strategies that move beyond stoichiometric antioxidant supplementation and instead aim to bolster the brain's endogenous redox-resilience systems, which intrinsically couple ROS management with metabolic support.

The Thioredoxin System and ATM Signaling in Neural Protection

Faced with the limitations of direct antioxidant supplementation, research has pivoted towards enhancing the brain's endogenous defense systems. Among these, the thioredoxin system (TrxS) stands out as a master regulator of cellular redox homeostasis. The TrxS is a central antioxidant system, composed of thioredoxin (Trx), thioredoxin reductase (TrxR), and NADPH [32]. Trx1, the predominant cytosolic isoform, is a 12-kDa protein with a conserved catalytic site (-Cys-Gly-Pro-Cys-) that enables it to reduce disulfide bonds in target proteins, thereby scavenging ROS directly and regenerating other antioxidants like peroxiredoxins [33,34]. Beyond its fundamental role in redox maintenance, Trx1 exerts profound influence over cell survival by modulating key signaling pathways. It negatively regulates apoptosis signal-regulating kinase 1 (ASK1) by binding to and inhibiting it under reducing conditions; oxidative

stress disrupts this complex, freeing ASK1 to initiate pro-apoptotic cascades [35,36]. Furthermore, Trx1 can translocate to the nucleus, where it modulates the activity of transcription factors such as NF- κ B and Ref-1-dependent AP-1, thereby influencing inflammatory and repair responses [37,38].

In the context of TBI, evidence indicates that Trx1 expression is upregulated as an adaptive, protective response to mitigate oxidative damage [39,40]. However, the dynamics of this response are crucial. Studies suggest that the endogenous induction of Trx1 is often transient and insufficient to counteract the massive and sustained oxidative burst during the subacute phase of TBI, leaving neurons vulnerable to ferroptosis and apoptosis [41,42]. This insufficiency highlights the therapeutic potential of augmenting the Trx1 pathway.

Another key player in the neuronal response to stress is the ataxia-telangiectasia mutated (ATM) kinase. Traditionally recognized as the master regulator of the DNA damage response (DDR), ATM is also exquisitely sensitive to oxidative stress [43,44]. In neurons, which are predominantly post-mitotic, this redox-sensing function may be particularly critical. ATM exists as inactive dimers in the unstressed state. Upon exposure to ROS, these dimers undergo monomerization through disulfide bond formation, leading to autophosphorylation and activation independently of the canonical DDR pathway [45,46]. Once activated, redox-ATM orchestrates a multifaceted defense program. A pivotal downstream effect is the promotion of metabolic flux through the pentose phosphate pathway (PPP), a crucial adaptation for generating NADPH [47,48].

The mechanistic link between the Trx system and ATM activation represents a significant advance in our understanding. Recent research proposes that reduced Trx1 can physically interact with ATM, potentially reducing specific cysteine residues and facilitating its monomerization and activation under oxidative stress [49,50]. This interaction positions Trx1 not merely as a passive antioxidant, but as an active upstream regulator of a major stress-response kinase. In models of neural injury, Trx1 overexpression has been shown to enhance ATM phosphorylation and subsequently elevate NADPH levels without altering total ATM phosphorylation expression, providing functional evidence for this axis [51]. Collectively, these findings crystallize the concept of a Trx1–ATM–PPP axis, where Trx1 acts as a redox sensor and initiator, ATM as a signal amplifier and integrator, and the PPP as the metabolic effector, working in concert to bolster neuronal resilience.

Pentose Phosphate Pathway as a Metabolic Switch

The pentose phosphate pathway (PPP) represents a critical metabolic divergence from glycolysis, serving as an essential source of cellular reducing power and biosynthetic precursors. This pathway branches off from glycolysis at glucose-6-phosphate (G6P) and operates in two distinct phases: an oxidative phase that generates ribulose-5-phosphate and, most importantly, NADPH; and a non-oxidative phase that produces various sugar phosphates for nucleotide synthesis [52,53]. The oxidative phase, catalyzed by glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD), is the sole dedicated cytoplasmic source of NADPH, a cofactor indispensable for maintaining redox homeostasis [54].

NADPH functions as the primary electron donor for the regeneration of reduced glutathione (GSH) from its oxidized form (GSSG) via glutathione reductase, and for the reduction

of thioredoxin (Trx) via thioredoxin reductase (TrxR) [55]. Consequently, the flux through the PPP, and specifically the activity of the rate-limiting enzyme G6PD, directly governs the capacity of the Trx and GSH systems to counteract ROS, detoxify peroxides, and repair oxidative damage [56]. Under physiological conditions, the majority of glucose carbon is directed through glycolysis for ATP production, with only a minor fraction entering the PPP. However, this pathway possesses a large reserve capacity that can be rapidly mobilized in response to oxidative stress, effecting a metabolic switch from energy production to redox defense [57,58].

The mechanism underlying this metabolic reprogramming has been a focus of recent research. Evidence indicates that the ATM kinase plays a pivotal role in this process. Upon activation by oxidative stress—a process facilitated by Trx1 as previously discussed—ATM can phosphorylate and activate G6PD, thereby directly stimulating the oxidative arm of the PPP to boost NADPH production [59,60]. This creates a powerful feed-forward loop: oxidative stress activates the Trx1-ATM axis, which in turn enhances PPP flux and NADPH generation, providing the essential reducing equivalents needed to sustain Trx1 and GSH system activity, thus restoring redox balance and promoting cell survival [61].

In the context of TBI, where oxidative stress and metabolic crisis are paramount, the Trx1-ATM-PPP axis emerges as a crucial endogenous neuroprotective mechanism. Preclinical models have demonstrated that strategies aimed at enhancing this axis, such as Trx1 overexpression or ATM activation, lead to increased NADPH/NADP⁺ ratios, attenuated oxidative damage markers (e.g., reduced levels of 4-HNE and protein carbonylation), and improved functional outcomes [50]. This axis tightly links redox imbalance sensing—mediated by Trx1 and ATM—to a coordinated metabolic response that elevates PPP-derived NADPH, forming an integrated and potentially more effective therapeutic target than direct ROS scavenging. Enhancing this intrinsic metabolic flexibility may thus represent a superior strategy to bolster neuronal resilience within the oxidative milieu that follows TBI.

Clinical and Translational Perspectives

The delineation of the Trx1–ATM–PPP axis as an integral neuroprotective pathway opens up novel and promising translational avenues for TBI treatment. Targeting this axis shifts the therapeutic paradigm from simple ROS scavenging to strengthening the brain's intrinsic capacity to sustain redox and metabolic homeostasis. This approach offers the potential for a wider therapeutic window and more sustained efficacy, as it aims to correct the underlying dysregulation rather than merely neutralizing its toxic byproducts [62,63].

The therapeutic potential of modulating this axis extends beyond the acute phase of TBI. Given that chronic oxidative stress and metabolic dysfunction are implicated in the long-term sequelae of TBI, including an increased risk of neurodegenerative diseases such as Alzheimer's disease and chronic traumatic encephalopathy, strategies that bolster this endogenous defense system could have profound implications for improving long-term neurological outcomes [64,65]. Furthermore, the principles of this pathway are universally critical for neuronal survival, suggesting that its modulation may hold therapeutic value in a spectrum of other acute and chronic CNS disorders characterized by oxidative stress, including ischemic stroke, intracerebral hemorrhage, and even primary neurodegenerative conditions [31,36,66].

However, several challenges must be overcome to translate this knowledge into clinical reality. From a preclinical research standpoint, a more granular understanding of the axis is required. Future studies should incorporate advanced metabolic tracing approaches—such as isotopically labeled glucose—to precisely quantify PPP flux dynamics across distinct cell types and at different temporal stages following TBI [67]. Genetic loss-of-function studies, utilizing cell-type-specific knockout models of Trx1 or ATM, are necessary to unequivocally confirm their causal, cell-autonomous roles in the neuronal response to trauma [68]. The interplay between this axis and other programmed cell death pathways, such as ferroptosis, which is tightly linked to GPX4 activity and glutathione metabolism, represents another critical area for investigation [41,69].

From a drug development perspective, the major challenge is the current lack of clinically available and specific modulators of the Trx1–ATM–PPP pathway. To bridge this gap, discovery efforts could focus on several strategic avenues. One approach involves targeting Trx1 itself, by identifying small-molecule agonists that can stabilize its reduced, active form or enhance its expression, for instance through upstream activation of the Nrf2 antioxidant pathway [70]. A more precise strategy entails targeting the Trx1-ATM interaction interface, with the aim of developing peptide mimetics or small molecules that stabilize this physical association to facilitate ATM activation under oxidative stress [71]. Alternatively, directly targeting ATM activation represents another viable route, which would involve exploring the therapeutic window and neurological efficacy of existing or novel ATM activators, while carefully weighing their potential systemic effects [72].

Finally, the development of sensitive biomarkers is crucial to identify patients who would most benefit from such targeted therapies and to monitor treatment response. Imaging techniques capable of assessing regional brain metabolism, coupled with assays measuring oxidative stress markers or components of the axis in biofluids, could serve this purpose.

Conclusion

Secondary injury in TBI is driven by oxidative stress and metabolic dysfunction, for which effective therapies are urgently needed. The emerging evidence for the Trx1–ATM–PPP axis provides a mechanistic framework linking redox sensing with metabolic adaptation. By enhancing PPP flux and NADPH production, this pathway supports antioxidant defenses and promotes neuronal survival. Further investigation of its regulation and therapeutic potential could pave the way for novel interventions in TBI and other CNS disorders characterized by oxidative stress.

Declarations

Conflict of interest

All authors declare that there were no competing interests.

Authors' contributions

Yutong Mei: Conception, Writing – drafting the original manuscript

Yuanqing Zhang: Validation, Writing – drafting the original manuscript

Zongqi Wang: Conception, Supervision, Writing – review & editing

Jiangang Liu: Supervision, Writing – review & editing

Reviewing and Approval of the final version for publication: All the author.

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