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The role of regulatory necrosis in traumatic brain injury

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Traumatic brain injury (TBI) is a major cause of death and disability in the population worldwide, of which key injury mechanism involving the death of nerve cells. Many recent studies have shown that regulatory necrosis is involved in the pathological process of TBI which includes necroptosis, pyroptosis, ferroptosis, parthanatos, and Cyclophilin D (CypD) mediated necrosis. Therefore, targeting the signaling pathways involved in regulatory necrosis may be an effective strategy to reduce the secondary injury after TBI. Meanwhile, drugs or genes are used as interference factors in various types of regulatory necrosis, so as to explore the potential treatment methods for the secondary injury after TBI. This review summarizes the current progress on regulatory necrosis in TBI.

KEYWORDS

traumatic brain injury (TBI), regulatory necrosis, ferroptosis, necroptosis, pyroptosis, parthanatos, cell death

Introduction

Traumatic brain injury (TBI) is a common traumatic disease and a serious factor causing death and disability in adults worldwide. Each year, more than 27 million new TBI cases are diagnosed around the world, imposing a huge burden on society and families (Jiang et al., 2019; Ponsford et al., 2022). TBI is a relatively complex disease, which will lead to structural damage and functional defects through primary and secondary injury mechanisms. Secondary injury occurs after primary injury, resulting from a cascade of metabolic, cellular and molecular events, and will eventually lead to brain cell death, tissue damage and atrophy (Ng and Lee, 2019). However, the cellular pathophysiological changes occurring in brain after TBI are mainly based on four major factors, namely excitotoxicity, cytokines, reactive oxygen species (ROS), and cell death (Ladak et al., 2019). In recent years, more and more studies have shown that some cell death is regulated by a certain kind of mechanism called regulatory necrosis, including

necroptosis, pyroptosis, ferroptosis, parthanatos, and Cyclophilin D (CypD) mediated cell necrosis (Galluzzi et al., 2018). The details of regulatory necrosis in TBI and its differences in various features are provided in **Table 1**.

Regulatory necrosis has been found in many diseases in central nervous system, such as traumatic brain injury, spinal cord injury, epilepsy, Alzheimer's disease (AD), Parkinson's disease (PD), stroke, etc. (Liu et al., 2015; Sekerdag et al., 2018; Weiland et al., 2019; Hu et al., 2020; Dionísio et al., 2021). In Alzheimer's disease, pTau can cause neuronal death by inducing necroptosis (Dong et al., 2022), while introducing the gene of amyloid precursor protein (App) can enhance necroptosis (Pang et al., 2022). In PD, fibrillar alpha-synuclein promotes the activation of neurotoxic astrocytes through RIP kinase signaling pathway (Chou et al., 2021). This review focuses on the role and the current studies of regulatory necrosis in the secondary injury after TBI, which may provide new targets for the treatment of craniocerebral injury.

The necroptosis involved in traumatic brain injury

Necroptosis is induced by the combination of related ligands with Tumor Necrosis Factor (TNF) family death domain receptors, pattern recognition receptors, and virus sensors. It is a regulated cell death mode independent of caspase activity, which is mediated by mixed lineage kinase domain-like protein (MLKL) by activating receptor interacting protein kinase 1 (RIPK1)/receptor interacting protein kinase 3 (RIPK3) (Galluzzi et al., 2018). The process of necroptosis is characterized by cell swelling and the loss of plasma membrane integrity (Holler et al., 2000; Cho et al., 2009; Murphy et al., 2013; Grootjans et al., 2017; Degterev et al., 2019).

Previous studies have reported that necroptosis is involved in TBI (Liu et al., 2015; Yuan et al., 2019). Necroptosis would occur after a controlled cortical impact (CCI) in mice. RIPK3 is highly expressed in the hippocampus of CCI-TBI mice. Knockout of RIPK3 gene can inhibit oxidative stress, inflammation and apoptosis after TBI through AMPK signaling pathway (Liu Z. et al., 2018). The mice with RIPK3 gene knockout and RIPK1-deficient improved cognitive function within 3 months after TBI, demonstrating that the loss of RIPK1/RIPK3 could prevent progressive neuronal death and improve cognitive memory function (Wehn et al., 2021). But Wu et al. (2021) noted that the knockout of RIPK3 and MLKL in CCI mice model indicates RIPK3 is a disease driver independent of necroptosis mechanisms, while MLKL and the drug therapy of necroptosis may have no clinical effect on the patients with cerebral contusion. In PD animal model, the knockout of RIPK3 and MLKL can reduce the degeneration of dopaminergic neuron, improving the motion performance of mice (Oñate et al., 2020). The contribution of necroptosis to TBI needs to be further confirmed.

As the role of necroptosis in TBI has already been well recognized, many relevant studies started their research on the mechanisms that affected RIPK1/RIPK3/MLKL. Recently, Carsten Culmsee et al. found that mice with the knockout of tumor-suppressor cylindromatosis (CYLD) gene have relieved nerve damage after TBI. As a key regulator of deubiquitinase, cell proliferation and inflammation, the down-regulation of CYLD can increase the ubiquitination of RIP1, inhibit the formation of RIPK1/RIPK3 complex, and reduce necroptosis to protect neuronal cells (Ganjam et al., 2018). The 2-benzofuranyl-imidazoline (2-BFI) is an effective analgesic. In recent studies, 2-BFI treatment could significantly improve the neurological dysfunction and brain edema after TBI, of which mechanism is to reduce the level of receptor interacting proteins (RIPK1), (RIPK3), and MLKL (Ni et al., 2019). Other studies have shown that TNF Alpha induced protein 3 (TNFAIP3, also known as A20) can inhibit the synthesis of protein complexes composed of RIPK1, RIPK3, and MLKL, and thus reducing necroptosis in TBI, while Nec-1 and melatonin can reduce necroptosis and inhibit HMGB1, RAGE and proinflammatory cell factors in an A20 dependent manner (Bao et al., 2019). When MLKL maps to the site of damaged membrane bubble, it will recruit transport complex III (ESCRT-III) component (Gong et al., 2017; Guo and Kaiser, 2017), including the charged multivesicular body protein 4b (CHMP4B), which can alleviate the cell membrane damage caused by p-MLKL and the necroptosis level of microglia to a great extent. The transcription factor FOXO1 enhances the transcription of CHMP4B by binding to the promoter region in microglia. Stable knockdown of FOXO1 can reduce the expression of CHMP4B, thereby increasing the level of necroptosis after microglia damage, and further reducing the pro-inflammatory effect of microglia while improving the recovery of neural function after TBI (Zhao et al., 2020). According to current studies, the immediate-early gene (IEG) encoding the protein activity-regulated cytoskeletal (Arc) is a brain-specific postsynaptic density (PSD) protein. Arc can reduce the traumatic injury (TNI) in cortical neurons by inhibiting necroptosis. The arc silencing can activate the metabotropic glutamate receptor-1 (mGluR1) -mediated ER stress-calcium overload pathway and the RIP1-dependent necroptosis (Chen et al., 2020). As a AMPAR antagonist, perampanel has recently been reported as a neuroprotective factor in hemorrhagic and ischemic stroke models, while Wang et al. found that perampanel can also act as a protective factor in the TBI-*in vitro* model, reducing RIPK1 and RIPK3 expression and subsequently alleviating necroptosis through the activation of Akt/GSK3β signaling (Chen et al., 2021b).

In fact, studies have shown that hydrogen or hydrogen-containing saline can modulate neuronal death. Hu et al. (2022) found that hydrogen-rich saline inhibits necroptosis

TABLE 1 Main morphological features, key regulators, inducers, and inhibitors of necroptosis, pyroptosis, ferroptosis, parthanatos, and CYPD-dependent necrosis.

Regulated necrosis	Main morphological features	Key regulators	Inducers	Inhibitors
Necroptosis	Loss of cytoplasmic membrane integrity, secretion of DAMP; swelling of cell bodies and organelles, chromatin fragmentation, nucleus disintegration	RIPK1, RIPK3, RIP1, RIP3, and MLKL	TNF-α,Fas, TRAIL, IFN, TNFR, TLR, and z-VAD-fmk	Nec-1, CYLD, 2-BFI, A20, CHMP4B, Arc, Hydrogen-rich saline, Perampanel, and HT
Pyroptosis	Cell swelling, cell membrane pore formation, release of bubble-like protrusions; cell membrane rupture, release of cell contents, DNA breakage; chromatin condensation, intact nuclei	NLRP3, ASC, Caspase-1, AIM2, GSDMD, IL-1β, and IL-18	ATP, LPS, PRR, HMGB1, and HIF-1α	Ac-YVAD-CMK, Ac-FLTD-CMK, PGAM5, VX765, JC124, NEK7, 2-BFI, ACE2, Dexmedetomidine, Artesunate, Resveratrol, Rhein, CORM-3, H2, and Ghrelin
Ferroptosis	Cellular mitochondria shrink in size and become smaller, with increased membrane density and reduced cristae. Insignificant morphological changes in the nucleus	Fe, GPX4, ROS, GSH, P53, and SLC7A11	Erastin, Erastin derivatives, RSL3, Glutamate, PEBP1, and 15LO	Ferrostatin-1, Liproxstatin-1, Deferoxamine, Ferristatin II, Baicalein, Prokineticin-2, Polydatin, Ruxolitinib, Tetrandrine, Melatonin, and SIRT2
Parthanatos	Loss of cell membrane integrity, intranuclear chromatin condensation, DNA breakage, and production of large amounts of DNA fragments; irreversible $\Delta\psi m$ dissipation, ATP and NADH depletion	PARP-1, PAR, AIF, and MIF	PAR polymer, AIFsol (soluble AIF)	PARP-1 inhibitors, DPQ, GPI 6150, PJ34, INO-1001, Ghrelin, TSG, OLA, and Iduna
CYPD-dependent necrosis	Mitochondrial membrane potential damage; mitochondrial swelling, mitochondrial matrix expansion; massive intracellular vacuoles, outer membrane rupture	CypD, p53, and mPTP	CypD, VDAC (anion channel)	CsA, NIM811, Resveratrol, SIRT1, and BDNF

TRAIL, TNF-related apoptosis-inducing ligand; IFN, interferon; TNFR1, TNF-receptor 1; TLR, toll-like receptors; A20, TNF-inducible protein 3; CHMP4B, multivesicular body protein 4b; Arc, activity-regulated cytoskeletal; Perampanel, an (AMPAR) antagonist; HT, hypothermia treatment.

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and neuroinflammation based on the ROS/heme oxygenase-1 (HO-1) signaling, reducing neuronal death after TBI. As a research hotpot, Nec-1 is often used to verify the contribution of necroptosis. For example, Nec-1 can alleviate brain tissue injury, motor dysfunction and spatial learning impairment after CCI in mice, and has an anti-inflammatory effect in acute brain injury (You et al., 2008). Mu et al. (2021) found that Nec-1 can protect neuronal cells and oligodendrocytes by inhibiting the nuclear transposition of cellular AIF induced by the pro-apoptotic protein called Bcl-2/adenovirus E1B 19-kDa interacting protein 3 (BNIP3). At the same time, changes in external environment can also affect necroptosis. The hypothermia (HT) treatment can significantly reduce the upregulation of RIPK-1 and protect injured CNS from tissue damage and inflammation by targeting necroptosis through TNF signaling (Liu et al., 2016; Zhang et al., 2017) after TBI. The controlled decompression (CDC) surgery can reduce brain injury, and Chen et al. (2021a) stated that performing CDC for 2 or 3 h *in vitro* and for 20 or 30 min *in vivo* can exert neuroprotective effects. CDC can inhibit neuronal necroptosis through the TREK-1-mediated intracellular Ca^{2+} overload and the depression of RIPK3 activation. As indicated by Nec-1, necroptosis can affect acute neuronal injury, and the activation of RIPK1 and RIPK3 are both observed in the rat model of liquid impact brain injury and MCAO model with TBI (Liu et al., 2016; Ni et al., 2018). Interestingly, post-traumatic hypothermia (33°C) also reduces brain damage after stroke, resulting in decreased levels of RIPK1, RIPK3, and MLKL (You et al., 2008). Thus indicates that there may exist common target for the treatment of TBI and stroke by improving necroptosis. In conclusion, these studies have emphasized the potential therapeutic significance of necroptosis related therapy for TBI. The possible signal pathways of necroptosis involved in TBI are summarized in **Figure 1**.

The pyroptosis involved in traumatic brain injury

Pyroptosis is mediated by Gasdermin D (GSDMD), the formation of plasma membrane pores as well as the extracellular release of inflammatory cytokines. In typical caspase-1 inflammatory pathway, caspase-1 is activated by apoptosis related CARD containing spotted protein (ASC) or pyridine domain 3 (NLRP3) in Nucleotide oligomerization domain (NOD) like receptor family, and processed into inflammatory cytokines such as IL-1β, IL-18 which can finally induce the release of inflammatory factors through the activation of GSDMD, resulting in cell death (Shi et al., 2017; Hu et al., 2020; Irrera et al., 2020; Zhou et al., 2022).

Therefore, most studies have been designed to explore the potential role of pyroptosis in TBI based on the regulation of inflammasome, such as caspase-1, NLRP1, NLRP3, AIM2, etc. Up to now, many of these studies have confirmed the contribution of pyroptosis to TBI by targeting inflammasomes. In the animal model of TBI, the caspase-1 plays a critical role, of which inhibition can reduce the level of IL-1β, IL-18, and GSDMD, and finally reduce the neuroinflammation and neuronal damage after TBI (Liu W. et al., 2018). Blocking the increasing level of phospho-Tau by IL-1R1$^{-/-}$ in cortex and cerebellum suggests that inflammasome activation can drive Tau phosphorylation, while the aberrantly phosphorylated Tau may also contribute to neuronal IL-1β production and impaired proteostasis in feed forward loops, leading to neuronal death (Wu L. et al., 2022). The inflammasome plays a dominant role in the development of neuroinflammation after TBI, as NLRP3-GSDMD is dominant in the regulation of neuroinflammation and neuropathology after TBI. The level of GSDMD and N-GSDMD reach the peak 3 days after TBI, equivalent to the level of NLRP3 inflammasome. After TBI, GSDMD is mainly located in microglia cells, indicating that GSDMD may involve in the polarization of microglia cells. GSDMD-KO can alleviate the neuropathological changes (synaptic protein loss, microglia activation, astrocyte increase, dendritic damage and neuronal death) caused by TBI to a great extent (Du et al., 2022). The inhibition of GSDMD is conducive to a better prognosis, as the inhibition of inflammasome can prevent the neurological dysfunction in patients with TB1, PD, AD, subarachnoid hemorrhage, vascular dementia, etc. (Wnuk and Kajta, 2017; Ising et al., 2019; Rui et al., 2020; Poh et al., 2021). After TBI, NLRs, and AIM2 inflammatory corpuscles are activated in the cerebral microvascular endothelial cells (BMVECs) in cerebral cortex. As caspase-1 inhibitors, Ac-YVAD-CMK and Ac-FLTD-CMK can block the cleavage of GSDMD and ASC oligomerization by inhibiting caspase-1, which can reduce pyroptosis (Ge et al., 2018; Wang et al., 2021). Pgam5 is a mitochondrial protein that promotes the activation of microglial inflammasome after TBI, reduces the amount of pyroptosis-related molecules, promotes the polymerization of ASC and the activation of caspase1, and ameliorates the neuronal damage and dysfunction in TBI (Chen et al., 2021e). VX765, a known caspase-1 inhibitor, can inhibit pro-inflammatory cytokines against pyroptosis through HMGB1/TLR4/NF-κB pathway (Sun et al., 2020).

Pyridine domain 3 inflammasome is an intracellular multiprotein complex which can activate the release of inflammatory factors in TBI, causing cell pyroptosis (Irrera et al., 2017). Many researchers have found that NLRP3 inhibitors can inhibit cell death and play a neuroprotective role in TBI. JC124 is a specific NLRP3 inflammatory inhibitor, which is developed from the structural optimization of sulfonylurea drugs. It can block the aggregation of ASC, inhibit the activation of caspase-1 and protect brain from TBI (Kuwar et al., 2019). NIMA-associated kinase 7 (NEK7) is an important vector for NLRP3 inflammasome activation. Liu et al. have demonstrated that the NEK7 knockdown can inhibit the activation of NLRP3 inflammasome and caspase-1 through K^+ outflow and reduce

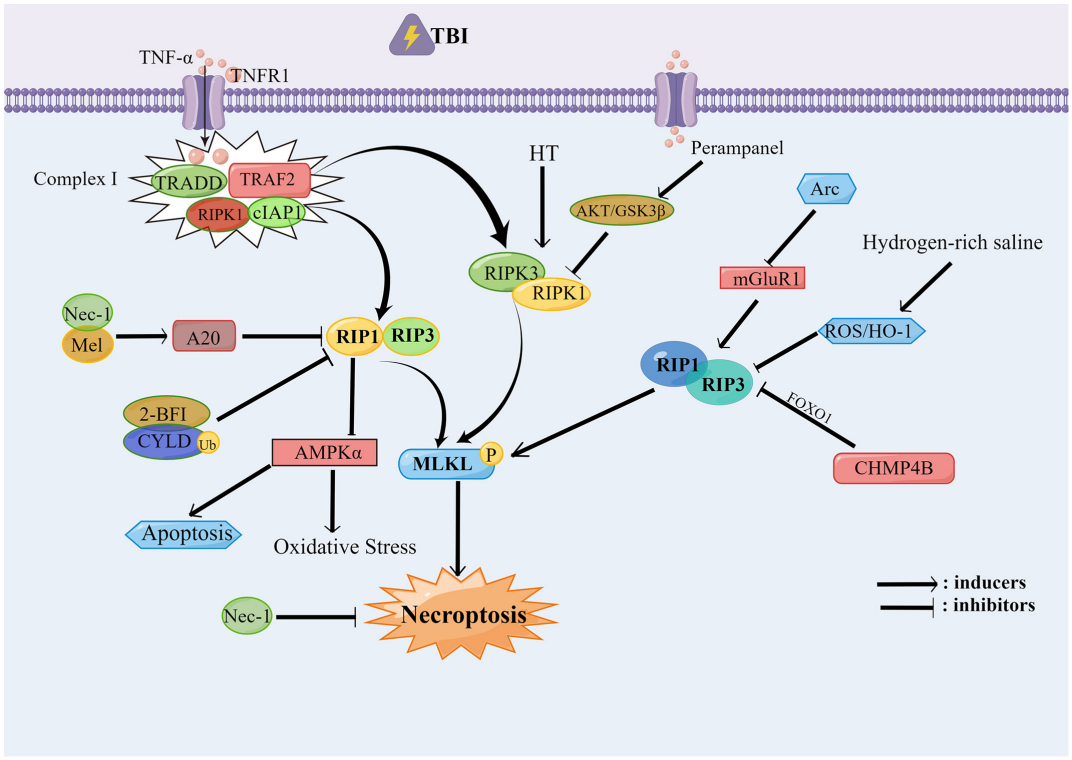

FIGURE 1
The necroptosis involved in traumatic brain injury (TBI). After TBI occurs, the RIPK1/RIPK3/MLKL pathway is activated, in which the Nec-1, Mel, 2-BFI, CYLD, and CHMP4B can alleviate the necroptosis and protect the neural function by inhibiting the RIP1 and RIP3. Hydrogen-rich saline can inhibit the RIP1 and RIP3 through the ROS/HO-1 pathway. While RIP1 can inhibit the oxidative stress and the apoptosis which occurred after TBI through the AMPK signal pathway. Perampanel can inhibit the RIPK1/RIPK3/MLKL pathway through the AKT/GSK3β pathway, thereby alleviating the necroptosis.

posttraumatic nerve injury (Chen et al., 2019). After TBI, the NLRP3 inflammasome inhibitor 2-BFI will induce inflammation and play an important role in BBB destruction and brain edema (Ni et al., 2019). Meanwhile, HIF-1α will recruit and activate microglia during the release of inflammatory factor, leading to the NLRP3 inflammasome-mediated cell pyroptosis (Yuan et al., 2021). Angiotensin converting enzyme 2 (ACE2) is an enzyme that catalyze the convert of angiotensin II to angiotensin, exerting neuroprotective effect. As proved by Meng Liang Zhou et al., ACE2 can reduce the mitogen activated protein kinase and NF in TBI- κ Phosphorylation of B, leading to the reduction of activated NLRP3 and caspase-3, thereby alleviating cell death (Li T. et al., 2022). As another effector molecule induced by the activation of NLRP3 inflammasome, high mobility group box 1 (HMGB1) is also involved in a typical damage-associated molecular pattern (DAMP), which is associated with the initiation process of NLRP3 inflammasome (Frank et al., 2015). Zhou et al. showed that NLRP3 inflammasome can impair the memory function in late TBI stages mainly through the upregulation of HMGB1 (Tan et al., 2021). Researchers have also studied some related drugs and found that dexmedetomidine, artesunate, and resveratrol can inhibit the activation of NLRP3 inflammasome, and thus presenting an anti-inflammatory function (Gugliandolo et al., 2018; Zheng et al., 2018; Zou et al., 2018).

In addition, some natural products and gas molecules can also inhibit pyroptosis to improve the prognosis of brain injury such as Rhein, which protects the neurological dysfunction after TBI by inhibiting neuronal cell pyroptosis (Bi et al., 2020). Carbon monoxide releasing molecule-3 (CORM-3) is a water-soluble exogenous carbon monoxide involved in the two-way interaction between intestinal and brain, which can inhibit cell death and improve brain injury (Zhang et al., 2021). In terms of the complications after TBI, it has been reported that molecular hydrogen (H_2) can improve the acute lung injury (ALI) after TBI in rats by reducing pyroptosis (Li T. T. et al., 2022). Meanwhile, as a neuroendocrine hormone and a new gastrointestinal hormone which can block NF-κB signaling pathway, ghrelin can improve the inflammasome induced focal necrosis and reduce the TBI induced ALI (Shao et al., 2020). Another study also showed that microglia and infiltrating $CD11b^{+}$ leukocytes, which include macrophages and neutrophils, can actively participate in the innate immune response to penetrating brain injury (PBBI) and pyroptosis,

which would lead to cell loss (Lee et al., 2019). These studies reported that pyroptosis signaling pathway might be a novel therapeutic target for TBI. The possible signal pathways of pyroptosis involved in TBI are summarized in **Figure 2**.

The ferroptosis involved in traumatic brain injury

Ferroptosis is an iron dependent regulatory form of cell death driven by lipid peroxidation. It is characterized by the accumulation of intracellular iron and lipid ROS, the reduction of glutathione (GSH) level, and the inactivation of glutathione peroxidase 4 (GPX4) (Dixon et al., 2012; Stockwell et al., 2017; Yu et al., 2017; Chen et al., 2021d). Ferroptosis has been reported to be involved in TBI (Wenzel et al., 2017; Tang et al., 2020; Geng et al., 2021; Yao et al., 2021). Meanwhile, lipid peroxidation also plays an important role in the traumatic injury of nerve tissue (Anthonymuthu et al., 2018). In the TBI animal model, iron overload, the increased expression of transferrin, the accumulation of lipid ROS and mitochondrial atrophy associated with iron metabolic pathway further verified the existence of ferroptosis. While the treatment of ferroptosis with the inhibitor Fer-1 can reduce neuronal death and improve long-term cognitive and motor function (Xie et al., 2019). TfR1 is a recognized marker of ferroptosis. Researchers reported that ferristatin II (an iron absorption and TfR1 inhibitor) can inhibit the formation of ferritin by reducing Fe^{3+} and iron positive deposits, leading to the alleviation of the neuronal damage caused by TBI (Cheng et al., 2022).

In terms of the lipid metabolism pathway, some scholars have reported that in animal models of TBI, the expression levels of 15-HpETE-PE and 15LO2, GPX4 levels and enzyme activity are decreased in cerebral cortex and hippocampus, proving the existence of PEBP1/15LO-driven ferroptosis in TBI (Wenzel et al., 2017). Lipoxygenase (LOXs) is considered to be a key factor of ferroptosis. It inhibits 12/15-LOX while also reducing infarct size and improving behavioral parameters in ischemic stroke, which confirms the feasibility of 12/15-LOX inhibitors in the treatment of stroke (Karatas et al., 2018). It is reported that the redox lipomics method with liquid chromatography tandem mass spectrometry (LC-MS/MS) identify the oxidation of phosphatidylethanolamine (PEoX) and the reduction of glutathione levels. After the identification of PEoX as a predictive biomarker in ferroptosis by gas cluster ion beam secondary ion mass spectrometry (GCIB-SIMS) imaging and cluster ion beam, mapping the distribution of PEoX in cortical/hippocampal neurons after traumatic brain injury with a spatial resolution of 1.2 mm at single cell/subcellular level can help researchers visualize lipid peroxidation (Sparvero et al., 2021). At the same time, the baicalein administration (a 12/15-lipoxase inhibitor) can significantly reduce ferroptosis in TBI (Kenny et al., 2019). Moreover, baicalin also plays a neuroprotective effect against the seizures after TBI by inhibiting ferroptosis (Li et al., 2019). In addition, it is reported that prokineticin-2, as an important secretory protein, can participate in the pathogenesis of acute and chronic nervous system diseases. It reduces ferroptosis and protect nervous function through the ubiquitination of Fbxo10, the degradation of long chain acyl-CoA synthetase 4 (ACSL4) and the inhibition of lipid peroxidation (Bao et al., 2021).

In addition, there are some molecular compounds and drugs that involved in the mechanism of GPX4 inhibition that can cause ferroptosis. These compounds and drugs include polydatin, ruxolitinib, and tetrandrine. Among them, polydatin generally plays an anti-inflammatory effect, which can improve the activity of GPX4 enzyme and reduce MDA accumulation and lipid peroxidation deposition (Huang et al., 2021). As an inhibitor of janus kinase (JAK) 1 and 2, ruxolitinib is used to treat bone marrow fibrosis, which has an inhibitory effect on ferroptosis, and can also alleviate brain edema and nerve deformation (Chen et al., 2021c). Tetrandrine is a natural bisbenzylisoquinoline alkaloid that can ameliorate TBI by activating autophagy to reduce ferroptosis (Liu et al., 2022). Meanwhile, carotenoids can inhibit ferroptosis from I/R by increasing the expression of GPX4 (Guan et al., 2019). Selenium (Se) effectively inhibits GPX4-dependent ferroptosis, thereby protecting neurons and reducing cerebral infarction (Alim et al., 2019). Regulating the inhibition of ferroptosis by GPX4 may be an effective treatment for patients with ischemic stroke and TBI.

Some non-coding RNAs also exert function in the process of ferroptosis. The miR-212-5p can regulate Ptgs2 to inhibit ferroptosis and protect injured brain (Xiao et al., 2019). Melatonin is a neuroprotective factor which can mitigate lipid peroxidation through circPtpn14/miR-351-5p/5-LOX signaling. It can also antagonize ferroptosis and relieve ER stress in TBI (Wu C. et al., 2022). Referring to the protective mechanism of melatonin, Rui et al. (2021) found that melatonin could inhibit the neuronal FTH mediated ferroptosis after TBI. Meanwhile, p53 is another factor involved in ferroptosis, of which possible target is SLC7A11 (Jiang et al., 2015). Sirtuin 2 (SIRT2) is a member of nicotinamide adenine dinucleotide (NAD+) dependent protein deacetylase family which has neuroprotective effects on TBI by inhibiting the p53 mediated ferroptosis (Gao et al., 2021). To sum up, inhibiting ferroptosis can probably improve the damage caused by TBI. The possible signal pathways of ferroptosis involved in TBI are summarized in **Figure 3**.

The parthanatos involved in traumatic brain injury

Parthanatos is a novel form of programmed cell death based on DNA damage and PARP-1 activation. In this process, the DNA repairment of poly ADP-PARP1 is over activated

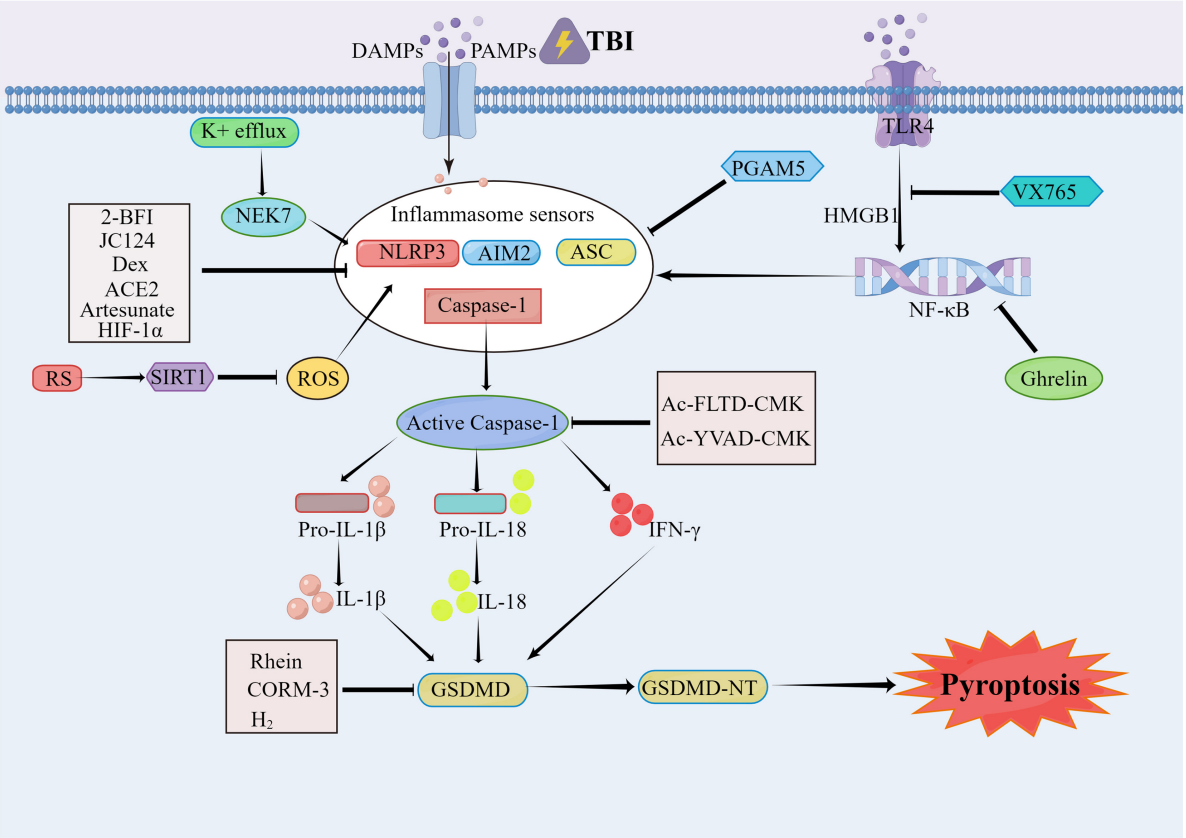

FIGURE 2
The pyroptosis involved in traumatic brain injury (TBI). After TBI occurs, the caspase-1 is mainly activated by NLRP3, AIM2, ASC, and other inflammasomes. The activated caspase-1 includes the IL-1β/18 lysed from the pro IL-1β, and the N-terminal segments of the GSDMD (GSDMD-NT) lysed from the Gasdermin D (GSDMD). The 2-BFI, JC124, Dex, ACE2, Artesunate, HIF-1α, and PGAM5 can alleviate the pyroptosis by inhibiting the inflammasomes. The VX765 can exert the neural protect function through the HMGB1/TLR4/NF-κB pathway. The Rhein, CORM-3, and H2 can inhibit the pyroptosis as well. The RS can activate the SIRT1 to inhibit the activation of NLRP3, thereby relieving the TBI. As the inhibitors of the Caspase-1, the Ac-YVAD-CMK and Ac-FLTD-CMK can inhibit the lysis of GSDMS and the oligomerization of ASC to alleviate the pyroptosis.

with the accumulation of intracellular poly ADP ribose (PAR) polymer, resulting in the depletion of NAD^+ and ATP. PAR also combines with mitochondrial apoptosis which can induce the release of factor AIF to cell membrane. Combined macrophage migration inhibitory factor (MIF) can move to nucleus and split the genomic DNA into large fragments, causing chromatin condensation and fragmentation, and further leading to cell death (Virag and Szabó, 2002; Yu et al., 2006; Wang et al., 2011; Fatokun et al., 2014).

Multiple lines of evidence can support a certain role of parthanatos in TBI (Fatokun et al., 2014; Galluzzi et al., 2018). Secondary damage caused by oxidative stress after TBI will lead to DNA strand breakage, the over activation of PARP-1, and neuronal death. In some studies, the functional prognosis of TBI was improved by inactivation of PARP. This protective effect was confirmed by the use of a new PARP inhibitor named GPI 6150 (Virag and Szabó, 2002). PJ34 and INO-1001 are the other two structural PARP inhibitors except benzamide, which can reduce cell death and the microglia activation of primary cortical neurons exposed to *n*-methyl-*n*'-nitro-*N*-nitrosoguanidine (MNNG). They can also reduce reactive oxygen species neuroinflammation, and protect the neurons in cerebral cortex and thalamus. While neither of them can improve cognitive performance in morris water maze (MWM) test, nor can they reduce the loss of nerve cells in hippocampus (Stoica et al., 2014). INO-1001 can exert a neuroprotective effect in the rat TBI model by preventing NAD^+ depletion (Besson et al., 2005; Clark et al., 2007). Meanwhile, the inhibition of NF-B-dependent gene transcription by PARP inhibition will prevent microglial activation. The inhibitor should be administered within 20 h after TBI, which will alleviate inflammation and improve histological and functional outcomes (d'Avila et al., 2012). Ghrelin also has the functions about improving sensormotor and reflex function and reducing cleaved PARP-1 levels in cortex, the PARP-1-dependent cell death, and the mortality after TBI (Qi et al., 2012). It is

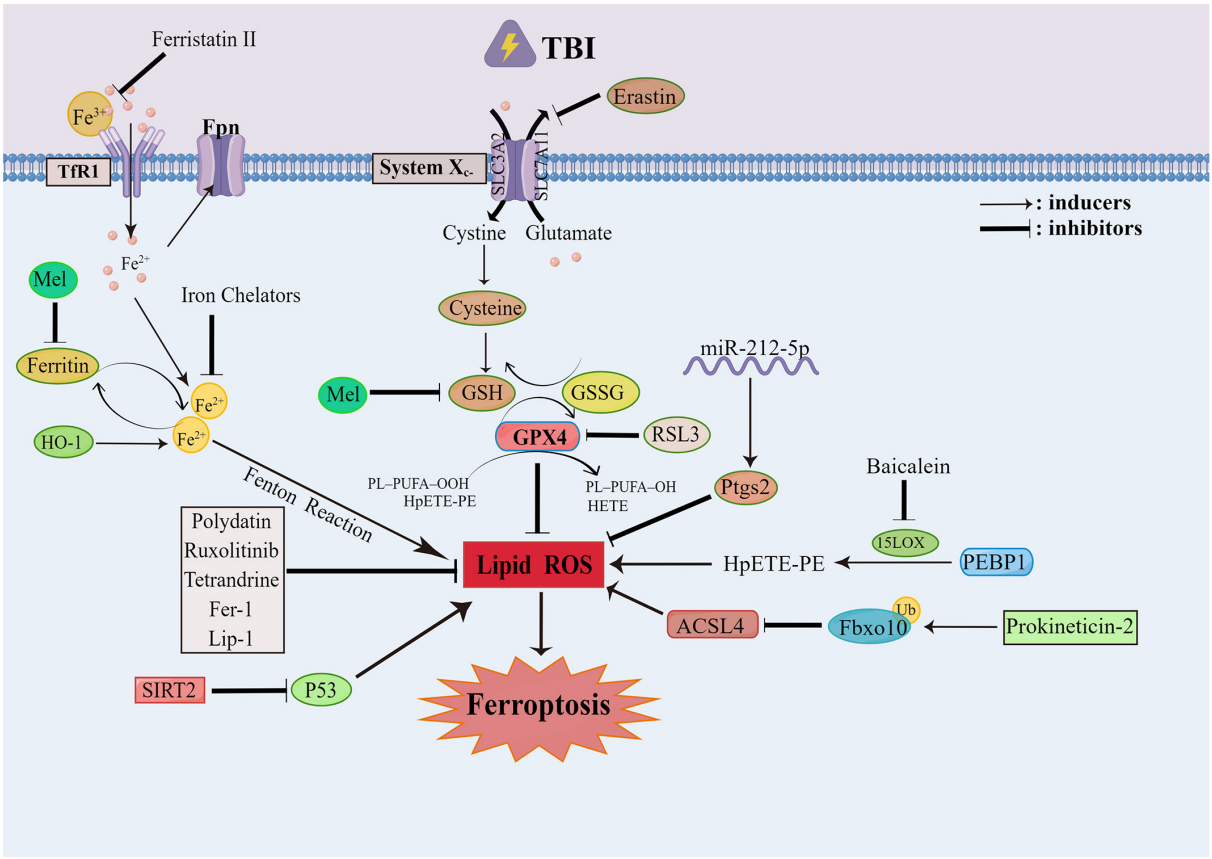

FIGURE 3
The ferroptosis involved in traumatic brain injury (TBI). The ferroptosis generally occurs after TBI, which can be targeted to improve the prognosis of TBI. The ferroptosis can be alleviated by the inhibition of the Xc-system and GPX4. The Mel can reduce the fenton reaction by inhibiting Ferritin. The Polydatin, Ruxolitinib, Tetrandrine can all alleviate the ferroptosis by mitigating the lipid peroxidation. While the SIRT2 can mitigate the lipid peroxidation through the inhibition of P53. The Prokineticin-2 can promote the ubiquitination of Fbxo10 to accelerate the degradation of Acsl4 and inhibit the lipid peroxidation. The miR-212-5p can inhibit the lipid peroxidation through Ptgs2. And the PEBP1/15LO can drive the occurrence of ferroptosis.

reported that tetrahydroxystilbene glucoside (TSG) is an active component of the traditional Chinese herbal medicine called polygonum multiflorum, which has neuroprotective effect. Its specific mechanism may be explicated as the reduction of oxidative stress and neuroinflammation and the inhibition of PARP1 to negatively regulate Ras/JNK signaling pathway (Cao et al., 2020). A large number of studies have focused on the pathway about transporting PARP inhibitors. Nanostructured lipid carriers (RBCNLCs) encapsulated by red blood cells (RBC) were used in brain neuron mitochondria together with C3 and ss31 peptides (C3/SS31-RBCNLCs). The high-concentration delivery of PARP inhibitor olapali (Ola) to brain mitochondria by C3/SS31-RBCNLCs-Ola has effectively improved mitochondrial function (Sun et al., 2022). Various lines of evidence suggested that the inhibition of PARP1 has a protective effect, as some studies found that PARP1 inhibition in ShRNA could promote axon regeneration, while the inhibition of other PARP isoforms would reduce axon regeneration with no improvement of motor function (Wang et al., 2016). The timing of pharmacological inhibition and the direction of inhibitor selection also need to be further investigated.

In addition to directly inhibiting PARP-1, aiming at PAR/MIF or NAD^+ depletion pathway is also an option to improve the prognosis of TBI. It has been reported that the intranasal delivery of NAD^+ can increase NAD^+ levels in hippocampus and reduce the TBI induced hippocampal neuronal death (Won et al., 2012). Furthermore, MIF can mediate the TBI-induced neurodegeneration, neuronal death, and neurobehavioral dysfunction via its nuclease activity, while it shows no pro-inflammatory effects (Ruan et al., 2021). Recent studies demonstrated that iduna is a newly discovered ubiquitin E3 ligase and an endogenous regulator of parthanatos, which can reduce PARP activation and nuclear translocation of AIF to prevent parthanatos, indicating that ubiquitin-proteasome pathway may also play a role in parthanatos (Xu et al., 2019). At the same time, iduna may promote docosahexaenoic acid

(DHA) through Wnt/MDM2 pathway and reduce the damage of TBI cell and mitochondrial dysfunction (Shi et al., 2022). Based on these reports, targeting PARP1-dependent parthanatos may be a potential strategy for the treatment of secondary injury after TBI.

The cyclophilin D-mediated necrosis involved in traumatic brain injury

Cyclophilin D (CypD) is a member of cyclophilin family with various biological functions which can cause mitochondrial dysfunction through promoting the opening of mitochondrial permeability transitionpore (mPTP). For example, the loss of mitochondrial membrane potential, ATP depletion, mitochondrial swelling, and final mitochondrial outer membrane rupture can all induce the CypD pathway-dependent cell necrosis (Baines et al., 2005; Schinzel et al., 2005; Yamaguchi et al., 2005; Alam et al., 2015).

Evidence suggests that in the secondary damage generated after TBI, Cyclosporin A (CsA) can inhibit the opening of mPTP by interacting with CypD, resulting in the alleviation of mitochondrial dysfunction and neuronal damage in a TBI rat model (Sullivan et al., 2005; Kim et al., 2014; Springer et al., 2018). Studies have shown that the mice lacking CypD coding gene Ppif can retain mitochondrial function for 6 h after injury with fewer loss of subacute cortical tissue and hippocampal cells within 18 days after injury. As an effective inhibitor of CypD, CSA has many benefits about its usage on disease treatment (Readnower et al., 2021). There are many CSA related studies, some of them reported the function of CSA about suppressing mPTP opening that can maintain mitochondrial membrane potential and calcium balance in isolated mitochondria, and alleviate acute mitochondrial dysfunction after TBI (Sullivan et al., 1999). However, synaptic mitochondria will suffer more damage than non-synaptic mitochondria 24 h after CCI. While the intraperitoneal injection of CSA (20 mg/kg) at 15 mins after injury can improve synaptic and non-synaptic respiration to a significant extent, especially in the synaptic groups enduring more severe damage (Kulbe et al., 2017). As a non-immunosuppressive CSA analog, NIM811 as well as CSA can significantly reduce lipid peroxidation and protein nitrating damage of mitochondria 12 h after TBI. The neuroprotection provided by nim811 is dose-dependent with the most appropriate dose of 10 mg/kg. This dose can improve cognitive function and reduce mitochondrial damage (Mbye et al., 2008; Readnower et al., 2011). In preclinical experiments, positive improvements in brain metabolism and mitochondrial function were observed in TBI models in large animals, validating the neuroprotective effects of cyclosporine (Karlsson et al., 2019). At the same time, researchers have employed some research on the intervention of CypD. For example, CypD knockout can improve the abnormalities of excitatory synapses, while inhibiting CypD can reduce the synaptic overexcitation after TBI (Sun and Jacobs, 2016). But the knockdown of CypD was unable to reduce the pathology within axon initiation node (AIS), suggesting that axonal interval is regulated under different mechanism (Hanell et al., 2015).

Other studies have focused on the regulation of Cypd/mPTP in drugs or targeted molecules to improve mitochondrial function and produce protective effects. (1) Resveratrol can reduce mPTP opening by inhibiting the ROS mediated function, and protect the TBI mitochondrial function of GSK3 (Lin et al., 2014). (2) With an neuroprotective activity in p38 MAPK pathway, SIRT1 has been reported to protect mitochondria from damage (Yang et al., 2017). (3) Treatment of recombinant human erythropoietin or carbamylated erythropoietin can reduce mPTP opening caused by TBI, thereby improving mitochondrial disorders (Millet et al., 2016). (4) In rat brain mitochondria (RBM), the oxidative phosphorylation capacity (OXPHOS) can evaluate the respiratory effect of mitochondria. Etofoxine can restore mitochondrial oxidative phosphorylation and improve cognitive recovery after TBI (Palzur et al., 2021). (5) Brain-derived neurotrophic factor (BDNF) can inhibit the opening of MPTP, promote the accumulation of pCREB in mitochondrial intima and matrix and the synthesis of mitochondrial complex V, while alleviate the metabolic defects of neurons after mechanical injury (Xu et al., 2018). To sum up, the role of CypD-mediated necrosis in TBI can provide therapeutic implications for mitochondrial dysfunction after TBI.

Discussion

Necroptosis, pyroptosis, ferroptosis, parthanatos, and CypD mediated necrosis are all important to the secondary injury after TBI. Several different types of regulatory necrosis can be triggered by nerve cells under death-inducing stimuli. However, under various complex pathophysiological mechanisms in TBI, these kinds of regulated necrosis may be interrelated and coexist with each other, or be alterable in cells with ever-changing levels. For example, (1) necroptosis may play a major role in the early stage after CCI, but other cell death pathways such as autophagy, apoptosis, pyroptosis, and ferroptosis are associated with the subsequent pathological process (Ganjam et al., 2018). (2) Silencing of RIPK1 can alleviate TBI by inhibiting inflammation and autophagy in neurons through NF-κB signaling pathway (Liu et al., 2020). (3) Nec-1 can prevent BNIP3 from integrating into mitochondria by modifying the binding site of BNIP3 on mitochondria. Therefore, Nec-1 can effectively inhibit the collapse of mitochondrial membrane potential induced by BNIP3 and reduce the opening efficiency of mPTP (Mu et al., 2021). Autophagy is significantly enhanced

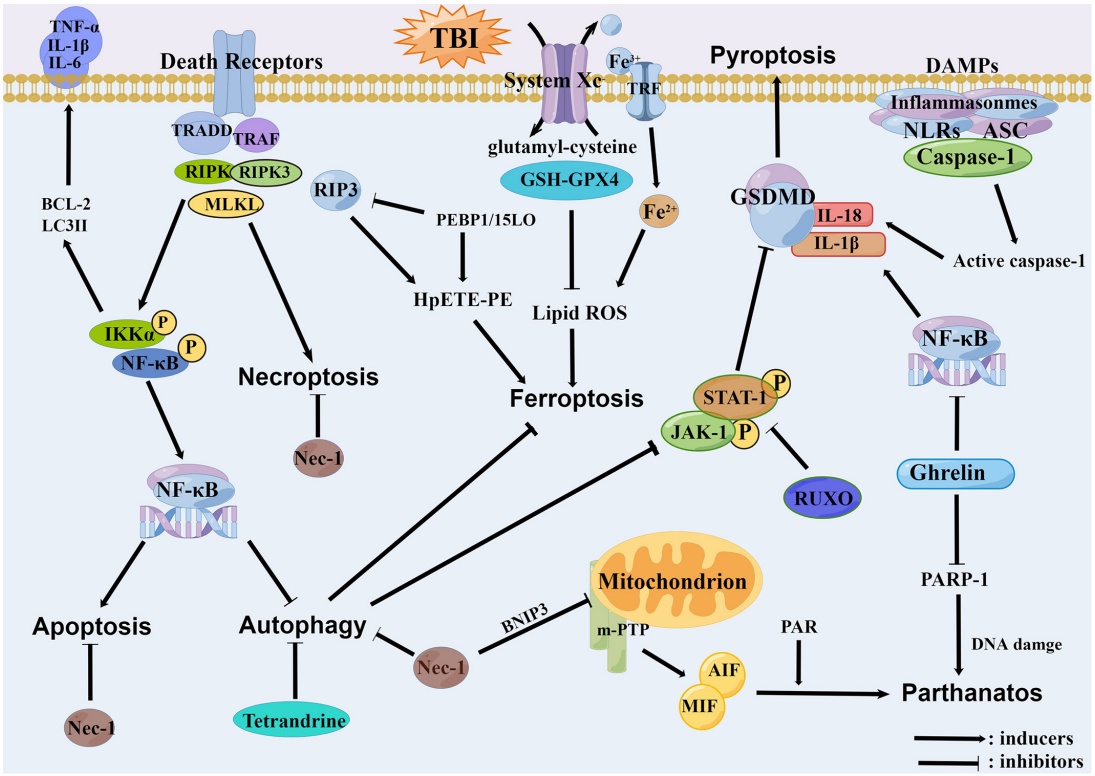

FIGURE 4
The relationships among all the regulatory necrosis involved in traumatic brain injury (TBI). The necroptosis can promote the apoptosis and inhibit the autophagy through the NF-κB pathway. The PEBP1 can interact with RIP3 or 15LOX to initiate the necroptosis and the ferroptosis. The Tetrandrine can inhibit the ferroptosis through the inhibition of autophagy. Meanwhile, the autophagy can inhibit the pyroptosis through the JAK1/STAT1 pathway. As an inhibitor of the necroptosis, the Nec-1 can concurrently inhibit the BNIP3 and decrease the open efficiency of mPTP, thereby reducing the parthanatos. The Ghrelin also has anti-inflammatory properties, which can alleviate the pyroptosis, and furthermore alleviate the parthanatos by reducing the PARP-1.

in TBI and ischemic stroke. The knockout of BNIP3 in mice can inhibit mitosis through the interaction of BNIP3 and LC3, with the manifestations of increased autophagy, decreased apoptosis and reduced cerebral infarction, indicating that the silencing of BNIP3 may be conducive to the neuroprotection after stroke (Shi et al., 2014). Meanwhile, Nec-1 can also inhibit the activation of necrotizing apoptosis as well as cell apoptosis and autophagy, while reducing the tissue damage and functional defects caused by TBI (Wang et al., 2012). (4) Autophagy activation can inhibit cell death in a mouse model of moderate traumatic brain injury through IL-13 and JAK1/STAT1 pathways (Gao et al., 2020). Inactivation of RIPK3 K51A kinase can enhance ferroptosis, causing worse outcomes after TBI. As a regulator of cell death, PEBP1 can inhibit the activity of pro-metabolic RIP3, and activate 15LOX to trigger pro-ferroptotic HpETE-PE signaling (Lamade et al., 2022). All these kinds of regulatory necrosis may occur simultaneously.

Interestingly, there are interactions between different types of cell death. Some reports showed that some inhibitors or hormones could be sensitive to another by blocking any way of cell death. For example, tetrahydropyrrole can improve TBI by regulating autophagy and reducing ferroptosis (Liu et al., 2022). It has been shown that treatment with 2-BFI could reduce both necroptosis and pyroptosis, thus exerting a role of neurofunctional protection (Ni et al., 2019). In some hormone treatments, ghrelin can reduce the level of cleaved PARP-1 in cortex, the PARP-1 dependent cell death and the mortality after TBI, while improving the sensorimotor and reflex functions. Its protective effect is related to its anti-inflammatory properties and pyroptosis (Shao et al., 2020). Upregulation of NIX reduces neuronal apoptosis and brain water content by increasing mitophagy in TBI rat model (Ma et al., 2019). Inhibition of autophagy and apoptosis and reduction of neuronal death using intranasal WNT3α therapy in TBI mice model can reduce the death of neurons (Zhang et al., 2018). In clinical stroke, Dl-3n-butylphthalide (Dl-NBP) has neuroprotective effects with anti-inflammatory, antioxidant, anti-apoptotic and mitochondrial protective functions. Dl-NBP treatment improves motor recovery after TBI by inhibiting the activation of autophagy and consequently blocking connexin loss and neuronal apoptosis (Wu et al., 2020). Therefore, regulatory necrosis may occur simultaneously with mutual transformation

and interaction to some extent. The relationships among all the regulatory necrosis involved in TBI are summarized in **Figure 4**.

Secondary injury following TBI is a critical factor which affects prognosis. The cell death is an important cause of secondary injury and there is increasing number of researchers who have found that various regulatory necrosis could contribute to the development of TBI, providing many new perspectives for us to understand and treat TBI. Therefore, the intervention of regulatory necrosis related pathway may be an effective strategy to reduce the secondary injury after TBI, and the relationships among different necrosis are worthy of further study.

Author contributions

ZN and BW: concept and design. ZN, LT, JN, and BW: writing, review, and revision of the manuscript. ZN: figures design. All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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