Do pyroptosis, apoptosis, and necroptosis (PANoptosis) exist in cerebral ischemia? Evidence from cell and rodent studies

https://doi.org/10.4103/1673-5374.331539

Date of submission: August 3, 2021

Date of decision: September 15, 2021

Date of acceptance: November 1, 2021

Date of web publication: January 7, 2022

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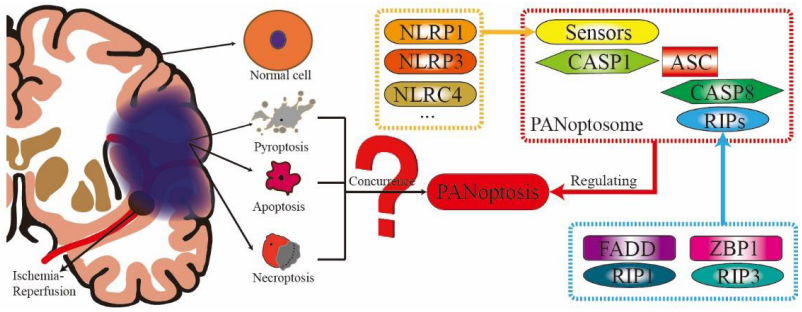
Graphical Abstract *PANoptosis in ischemic injury of the central nervous system*



Abstract

Some scholars have recently developed the concept of PANoptosis in the study of infectious diseases where pyroptosis, apoptosis and necroptosis act in consort in a multimeric protein complex, PANoptosome. This allows all the components of PANoptosis to be regulated simultaneously. PANoptosis provides a new way to study the regulation of cell death, in that different types of cell death may be regulated at the same time. To test whether PANoptosis exists in diseases other than infectious diseases, we chose cerebral ischemia/reperfusion injury as the research model, collected articles researching cerebral ischemia/reperfusion from three major databases, obtained the original research data from these articles by bibliometrics, data mining and other methods, then integrated and analyzed these data. We selected papers that investigated at least two of the components of PANoptosis to check its occurrence in ischemia/reperfusion. In the cell model simulating ischemic brain injury, pyroptosis, apoptosis and necroptosis occur together and this phenomenon exists widely in different passage cell lines or primary neurons. Pyroptosis, apoptosis and necroptosis also occurred in rat and mouse models of ischemia/reperfusion injury. This confirms that PANoptosis is observed in ischemic brain injury and indicates that PANoptosis can be a target in the regulation of various central nervous system diseases.

Key Words: apoptosis; brain; central nervous system; ischemia/reperfusion; middle cerebral artery occlusion; necroptosis; oxygen and glucose deprivation; PANoptosis; pyroptosis; regulated cell death

Introduction

Researchers studying forms of cell death found that the main processes of regulated cell death (RCD) included pyroptosis, apoptosis and regulated necrosis (including necroptosis) (Chen et al., 2021; Hu et al., 2021; Yan et al., 2021). The majority of the research topics on RCD focused on one of these three forms of cell death alone, but a few focused on the simultaneous interaction of these three forms of cell death. Some previous reports into cancer or bacterial/viral infection found that the key regulatory proteins of pyroptosis, apoptosis and necroptosis interacted with each other (Malireddi et al., 2010; Gurung et al., 2014, 2016; Malireddi et al., 2018, 2020b; Jiang et al., 2021; Meng et al., 2021). However, it was not clear how the regulatory mechanisms of pyroptosis, apoptosis and necroptosis intersected. The later research indicated that an innate immune response can simultaneously regulate pyroptosis, apoptosis and necroptosis after the transforming growth factor beta-activated kinase 1 (TAK1) was suppressed or knocked out (Malireddi et al., 2019, 2020b). This view was confirmed in research on coronavirus disease 2019 (COVID-19) (Karki et al., 2021). This suggests that, in the pathophysiological process of some diseases, pyroptosis, apoptosis and necroptosis can occur and be regulated at the same time. In a study by the team of Professor Kanneganti

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Funding: *The study was supported by the National Natural Science Foundation of China, Nos. 81772134 (to KX), 81971891 (to KX), 82172196 (to KX), 81571939 (to KX); the Fundamental Research Funds for the Central Universities of Central South University of China, No. 2020zzts218, (to WTY); Hunan Provincial Innovation Foundation For Postgraduate of China, Nos. CX20200116 (to WTY), CX20190139 (to LSL).*

How to cite this article: *Yan WT, Yang YD, Hu XM, Ning WY, Liao LS, Lu S, Zhao WJ, Zhang Q, Xiong K (2022) Do pyroptosis, apoptosis, and necroptosis (PANoptosis) exist in cerebral ischemia? Evidence from cell and rodent studies. Neural Regen Res 17(8):1761-1768.*

(Malireddi et al., 2019), this phenomenon when pyroptosis (P), apoptosis (A) and necroptosis (N) are regulated at the same time was named PANoptosis, and they showed that there is a multimeric protein complex, named a PANoptosome (Christgen et al., 2020; Samir et al., 2020), that can regulate the occurrence of PANoptosis.

A series of studies on PANoptosis reported by the Kanneganti team (Karki et al., 2020b, 2021; Kesavardhana et al., 2020; Malireddi et al., 2020a; Zheng et al., 2020; Briard et al., 2021) suggest that, in diseases caused by bacterial, fungal or viral infection, pathogens induce the autoimmune response and produce various inflammatory cytokines. These inflammatory cytokines activate the promoter proteins of pyroptosis, apoptosis and necroptosis through specific pathways, and drive them to assemble inflammasomes that are specific to different RCD forms (Cain et al., 2000; Chu et al., 2001; Acehan et al., 2002; Martinon et al., 2002; Agostini et al., 2004; Ogura et al., 2006; Kanneganti et al., 2007; Wallach et al., 2011; Lu et al., 2019b), and further assemble a protein complex, PANoptosome (Samir et al., 2020), that can simultaneously drive pyroptosis, apoptosis and necroptosis to aggravate cell death caused by the pathogens. Apart from diseases caused by pathogens, most other diseases or pathological conditions are more or less related to an immune response, which suggests that PANoptosis associated with an immune response is highly probable. For example, one study found that interferon regulatory factor 1, as the upstream regulator of PANoptosis, can induce cell death in the process of tumorigenesis in colorectal cancer (Karki et al., 2020a). In addition, in the exploration of the treatment of melanoma, a compound of metformin and doxorubicin initiated pyroptosis, apoptosis and necroptosis (PANoptosis) of melanoma cells, reducing the development of the melanoma (Song et al., 2021).

Published studies related to PANoptosis mainly focus on diseases induced by bacterial or viral infections plus a few types of tumors (Karki et al., 2020a, b; Malireddi et al., 2020b; Song et al., 2021). It is unknown whether PANoptosis and PANoptosomes exist in other types of diseases but it is worth further investigation. Many central nervous system (CNS) diseases involve the death of nerve cells, including PANoptosis (Yuan and Yankner, 2000; McKenzie et al., 2020; Yan et al., 2021). All these diseases or pathological conditions are generally associated with inflammatory reactions (Pender and Rist, 2001; Hoffmann et al., 2009; Degterev et al., 2019; Voet et al., 2019; Yuan et al., 2019; Lünemann et al., 2021). The expression of cell death and the pathophysiological mechanism related to inflammation in these CNS diseases are similar to the phenotype and mechanism in the existing studies of PANoptosis, which provides basic evidence for the possible existence of PANoptosis and PANoptosomes in CNS diseases.

In the Web of Science database, we investigated the experimental research articles about pyroptosis, apoptosis and necroptosis in the field of the nervous system and sorted the related articles according to the citation frequency, from high to low. Selecting the top 2% articles (referring to and expanding Essential Science Indicators standards) for keyword extraction and analysis, it was found that ischemia accounted for the highest proportion among the three death forms of PANoptosis in nervous system. Stroke is the second major cause of disability and death in adults, with ischemic stroke accounting for the majority of all stroke cases (Virani et al., 2020), and the main injury of ischemic stroke is caused by ischemia/reperfusion (I/R) (Meschia and Brott, 2018; Campbell et al., 2019; Yan et al., 2020a). The pathophysiological state of I/R can cause serious brain damage, and the pathophysiological process frequently involves an inflammatory reaction and immune system activation (Chamorro et al., 2016; Lambertsen et al., 2019; Shi et al., 2019; Yan et al., 2020b). Following the above argument we chose ischemia injury of the CNS as the analysis object.

We use bibliometrics, knowledge discovery and data-mining methods to capture evidence and analyze bibliometrics on the research of RCD related to ischemic injury of the CNS (Yan et al., 2020b) to assess the experimental research evidence on the involvement of PANoptosis in nervous system diseases. The demonstration of PANoptosis in ischemic injury of the CNS broadens the scope of PANoptosis research. This study takes a new approach to RCD research by exploring multiple RCD synchronously, pluralistically and comprehensively in ischemic injury of the CNS, and explores new ways to improve the intervention efficiency of RCD in nervous system diseases.

Materials and Methods

Data source

We chose PubMed, Scopus and Web of Science as the target databases. The key words were divided into three groups: (1) RCD, including pyroptosis, apoptosis and necroptosis; (2) CNS and their MeSH appositive words, hyponyms or hypernyms; and (3) ischemia. The refining function of the database limited the retrieval field to neuroscience or neurosurgery or neurology. The article type was limited to research articles. The retrieval of literature was completed on June 20, 2021. The end time of the publishing time range of the literature collections retrieved, with three cell death forms as the core theme, was June 20, 2021 but their start times differed as follows: (1) PubMed database: pyroptosis was on November 1, 2018; apoptosis was on May 1, 1995; necroptosis was on January 12, 2007. (2) Scopus database: The starting time of pyroptosis was on July 1, 2008; apoptosis on December 24, 1993. necroptosis started on July 1, 2005. (3) Web of Science database: The starting time of pyroptosis was on April 1, 2014; apoptosis on December 24, 1993; necroptosis on July 1, 2005. The retrieval strategy of each database was customized according to the usage standard of the database and the scale of the retrieved documents. Articles retrieved from each database were merged according to the three forms of cell death, and duplicate documents were screened and removed according to the inclusion criteria. The process of literature screening was shown in **Figure 1**.

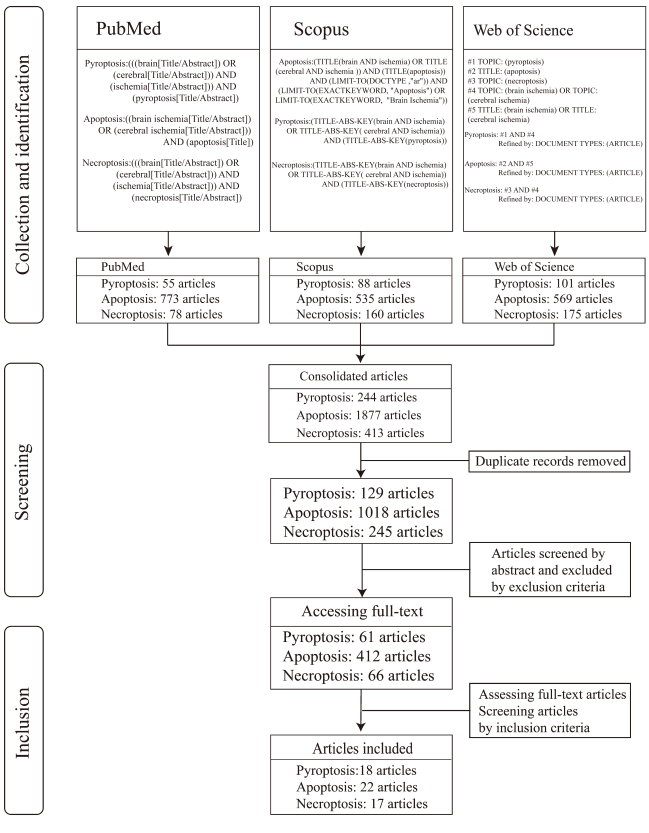

Figure 1 | **Flow chart of literature screening.**

Inclusion/exclusion criteria

Studies were potentially included if they met the following criteria: (1) The core content of the paper was to study ischemia or I/R injury or animal or cell models that can represent ischemia or I/R; (2) Rodents or primary cells or subculture cell lines were used as the experimental materials; (3) The target organ damaged in the experiment was either the brain or primary cells and subculture cells that can represent neurons; (4) The experimental results included two or more corresponding detection results that proved the existence of the three kinds of cell death: pyroptosis, apoptosis and necroptosis, one of which must be the key protein detection results of these three kinds of cell death forms; and (5) Damage treatment group and blank control group were included in the experimental design.

Studies were excluded if they met any of the criteria: (1) Drug-induced animal model or cell model; (2) The target cells of the experimental study were non-neuronal cells (glial cells, endothelial cells, etc.); (3) The process and standard description of establishing the model were not given; and (4) The experimental evidence to prove the existence of any of the three cell death forms was insufficient.

Data mining and sorting analysis

Data such as cell types, animal species, modeling methods, evaluation of cell death and detection results of representative molecules of different cell death types were extracted from the included literature. The literature items exported from the database were imported into the literature management software, and two researchers with medical and biological knowledge independently read the literature one by one, conducted article selection and data mining, and obtained relevant data from the literature. The data obtained by the two researchers were compared, and the consistent results were summarized in a table. When any inconsistent results occurred, the discussion and decision for inclusion involved the participation of the third researcher. The cluster analysis of *in vitro* experiments was based on the cell type and had to be that used in the study of pyroptosis, apoptosis and necroptosis. Cluster analysis of *in vivo* experiments of animals was carried out according to the classification of common rodents, ensuring that the I/R operations performed on animals were of the same class. To summarize, the acquired core data was collated and analyzed using EndNote software (version X7.8, Clarivate Analytics, Boston, MA, USA) and Microsoft Excel software (version 2016, Microsoft Corporation, Redmond, WA, USA).

Results

A total of 57 articles were included in this study (18 articles in pyroptosis, 22 articles in apoptosis, and 17 articles in necroptosis; **Figure 1**), of which 22 were conducted on rodents only (including rats and mice) and 31 were conducted on primary cultured cells or cell lines only and 4 studies included both *in vitro* cell and *in vivo* rodent experiments. One of the 31 articles that had experimented on two types of cell. From the included literature, we extracted 62 experiments that assessed pyroptosis or apoptosis or necroptosis. Of these studies, it was necessary to satisfy two conditions that would determine whether I/R injury in the experiment induced the occurrence of pyroptosis or apoptosis or necroptosis. One condition was that commonly used or academically recognized detection methods were used in the experiment, such as propidium iodide staining, terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick-end labeling (TUNEL) assay, flow cytometry, cell counting kit-8 assay or lactate dehydrogenase assay to evaluate the degree of cell death induced by I/R injury. The other condition was that the key proteins of pyroptosis or apoptosis or necroptosis were detected (**Table 1**) (Fink and Cookson, 2005; Bergsbaken et al., 2009; Kaczmarek et al., 2013; Nikoletopoulou et al., 2013; Czabotar et al., 2014; Kovacs and Miao, 2017; Hu et al., 2021) and that they should contain at least two or more key proteins. Both the conditions mentioned above had to give results that were statistically significant compared to the control group and be clearly stated in the paper.

Table 1 | **The key proteins of three forms of cell death in PANoptosis**

Cell death type	Key proteins
Pyroptosis	NLRP1, NLRP3, ASC, CASP-1, 4, 5, 11, C-CASP-1, GSDMD, IL-1β, IL-18
Apoptosis	CASP-3, 7, 8, 9, C-CASP-3, Bcl-2, Bax
Necroptosis	RIP1, p-RIP1, RIP3, p-RIP3, MLKL, p-MLKL

ASC: Apoptosis-associated speck-like protein containing a caspase recruit domain; Bax: B-cell lymphoma 2-associated X; Bcl-2: B-cell lymphoma 2; CASP: cysteinyl aspartate-specific protease; C-CASP: cleaved CASP; GSDMD: gasdermin D; IL: interleukin; MLKL: mixed lineage kinase domain-like pseudokinase; NLRP: nucleotide-binding domain and leucine-rich repeat pyrin-domain containing protein; p-MLKL: phosphorylation of MLKL; p-RIP: phosphorylation of RIP; RIP: receptor-interacting protein kinase.

In the 36 cell-model-based experiments, oxygen and glucose deprivation (OGD) or OGD/recovery was used in most cell experiments to simulate ischemia or I/R injury. The researchers used primary hippocampal cells, primary cortical cells, PC12 cells (rat adrenal pheochromocytoma cells) and SH-SY5Y (human neuroblastoma cells) cells for the experiments. We show the results according to the cell types used in the experiments (**Tables 2–5**). In the included studies, most were based on rodent models, middle cerebral artery occlusion (MCAO) or modified MCAO to simulate ischemia or I/R injury but some used the method of electric shock cardiac arrest and resuscitation. These modeling methods simulate cerebral I/R injury in experimental animals and are recognized in the research field. The studies used Sprague-Dawley rats or C57 mice, and we tabulated the results according to animal type and modeling method used in the experiment (**Tables 6** and **7**). In the process of data mining, we found that experimental models, apart from MCAO and OGD models, did not meet the condition that pyroptosis, apoptosis and necroptosis were studied simultaneously. We extracted 62 experiments from the 57 included papers. According to the experimental results included in our analysis it appears that in the same cell model or animal disease model three kinds of RCD, i.e., pyroptosis, apoptosis, necroptosis, were likely to occur simultaneously, which would mean that PANoptosis occurs in these experiments.

Discussion

In this study we selected MCAO and OGD as *in vivo* and *in vitro* experimental models, respectively, that can simulate I/R injury and its pathophysiology in the CNS. These two methods are the most widely used and generally recognized by researchers (Ryou and Mallet, 2018; Salvador et al., 2018). Many have studied RCD induced by I/R injury of CNS using MCAO and OGD (Yanamoto et al., 2003; Tuttolomondo et al., 2009; McBride and Zhang, 2017; Ryou and Mallet, 2018; Wang et al., 2018; Li et al., 2019; Zhang et al., 2019a), and these two methods have often been used to study the inflammatory reaction related to this kind of injury (Tuttolomondo et al., 2009; Rizzo and Leaver, 2010; Mo et al., 2020a; Stanzione et al., 2020; Huang et al., 2021). Therefore, it is pertinent to discuss PANoptosis in MCAO and OGD models.

Kanneganti's proposal is that PANoptosis is a newly defined form of cell death in diseases related to the immune response and can be regulated by a multimeric protein complex, named PANoptosome (Malireddi et al., 2019). This new form of cell death includes pyroptosis, apoptosis and necroptosis. He proposes that a PANoptosome can interfere with pyroptosis, apoptosis and necroptosis, each of which have been studied independently by other investigators. The existing research on PANoptosis suggests cysteinyl aspartate-specific protease (CASP) 1 and CASP-11 that drive pyroptosis, CASP-8 that drives apoptosis and RIP3 that drives necroptosis can all be assembled into a PANoptosome, together with other components. The process of PANoptosis can be regulated by Z-DNA-binding protein 1 and TAK1 (Christgen et al., 2020; Samir et al., 2020). To support the theory that PANoptosis is a major factor in the I/R injury of the CNS first it is necessary to confirm that pyroptosis, apoptosis and necroptosis have been shown to occur simultaneously from reports in existing literature on I/R injury. Second, a PANoptosome has to have been identified in I/R injury, and have been confirmed that it can simultaneously initiate the three kinds of RCD. Third, there must be a regulatory system that controls PANoptosome activity.

The data we mined from the literature showed that in the study of cerebral I/R, under the same model condition, the three forms of cell death could occur simultaneously. According to our integrated data, after MCAO induced I/R injury in rat or mouse brain tissue and OGD induced ischemia-hypoxia injury in neurons or cell lines derived from nerve cells, pyroptosis, apoptosis and necroptosis coexisted. This phenomenon accords with the first condition of the PANoptosis definition, and suggests that it is very possible that PANoptosis exists in nervous system diseases from the phenomenon level or the phenotype level of cerebral ischemia injury. We can see from the related studies of the three kinds of RCD—pyroptosis, apoptosis and necroptosis—that the molecular mechanisms of these three kinds of cell death all have inflammation-related parts (Linkermann et al., 2013; Lu et al., 2019a; Guo et al., 2020; Wang et al., 2020c, 2021b; Chen et al., 2021; Liu et al., 2021c). There are also reports that glial cells can interfere with these three forms of cell death after being stimulated by injury (Zhao et al., 2017; Xu et al., 2019; Naito et al., 2020; Wang et al., 2020a; Li et al., 2021a; Liu et al., 2021b; Lu et al., 2021) and these overlap with the inflammation-related and immune-related reports of existing studies of PANoptosis. This suggests the possibility of PANoptosis in CNS diseases at the pathological mechanism level.

Table 2 | **Oxygen-glucose deprivation/reperfusion (OGD/R) induces death of primary hippocampal cells**

Sources	Treatments	Injure duration	Reperfusion duration	Death type	Assessment	Critical protein	Reference
SD rats	OGD/R	1.5 h	20 h	Pyroptosis	Hoechst 33342	NLRP3, ASC, CASP-1, IL-1β, IL-18	Zhang et al., 2021
SD rats	H/R	12 h	24 h	Pyroptosis	CCK-8	NLRP3, ASC, CASP-1, C-CASP-1, CASP-11, C-CASP-11, GSDMDp30, IL-1β, IL-18	Diao et al., 2020
Mongolian gerbils	H/R	4 h	24 h	Pyroptosis	Hoechst 33342, MTT	NLRP1, NLRP3, pro-CASP-1, CASP-1, GSDMD, IL-1β, IL-18	Zhu et al., 2019
C57BL/6 mice	OGD/R	3 h	24 h	Apoptosis	TUNEL, LDH	CASP-3, C-CASP-3, Bcl-2, Bax	Yu et al., 2018
C57BL/6 mice	OGD/R	2 h	48 h	Necroptosis	PI, LDH	RIPK1, MLKL, p-MLKL	Yang et al., 2017
SD rats	OGD/R	2 h	24 h	Necroptosis	PI (Nec-1), LDH	RIP1, RIP3, CASP-8	Vieira et al., 2014

ASC: Apoptosis-associated speck-like protein containing a caspase recruit domain; Bax: B-cell lymphoma 2-associated X; Bcl-2: B-cell lymphoma 2; CASP: cysteinyl aspartate-specific protease; C-CASP: cleaved CASP; CCK-8: cell counting kit-8; GSDMD: gasdermin D; H/R: hypoxia/reoxygenation; IL: interleukin; LDH: lactate dehydrogenase; MLKL: mixed lineage kinase domain-like pseudokinase; MTT: methylthiazolyldiphenyl-tetrazolium bromide; Nec-1: necrostatin-1; NLRP: nucleotide-binding domain and leucine-rich repeat pyrin-domain containing protein; OGD/R: oxygen and glucose deprivation/recovery; PI: propidium iodide staining; PI (Nec-1): Nec-1 inhibited necroptosis, and after the addition of Nec-1, PI staining was performed to verify the occurrence of necroptosis by comparing with the control group; p-MLKL: phosphorylation of MLKL; RIP: receptor-interacting protein kinase; SD rats: Sprague-Dawley rats; TUNEL: TdT-mediated dUTP nick-end labeling.

Table 3 | **Oxygen-glucose deprivation/reperfusion (OGD/R) induces death of primary cortical cells**

Sources	Treatments	Injury duration	Reperfusion duration	Death type	Assessment	Critical protein	Reference
C57BL/6 mice	OGD/R	2 h	24 h	Pyroptosis	Hoechst 33342, PI, CCK-8	NLRP3, ASC, CASP-1, C-CASP-1, GSDMD-N, IL-1β,IL-18	Sun et al., 2020
C57BL/6 mice	H/R	1.5 h	4 h	Pyroptosis	PI, Flow cytometry	CASP-1, GSDMD, C-GSDMD, IL-1β, IL-18	Tang et al., 2018
Wistar Rats	OGD/R	4 h	24 h	Apoptosis	CCK-8, LDH, TUNEL	C-CASP-3	Wu et al., 2020a
SD Rats	OGD/R	2 h	24 h	Apoptosis	CCK-8, TUNEL	C-CASP-3, IL-1β	Mo et al., 2020b
SD Rats	OGD/R	2 h	48 h	Apoptosis	TUNEL, MTT, Flow cytometry	Bcl-2, Bax	Zhou et al., 2019
SD Rats	OGD/R	3 h	24 h	Apoptosis	TUNEL	C-CASP-3, Bcl-2, Bax	He et al., 2019
SD Rats	OGD/R	3 h	6, 24, 48, 72 h	Apoptosis	LDH, TUNEL	C-CASP-3, Bcl-2, Bax	He et al., 2016
Balb/C mice	OGD/R	3 h	21 h	Apoptosis	Flow cytometry	C-CASP-3, Bcl-2, Bax	Huang et al., 2014
C57BL/6J mice	OGD/R	1 h	24 h	Necroptosis	PI	RIP1, RIP3, MLKL	Yuan et al., 2020
C57BL/6J mice	OGD/R	1 h	24 h	Necroptosis	PI (Nec-1)	RIP1, RIP3, MLKL	Li et al., 2019
SD Rats	OGD	2 h	0	Necroptosis	PI (Nec-1)	RIP1, RIP3, p-RIP3, MLKL, p-MLKL	Wang et al., 2018
SD Rats	OGD	6 h	0	Necroptosis	LDH	RIP1, RIP3	Ni et al., 2018
SD Rats	OGD	6 h	24 h	Necroptosis	PI	RIP1, RIP3	Li et al., 2018
SD Rats	OGD/R	2 h	48 h	Necroptosis	PI (Nec-1)	RIP1, RIP3	Kong et al., 2017

ASC: Apoptosis-associated speck-like protein containing a caspase recruit domain; Bax: B-cell lymphoma 2-associated X; Bcl-2: B-cell lymphoma 2; CASP: cysteinyl aspartate-specific protease; C-CASP: cleaved CASP; CCK-8: cell counting kit-8; C-GSDMD: cleaved GSDMD; GSDMD: gasdermin D; GSDMD-N: N-terminal domain of gasdermin D; H/R: hypoxia/reoxygenation; IL: interleukin; LDH: lactate dehydrogenase; MLKL: mixed lineage kinase domain-like pseudokinase; MTT: methylthiazolyldiphenyl-tetrazolium bromide; Nec-1: Necrostatin-1; NLRP: nucleotide-binding domain and leucine-rich repeat pyrin-domain containing protein; OGD: oxygen and glucose deprivation; OGD/R: OGD/recovery; PI: propidium iodide staining; PI (Nec-1): Nec-1 inhibited necroptosis, and after the addition of Nec-1, PI staining was performed to verify the occurrence of necroptosis by comparing with the control group; p-MLKL: phosphorylation of MLKL; p-RIP: phosphorylation of RIP; RIP: receptor-interacting protein kinase; SD rats: Sprague-Dawley rats; TUNEL: TdT-mediated dUTP nick-end labeling.

Table 4 | **Oxygen-glucose deprivation/reperfusion (OGD/R) induces death of PC12 cells**

Treatments	Injury duration	Reperfusion duration	Death type	Assessment	Critical protein	Reference
OGD/R	12 h	1 h	Pyroptosis	Hoechst 33342, PI, CCK-8	NLRP3, C-CASP-1, GSDMD-N	Zeng et al., 2020
OGD/R	2 h	2 h	Pyroptosis	MTT, LDH, TUNEL	CASP-1, CASP-1p20, GSDMD, GSDMD-N	Li et al., 2021b
OGD/R	12 h	4 h	Pyroptosis	MTT, TEM	NLRP3, ASC, C-CASP-1, GSDMD, GSDMD-N	Liu et al., 2021a
OGD	2, 4, 8, 12, 24 h	0	Apoptosis	MTT	C-CASP-3, Bcl-2, Bax	Lin et al., 2015
OGD	12 h	0	Apoptosis	Hoechst 33342, MTT, Flow cytometry	C-CASP-3, CASP-12, Bcl-2	Cao et al., 2016
OGD/R	0, 2, 4 h	24 h	Apoptosis	TUNEL, CCK-8	Bcl-2, Bax	Ren et al., 2019
OGD	8 h	0	Necroptosis	PI (Nec-1)	RIP1, RIP3, MLKL	Wang et al., 2018
H/R	8 h	24 h	Necroptosis	LDH, Flow cytometry	RIP1, RIP3, MLKL/p-MLKL	Zhang et al., 2019b

ASC: Apoptosis-associated speck-like protein containing a caspase recruit domain; Bax: B-cell lymphoma 2-associated X; Bcl-2: B-cell lymphoma 2; CASP: cysteinyl aspartate-specific protease; C-CASP: cleaved CASP; CCK-8: cell counting kit-8; C-GSDMD: cleaved GSDMD; GSDMD: gasdermin D; GSDMD-N: N-terminal domain of gasdermin D; H/R: Hypoxia/reoxygenation; IL: interleukin; LDH: lactate dehydrogenase; MLKL: mixed lineage kinase domain-like pseudokinase; MTT: methylthiazolyldiphenyl-tetrazolium bromide; Nec-1: Necrostatin-1; NLRP: nucleotide-binding domain and leucine-rich repeat pyrin-domain containing protein; OGD: oxygen and glucose deprivation; OGD/R: OGD/recovery; PI: propidium iodide staining; PI (Nec-1): Nec-1 inhibited necroptosis, and after the addition of Nec-1, PI staining was performed to verify the occurrence of necroptosis by comparing with the control group; p-MLKL: phosphorylation of MLKL; RIP: receptor-interacting protein kinase; SD rats: Sprague-Dawley rats; TEM: transmission electron microscope; TUNEL: TdT-mediated dUTP nick-end labeling.

Table 5 | **Oxygen-glucose deprivation/reperfusion (OGD/R) induces death of SH-SY5Y cells**

Treatment	Injury duration	Reperfusion duration	Death type	Assessment	Critical protein	Reference
OGD/R	2, 4, 8, 12 h	24 h	Pyroptosis	MTT	C-CASP-1, ASC, GSDMD-N, IL-1β, IL-18	Liang et al., 2020a
OGD/R	6 h	24 h	Pyroptosis	LDH, Flow cytometry	NLRP3, CASP-1, ASC, GSDMD-N	Wang et al., 2020d
OGD	6 h	2 h	Apoptosis	Hoechst 33342	CASP-3, Bcl-2, Bax	Wang et al., 2013
OGD/R	4 h	48 h	Apoptosis	MTT	CASP-3, Bcl-2, Bax	Zhang et al., 2016
OGD	4 h	0	Apoptosis	MTT	Act-CASP-3, Bcl-2	Chang et al., 2017
OGD/R	8 h	24 h	Apoptosis	MTT, LDH, Flow cytometry	C-CASP-3, CASP-9, PARP, Bcl-2, Bax	Cai et al., 2020
OGD/R	4 h	24 h	Apoptosis	MTT, LDH, Hoechst 33342, TEM	C-CASP-3, Bcl-2, Bax	Yang et al., 2021
OGD/R	6 h	2 h	Necroptosis	CCK-8, LDH, Hoechst 33342	RIP3, MLKL, p-MLKL, CaMKII, p-CaMKII	Li et al., 2021c

ASC: Apoptosis-associated speck-like protein containing a caspase recruit domain; Bax: B-cell lymphoma 2-associated X; Bcl-2: B cell lymphoma 2; CaMKII: Calcium/calmodulin-dependent kinase II; CASP: cysteinyl aspartate-specific protease; C-CASP: cleaved CASP; CCK-8: cell counting kit-8; C-GSDMD: cleaved GSDMD; GSDMD: gasdermin D; GSDMD-N: N-terminal domain of gasdermin D; IL: interleukin; LDH: Lactate dehydrogenase; MLKL: mixed lineage kinase domain-like pseudokinase; MTT: Methylthiazolyldiphenyl-tetrazolium bromide; Nec-1: Necrostatin-1; NLRP: nucleotide-binding domain and leucine-rich repeat pyrin-domain containing protein; OGD: oxygen and glucose deprivation; OGD/R: OGD/recovery; PARP: poly ADP-ribose polymerase; p-CaMKII: phosphorylation of CaMKII; PI: propidium iodide staining; PI (Nec-1): Nec-1 inhibited necroptosis, and after the addition of Nec-1, PI staining was performed to verify the occurrence of necroptosis by comparing with the control group; p-MLKL: phosphorylation of MLKL; RIP: receptor-interacting protein kinase; SD rats: Sprague-Dawley rats; TEM: transmission electron microscope; TUNEL: TdT-mediated dUTP nick-end labeling.

Table 6 | **Brain injury induced by ischemia/reperfusion (I/R) injury in rats**

Treatment	Injury duration	Reperfusion duration	Death type	Assessment	Critical protein	Reference
MCAO	2 h	0	Pyroptosis	Nissl, TUNEL	NLRP3, ASC, C-CASP-1	An et al., 2019
MCAO	1.5 h	0	Pyroptosis	Nissl, TUNEL	NLRP3, ASC, pro-CASP-1, CASP-1, IL-1β	She et al., 2019
MCAO/R	2 h	1, 3, 6, 24 h	Pyroptosis	TUNEL, Flow cytometry	NLRP3, total-CASP-1, IL-1β, IL-18	Jiang et al., 2020b
MCAO/R	2 h	24 h	Pyroptosis	HE, TUNEL	ASC, C-CASP-1, GSDMD-N, IL-1β, IL-18	Liang et al., 2020a
MCAO	6, 12 h, 1, 2, 3 d	0	Pyroptosis	IF, TEM	NLRP3, ASC, CASP-1, C-CASP-1, GSDMD, C- GSDMD	Liang et al., 2020b
CA/CPR	7 min	24 h	Pyroptosis	HE, IHC, TEM	NLRP3, GSDMD, GSDMDp30, IL-1β	Zou et al., 2020
MCAO/R	2 h	24 h	Pyroptosis	HE, TUNEL	pro-CASP-1, CASP-1p20, GSDMD, GSDMD-N	Li et al., 2021b
CA/CPR	7 min	24 h	Pyroptosis	HE, IF	NLRP3, ASC, pro-CASP-1, CASP-1p20, IL-1β, GSDMD, GSDMD-N	Zou et al., 2021
MCAO/R	1 h	2, 12, 24 h	Apoptosis	TUNEL	CASP-3, C-CASP-3, IL-18	Yuan et al., 2013
MCAO/R	1 h	24 h	Apoptosis	TUNEL	CASP-3, C-CASP-3, Bcl-2	Zhang et al., 2013
MCAO/R	2 h	24 h	Apoptosis	TUNEL, Hoechst 33258, TEM	CASP-3, CASP-9, Bcl-2, Bax	Gao et al., 2016
MCAO/R	2 h	14 d	Apoptosis	TUNEL, TEM	CASP-3, Cyt-c, Bcl-2, Bax	Chen et al., 2017
MCAO/R	-	24 h	Apoptosis	Nissl, TUNEL	C-CASP-3, Cyt-c, Bcl-2, Bax	Yang et al., 2021
4VO/R*	0.5 h	1, 3, 6, 12, 24, 48 h	Necroptosis	IF	RIP1, RIP3	Ryan et al., 2018
MCAO/R	0.5 h	12, 24, 72 h	Necroptosis	IHC	RIP1, p-RIP1, RIP3, MLKL, p-MLKL	Deng et al., 2019
4VO/R	20 min	5 d	Necroptosis	HE, IF	RIP3	Hu et al., 2020
CA/CPR	7 min	24 h	Necroptosis	HE, Nissl, TEM	RIP1, RIP3, MLKL, p-MLKL	Wang et al., 2021a

*Wistar rats were used in this study, and SD rats were used in all other experiments. 4VO/R: 4-Vessel occlusion and reperfusion; ASC: apoptosis-associated speck-like protein containing a caspase recruit domain; Bax: B-cell lymphoma 2-associated X; Bcl-2: B cell lymphoma 2; CA/CPR: cardiac arrest/cardiopulmonary resuscitation; CASP: cysteinyl aspartate-specific protease; C-CASP: cleaved CASP; C-GSDMD: cleaved GSDMD; Cyt-c: cytochrome C; GSDMD: gasdermin D; GSDMD-N: N-terminal domain of gasdermin D; HE: hematoxylin-eosin staining; IF: immunofluorescence; IHC: immunohistochemistry; IL: interleukin; LDH: lactate dehydrogenase; MCAO: middle cerebral artery occlusion; MCAO/R: MCAO/reperfusion; MLKL: mixed lineage kinase domain-like pseudokinase; MTT: methylthiazolyldiphenyl-tetrazolium bromide; Nec-1: Necrostatin-1; Nissl: Nissl staining; NLRP: nucleotide-binding domain and leucine-rich repeat pyrin-domain containing protein; p-MLKL: phosphorylation of MLKL; p-RIP: phosphorylation of RIP; RIP: receptor-interacting protein kinase; SD rats: Sprague-Dawley rats; TEM: transmission electron microscope; TUNEL: TdT-mediated dUTP nick-end labeling.

The latest research suggests that a PANoptosome includes three kinds of protein: (1) Z-DNA-binding protein 1, a nucleotide-binding domain and a leucine-rich repeat pyrin-domain containing protein 3 that play the role of sensor, (2) an apoptosis-associated speck-like protein, containing a caspase recruit domain, and a Fas-associated protein with death domain that are composite adapters and (3) a receptor-interacting protein kinase (RIP) 1, RIP3, CASP-1 and CASP-8 that have a catalytic effect (Christgen et al., 2020; Samir et al., 2020; Zheng and Kanneganti, 2020a, b). These studies on the PANoptosome are related to infectious diseases and cancer, but there has been no study on PANoptosomes in the study of I/R injury of CNS. It can be seen from the data mined by us that nucleotide-binding domain and leucine-rich repeat pyrin-domain containing protein 3, CASP-1 and apoptosis-associated speck-like protein containing a caspase recruit domain related to pyroptosis, CASP-8 and Fas-associated protein with death domain related to apoptosis, RIP1 and RIP3 related to necroptosis have all been detected as marker proteins in animal models of I/R and/or cell models of OGD/recovery (**Tables 2–7**). All these proteins are considered to be components of a PANoptosome in infectious diseases. Although there is no study on the assembly of components of a PANoptosome in I/R injury of CNS, the existing data of the "raw materials" that make up a PANoptosome are highly expressed, indicating that there is a molecular basis for finding PANoptosomes in ischemia-induced brain injury.

There are studies that showed there are some molecules that can interfere with two of the components of PANoptosis simultaneously under the condition of I/R injury. For example, nucleotide oligomerization domain-like receptors with caspase activation and recruitment domain 4 inflammasome complex can regulate apoptosis and pyroptosis (Poh et al., 2019). Also blocking thromboxane A synthase/thromboxane A2/thromboxane prostanoid signal can inhibit apoptosis and pyroptosis at the same time (Chueh et al., 2020). RIPK3, as the key molecule of necroptosis (Kikuchi et al., 2012; Sun et

Table 7 | **Brain injury induced by ischemia/reperfusion (I/R) injury in mice**

Species	Treatment	Injury duration	Reperfusion duration	Death type	Assessment	Critical protein	Reference
Mongolian gerbils	CAO/R	5 min	7 d	Pyroptosis	Nissl, TUNEL	NLRP1, NLRP3, GSDMD, CASP-1, C-CASP-1, IL-1β, IL-18	Zhu et al., 2019
C57BL/6 mice	PT	5 min	1, 3, 7 d	Pyroptosis	IF, TEM	NLRP1, NLRP3, ASC, GSDMD, CASP-1, C-CASP-1, IL-1β, IL-18	Li et al., 2020a
ICR mice	tMCAO	45 min	24 h	Pyroptosis	IF	NLRP3, ASC, C-CASP-1, IL-1β, GSDMD, GSDMD-N	Wang et al., 2021c
ICR mice	MCAO/R	2 h	24 h	Apoptosis	TUNEL	CASP-3, Bcl-2, Bax	Wu et al., 2015
C57BL/6 mice	MCAO/R	1 h	2, 6, 12, 24 h	Apoptosis	TUNEL	CASP-3, C-Casp-3	Ma et al., 2017
Swiss albino mice	MCAO/R	45 min	23 h	Apoptosis	TUNEL, PI	CASP-3, Bcl-2, Bax	Asadi et al., 2018
ICR mice	MCAO/R	1 h	24 h	Necroptosis	PI (Nec-1)	RIP1, RIP3, MLKL, p-MLKL	Chen et al., 2018
C57BL/6J mice	MCAO	1 h	12, 24, 72 h, 5, 7 d	Necroptosis	TUNEL	RIP1, p-RIP1, RIP3, p-RIP3, MLKL, p-MLKL	Li et al., 2020b
C57BL/6J mice	MCAO	1 h	24 h	Necroptosis	TUNEL	RIP1, RIP3, MLKL	Zhang et al., 2020

ASC: Apoptosis-associated speck-like protein containing a caspase recruit domain; Bax: B-cell lymphoma 2-associated X; Bcl-2: B cell lymphoma 2; CAO: carotid arteries occluded; CASP: cysteinyl aspartate-specific protease; C-CASP: cleaved CASP; C-GSDMD: cleaved GSDMD; Cyt-c: cytochrome C; GSDMD: gasdermin D; GSDMD-N: N-terminal domain of gasdermin D; IF: immunofluorescence; IL: interleukin; MCAO: middle cerebral artery occlusion; MLKL: mixed lineage kinase domain-like pseudokinase; Nec-1: Necrostatin-1; Nissl: Nissl staining; NLRP: nucleotide-binding domain and leucine-rich repeat pyrin-domain containing protein; PI: propidium iodide staining; PI (Nec-1): Nec-1 inhibited necroptosis, and after the addition of Nec-1, PI staining was performed to verify the occurrence of necroptosis by comparing with the control group; p-MLKL: phosphorylation of MLKL; p-RIP: phosphorylation of RIP; PT: photothrombotic model; RIP: receptor-interacting protein kinase; SD rats: Sprague-Dawley rats; TEM: transmission electron microscope; tMCAO; transient middle cerebral artery occlusion; TUNEL: TdT-mediated dUTP nick-end labeling.

al., 2012; Kim and Li, 2013; Thapa et al., 2013; Guo et al., 2020; Wang et al., 2020b; Liao et al., 2021), can interact with the Jun N-terminal kinase-mediated inflammatory signaling pathway (Hu et al., 2020) that is closely related to neuronal apoptosis induced by ischemia (Wang et al., 2011; Liu et al., 2016, 2018) and to cell pyroptosis (Chen et al., 2019; Jiang et al., 2020a). All this information suggests that pyroptosis, apoptosis and necroptosis (PANoptosis) induced by I/R injury could be subject to intervention and regulation simultaneously.

The existing studies on PANoptosis show that TAK1 and Z-DNA-binding protein 1 intervene in PANoptosome activity, and thus participate in the regulation of PANoptosis (Malireddi et al., 2019; Banoth et al., 2020; Kesavardhana et al., 2020; Samir et al., 2020; Zheng and Kanneganti, 2020b). We have not found any internal or external molecules that can interfere with all three of pyroptosis, apoptosis and necroptosis in cerebral ischemia injury, but some studies have shown that inhibiting TAK1 can reduce neuronal death induced by cerebral I/R (Neubert et al., 2011). This indicates that TAK1 can be used as an important target in RCD induced by hypoxia-reperfusion injury (Neubert et al., 2011; Ridder and Schwaninger, 2013; Wang et al., 2019; Wu et al., 2020b). TAK1 can affect the function of microglia and interact with inflammatory pathway, thus affecting neuronal apoptosis and pyroptosis (Gong et al., 2015; Zeyen et al., 2020). It also plays an important role in the interaction between programmed necrosis and apoptosis of neurons mediated by RIP3 during cerebral I/R injury (Naito et al., 2020). All these data suggest that there may be molecules, like TAK1, that can regulate PANoptosomes in a brain subject to I/R injury.

Limitations

Although this paper verifies the possibility of PANoptosis in cerebral ischemia reperfusion injury by collecting data from cell experiments and animal experiments, we admit that this paper has some limitations. First, the limits of paper length and research scale meant we could not conduct data mining for all CNS diseases, therefore we selected only cerebral I/R injury as the research object. This limited the outcome to only showing whether PANoptosis exists in cerebral I/R injury. Whether PANoptosis occurs in other CNS diseases remains to be studied. Second, the data we mined were mainly cell experiments and animal experiments, without clinical samples. Whether PANoptosis occurs in actual clinical stroke needs further verification. Third, the disease models we analyzed were only MCAO and OGD, therefore other ischemia/reperfusion models would need to be studied. Fourth, we only selected three databases for retrieval, whereas there are other databases. Fifth, our retrieval fields are mainly from title, abstract and keywords, so some relevant papers may have been missed. These limitations need to be addressed in future studies.

Summary and future directions

Analysis of existing research highlights how important PANoptosis is and shows how its interaction network of processes is associated with RCD in infectious diseases. The concept of PANoptosis improves our understanding of RCD, suggesting that we should treat and understand RCD systematically, plurally and as a network. Although the current research focuses mainly on infectious diseases, this review proposes expanding investigations of PANoptosis to other diseases. In the pathophysiological mechanism of CNS diseases the inflammatory response and immune response play important roles that are similar to their effects in infectious diseases. Moreover, there are interactions between regulatory proteins that regulate the disease response and immune response of CNS diseases. However, systematic and comprehensive research on these interactions still needs further study. In future, the research on PANoptosis in CNS diseases should examine the interaction network of key regulatory proteins, identify a PANoptosome linked to CNS diseases, find the target of PANoptosis that can intervene in neurons and find new treatment strategies for diseases related to RCD.

Author contributions: *All authors contributed equally to the manuscript, read and approved the final version of the paper for publication.*
Conflicts of interest: *The authors declare that there is no potential conflict of interest.*

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