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# Mitochondrial Quality Control in Traumatic Brain Injury: From Mechanisms to Therapeutic Opportunities

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**Abstract:** ***Traumatic brain injury (TBI) remains a leading cause of death and disability, and secondary injury—evolving over hours to weeks after the insult—constitutes the principal therapeutic window. Mitochondrial dysfunction sits at the hub of this cascade. Mitochondria are actively maintained by an integrated mitochondrial quality control (MQC) system comprising mitochondrial dynamics, mitophagy, and mitochondrial biogenesis, and TBI disrupts every arm of this system. This review summarizes how mitochondrial dysfunction develops after TBI; dissects the three pillars of MQC with emphasis on recent advances such as PINK1/Parkin signalling and receptor-mediated mitophagy; discusses the crosstalk between defective MQC and apoptosis, ferroptosis, pyroptosis, and PANoptosis; and evaluates therapeutic strategies targeting MQC. We further highlight unresolved questions, including the dual, dose-dependent nature of mitophagy, cell-type-specific MQC responses, and the challenge of therapeutic timing. A refined understanding of MQC may help convert mitochondrial biology into clinically useful interventions for TBI.***

**Keywords:** Traumatic brain injury, Mitochondrial quality control, Mitophagy, Mitochondrial dynamics, Mitochondrial biogenesis, Secondary brain injury.

## 1. Introduction

Traumatic brain injury (TBI) is among the leading causes of trauma-related death and disability worldwide [1], yet no pharmacological intervention has reliably improved functional outcomes [2]. The mechanical insult produces an irreversible primary injury and initiates a secondary cascade—excitotoxicity, calcium dysregulation, oxidative stress, neuroinflammation, blood–brain barrier (BBB) disruption, and progressive cell death—that unfolds over hours to weeks and constitutes the realistic target of therapy [2]. Mitochondrial dysfunction is central to this cascade: TBI rapidly and persistently suppresses mitochondrial bioenergetics [3], producing a “cerebral energy crisis” that drives irreversible neurodegeneration [4]. Mitochondria, however, are not passive victims. Cells surveil, remove, and replace them through an integrated network termed mitochondrial quality control (MQC), encompassing mitochondrial dynamics, mitophagy, and biogenesis [5]; when MQC fails, damaged mitochondria amplify oxidative stress, release damage-associated molecular patterns (DAMPs), and engage regulated cell death (RCD) programmes [6].

Earlier reviews have catalogued mitophagy in TBI or acute CNS injury [7,8,9,10], but the field has moved quickly: Parkin-mediated quality control now has causal in vivo evidence [11], metabolic–epigenetic regulation of mitophagy has been uncovered [12,13], and defective MQC has been linked to emerging death modalities such as ferroptosis and PANoptosis [14,15]. This review provides an updated, MQC-centred synthesis of mitochondrial dysfunction in TBI and evaluates the therapeutic landscape it has generated.

## 2. Mitochondrial Dysfunction after TBI

The immediate consequence of trauma is ionic disequilibrium: calcium influx forces mitochondria to buffer cytosolic calcium at the cost of membrane potential, triggering permeability transition pore opening and ATP collapse [3]. Defective endoplasmic reticulum–mitochondrial contact sites aggravate calcium mishandling and represent a druggable node [16], while combined ROS scavenging and calcium limitation protects in experimental TBI [17]. Damaged electron transport chains further leak superoxide, initiating lipid peroxidation, protein oxidation, and mtDNA damage; post-traumatic brains consistently show elevated malondialdehyde and 4-hydroxynonenal with depleted glutathione, changes that correlate with neurological severity [18,11]. Oxidative stress is thus both a cause and a consequence of MQC failure: oxidatively damaged mitochondria require efficient mitophagic clearance, while the ROS they release further impair the mitophagic machinery, creating a self-amplifying loop [8].

Injured mitochondria also release mtDNA and cardiolipin as DAMPs. Cytosolic mtDNA engages cGAS–STING signalling, and endothelial STING drives post-traumatic cerebrovascular thromboinflammation and BBB failure [19]; mitochondrial danger signals likewise feed neuronal death programmes, as neutrophil extracellular traps (NETs) promote neuronal ferroptosis via STING-mediated AMPK dysregulation [20]. Together, these observations place mitochondrial danger signalling at the intersection of vascular failure, innate immunity, and cell death after TBI.

## 3. Mitochondrial Dynamics: Fusion and Fission

Mitochondrial networks are shaped by fusion (mitofusins MFN1/2, OPA1) and fission (dynamin-related protein 1, DRP1), which together permit content mixing and segregation of damaged organelles [21,22]. After experimental TBI the balance shifts sharply towards fission, and acute blockade of

excessive fission not only protects neurons acutely but prevents chronic neurodegeneration months later [23]. Fusion is likewise disturbed: restoring MFN1-dependent homeostasis with metformin reduced mitochondrial ROS and suppressed neuronal pyroptosis, an effect abolished by Mfn1 silencing [24]. At the systems level, Parkin was recently shown to protect the injured brain by coordinately promoting fission and biogenesis, restraining fusion, and relieving the injury-induced blockade of mitophagic flux [11]. Dynamic modulation is nonetheless context-dependent: the DRP1 inhibitor Mdivi-1 alleviated BBB disruption in one paradigm [25], but excessive or mistimed fission blockade can worsen outcome elsewhere [8], arguing for stage-matched intervention. This duality is shared with mitophagy itself and cautions against a simplistic "fission is bad" interpretation of post-traumatic dynamics.

## 4. Mitophagy in TBI

### 4.1 PINK1/Parkin-mediated Mitophagy

Upon membrane-potential loss, PINK1 stabilizes on the outer mitochondrial membrane, phosphorylates ubiquitin, and recruits Parkin, whose ubiquitination of outer-membrane substrates engages autophagy adaptors and the LC3 machinery [5,26]. Direct causal evidence in TBI came from Wu and colleagues: Parkin rose after controlled cortical impact, and its overexpression restored autophagic flux and mitophagy, reduced apoptosis and oxidative stress, and improved motor and cognitive outcomes, whereas knockout exacerbated injury; a recombinant Parkin protein showed preliminary protective activity, pointing towards protein-based therapy [11]. Notably, Parkin exerted its protection not through mitophagy alone but by coordinately reshaping the entire MQC network, underscoring the value of the integrated framework adopted in this review. Pharmacological activation with pyrroloquinoline quinone similarly enhanced PINK1/Parkin mitophagy and attenuated secondary damage [27], and lipid-mediated clearance is also operative: cardiolipin externalization serves as an LC3-recognized "eat-me" signal that guides functional outcome after TBI [28].

### 4.2 Receptor-mediated Mitophagy

Ubiquitin-independent mitophagy is driven by outer-membrane receptors—BNIP3, BNIP3L/NIX, and FUNDC1—that bind LC3 directly through LC3-interacting region motifs and are typically hypoxia-induced [29]. BNIP3-mediated mitophagy alleviated neuronal apoptosis and oxidative stress in experimental TBI [30], whereas copper accumulation suppressed it and aggravated synaptic damage [31]. Clinically, amantadine engages the HIF-1α/BNIP3L/HMGB1 axis to attenuate secondary injury [32].

### 4.3 Regulation and the Dual Nature of Mitophagy

Post-traumatic mitophagy is gated by metabolic, epigenetic, and receptor-level checkpoints: AMPK promotes mitophagy and its STING-driven dysregulation worsens ferroptosis [20]; histone lactylation–PSMD14 signalling alleviates neuronal PANoptosis by activating PINK1-mediated mitophagy [13]; Tufm lactylation couples protein modification to neuronal fate [12]; and receptor-level inputs include the α7 nicotinic acetylcholine receptor—engaged by remimazolam to enhance mitophagy and suppress microglial pyroptosis [33]—and the Mas receptor, whose activation promoted mitophagy and preserved neuronal function [34]. Non-pharmacological neuromodulation converges on the same pathways: trigeminal nerve stimulation attenuated neuronal damage through a CGRP–PINK1 mitophagy axis [35], and acupuncture has been synthesized as a regulator of mitochondrial homeostasis in TBI [36]. Whether mitophagy helps or harms is dose- and timing-dependent: moderate flux clears damaged organelles, insufficient flux lets ROS-generating mitochondria accumulate, and excessive activation depletes the mitochondrial pool [8]. Future interventions will therefore need to titrate, rather than simply maximize, mitophagic flux.

## 5. Mitochondrial Biogenesis

Clearance must be matched by replacement through the PGC-1α–NRF1/2–TFAM cascade, with AMPK and SIRT1 upstream [37]. Evidence in TBI is sparser but growing: Parkin overexpression increased PGC-1α, and blocking PGC-1α abolished Parkin-mediated protection, indicating that biogenesis is an obligatory partner of clearance [11]; pterostilbene coupled biogenesis signalling to antioxidant defence via SIRT1/PGC-1α/NRF2 [38]; and Mas receptor activation improved biogenesis markers alongside enhanced mitophagy [34]. The relative paucity of dedicated studies makes biogenesis an open niche within the TBI–MQC field, particularly regarding its temporal coordination with mitophagy across the acute-to-chronic transition.

## 6. Crosstalk between Defective MQC and Regulated Cell Death

A major conceptual advance of recent years is the recognition that failed MQC does not kill cells through energy failure alone; it actively engages specific RCD programmes. This interface is where mitochondrial biology meets the fastest-moving area of TBI research.

### 6.1 Apoptosis

Mitochondrial outer-membrane permeabilization and cytochrome c release define the intrinsic apoptotic pathway [39], and mitophagy counteracts it by removing permeabilized mitochondria before the apoptotic threshold is crossed. In TBI models, enhancing BNIP3- or cardiolipin-dependent mitophagy consistently reduced caspase activation and neuronal apoptosis [30,28], while Parkin overexpression suppressed caspase-3 activation after traumatic neuronal injury [11].

### 6.2 Ferroptosis

Ferroptosis is an iron-dependent, lipid peroxidation-driven RCD modality [40] that has emerged as a prominent death pathway after TBI. Mitochondria supply both the ROS and the metabolic context for lipid peroxidation, and their quality control determines ferroptotic susceptibility: FTY720 attenuated BBB damage and ferroptosis after TBI in part by activating mitophagy [14], while microglial M2-polarization defects promoted ferroptosis via the BMP6/SMAD3 pathway

[41]. Several MQC-linked interventions—pterostilbene via SIRT1/PGC-1α/NRF2 [38], CDK1–USP29-mediated NRF2 stabilization [42], 7,8-dihydroxyflavone via TrkB–ERK/CREB–GPX4 [43], and sodium butyrate via JNK/p38 MAPK [44]—converge on the NRF2/GPX4 antioxidant axis, and NET-driven STING–AMPK dysregulation links innate immunity to neuronal ferroptosis [20]. These findings collectively frame ferroptosis after TBI as, in substantial part, a failure of mitochondrial quality control.

### 6.3 Pyroptosis and PANoptosis

Inflammasome-driven pyroptosis of microglia amplifies post-traumatic neuroinflammation, and mitophagy is a brake on this process: enhancing microglial mitophagy with nicotinamide N-oxide or remimazolam suppressed NLRP3-dependent pyroptosis and improved outcomes [45,33], microglial NLRP3 deletion dampened pyroptotic gene programmes [46], and restoring mitochondrial dynamics with metformin similarly suppressed neuronal pyroptosis [24]. Most recently, PANoptosis—the integrated programme combining pyroptotic, apoptotic, and necroptotic machinery—has been documented in TBI: the deubiquitinase USP4 stabilizes ZBP1 to drive microglial PANoptosis, and its pharmacological inhibition improved functional outcomes, with USP4 expression correlating with prognosis in severe TBI patients [15]; NET–AIM2 signalling drives endothelial PANoptosis and BBB disruption [47]; and epigenetic reactivation of PINK1-mediated mitophagy via the lactylation–PSMD14 axis alleviates neuronal PANoptosis [13]. Mitochondrial dysfunction and PANoptosis-related signalling are now viewed as mechanistically convergent across acute CNS injuries [48], and a systematic review of PANoptosis in microglia and neurons after traumatic CNS injury maps this rapidly consolidating field [49].

## 7. Therapeutic Strategies Targeting MQC

Interventions fall into three categories (Table 1): small molecules acting on MQC nodes (mitophagy enhancers such as pyrroloquinoline quinone [27]; dynamic modulators such as Mdivi-1 [25] and metformin [24]; biogenesis-coupled antioxidants such as pterostilbene [38]; repurposed drugs such as amantadine [32] and ticagrelor [50]; and natural products such as ginkgolide B [51]); physical and neuromodulatory approaches (trigeminal nerve stimulation [35], acupuncture [36]); and cell-free biologics, notably mesenchymal stem cell-derived exosomes acting through PINK1/Parkin mitophagy [52,53], with endothelial exosomes rescuing the post-traumatic energy crisis [4] and broader translational context reviewed elsewhere [54,55]. Most evidence, however, derives from rodent models treated at or before injury; delayed administration, clinically realistic dosing, BBB penetrance, and severity stratification remain inadequately tested [54]. Moreover, because mitophagy and fission exhibit threshold behaviour (Section 4.3), therapeutic windows are likely to be narrow and injury-stage dependent [8]. Future trials will therefore benefit from pharmacodynamic readouts of MQC engagement—such as circulating mtDNA or cardiolipin—and from severity-stratified enrolment rather than unselected TBI populations.

**Table 1:** Representative interventions targeting mitochondrial quality control in experimental TBI.

| Intervention | Model | MQC target | Principal outcome | Ref. |
|---|---|---|---|---|
| Pyrroloquinoline quinone | Mouse TBI | PINK1/Parkin mitophagy ↑ | Reduced secondary damage | [27] |
| FTY720 | TBI model | Mitophagy ↑; ferroptosis ↓ | Attenuated BBB damage | [14] |
| Pterostilbene | TBI model | SIRT1/PGC-1α/NRF2 | Reduced neuronal ferroptosis | [38] |
| Amantadine | Rat TBI | HIF-1α/BNIP3L/HMGB1 | Reduced oxidative and inflammatory injury | [32] |
| Remimazolam | TBI / BV2 microglia | α7nAChR-linked mitophagy ↑ | Reduced pyroptosis | [33] |
| Mdivi-1 | Rat CCI | Fission ↓; autophagic flux normalized | Reduced BBB disruption and cell death | [25] |
| Acute fission blockade | Mouse TBI | DRP1-dependent fission ↓ | Prevented chronic neurodegeneration | [23] |
| Metformin | Mouse TBI | MFN1-dependent dynamics | Reduced neuroinflammation and pyroptosis | [24] |
| Vialinin A | Mouse TBI | USP4–ZBP1 (PANoptosis) | Reduced microglial PANoptosis | [15] |
| Nicotinamide N-oxide | Rat TBI | Microglial mitophagy ↑ | Reduced pyroptosis and neural damage | [45] |
| Ticagrelor | TBI model | NLRP3-mediated pyroptosis ↓ | Reduced neuroinflammation | [50] |
| Ginkgolide B | Mouse TBI | HIF-1α/AKT/mTOR | Attenuated acute injury | [51] |
| Trigeminal nerve stimulation | TBI model | CGRP–PINK1 mitophagy | Attenuated neuronal damage | [35] |
| hUCMSC-derived exosomes | TBI model | PINK1/Parkin mitophagy | Suppressed programmed cell death | [52] |
| Endothelial cell-derived exosomes | TBI model | Cerebral energy rescue | Neuroprotection at injury site | [4] |

## 8. Conclusions and Future Perspectives

Mitochondrial quality control has matured into a mechanistic framework explaining how TBI converts a mechanical insult into weeks of progressive damage. Priorities for the field include: resolving the dose- and time-dependence of mitophagy with flux-based longitudinal measurements [11,8]; dissecting cell-type-specific MQC responses across neurons, microglia, astrocytes, and endothelium [46,19,47]; exploiting metabolic–epigenetic MQC control as drug targets [12,13]; and developing biomarker-guided timing, in which circulating mtDNA or cardiolipin could report MQC failure and inform patient selection [28,19]. Finally, mitochondrial biogenesis remains the least explored MQC arm in TBI and warrants dedicated study, particularly its temporal coordination with mitophagy across the acute-to-chronic transition [37,11]. Clinically, success will depend on matching the right MQC-directed intervention to the right injury stage in the right patient. Addressing these questions may allow mitochondrial biology to deliver what decades of neuroprotection trials have not: a mechanistically grounded therapy for traumatic brain injury.

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