Research Article

Research trends, hot spots and prospects for necroptosis in the field of neuroscience

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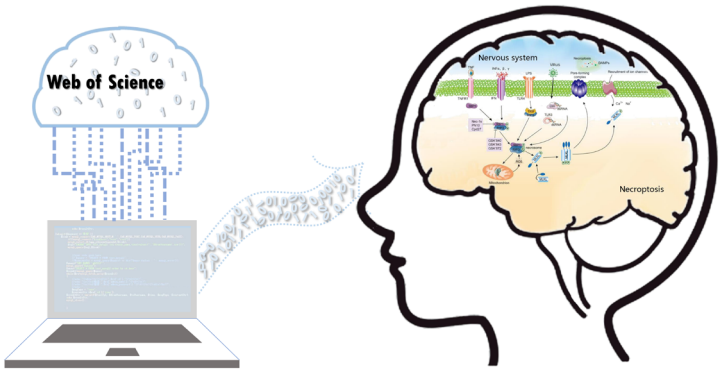
Graphical Abstract *The development trend of necroptosis in neuroscience*



Abstract

There are two types of cell death-apoptosis and necrosis. Apoptosis is cell death regulated by cell signaling pathways, while necrosis has until recently been considered a passive mechanism of cell death caused by environmental pressures. However, recent studies show that necrosis can also be regulated by specific cell signaling pathways. This mode of death, termed necroptosis, has been found to be related to the occurrence and development of many diseases. We used bibliometrics to analyze the global output of literature on necroptosis in the field of neuroscience published in the period 2007–2019 to identify research hotspots and prospects. We included 145 necroptosis-related publications and 2239 references published in the Web of Science during 2007–2019. Visualization analysis revealed that the number of publications related to necroptosis has increased year by year, reaching a peak in 2019. China is the country with the largest number of publications. Key word and literature analyses demonstrated that mitochondrial function change, stroke, ischemia/reperfusion and neuroinflammation are likely the research hotspots and future directions of necroptosis research in the nervous system. The relationship between immune response-related factors, damage-associated molecular patterns, pathogen-associated molecular patterns and necroptosis may become a potential research hotspot in the future. Taken together, our findings suggest that although the inherent limitations of bibliometrics may affect the accuracy of the literature-based prediction of research hotspots, the results obtained from the included publications can provide a reference for the study of necroptosis in the field of neuroscience.

Key Words: bibliometric analysis; citations; CiteSpace; h-index; necroptosis; network analysis; neuroscience; output; VOSviewer; Web of Science

Chinese Library Classification No. R459.9; R363; R364

Introduction

For many years, necrosis was considered accidental and unregulated, until Laster et al. (1988) found that tumor necrosis factor can induce both apoptosis and necrosis. Subsequent studies showed that there is a controllable form of cell necrosis. Degterev et al. (2005) showed that a small-molecule inhibitor, necrostatin-1 (Nec-1), could inhibit necrosis-like cell death, which they termed necroptosis (Degterev et al., 2005). Necroptosis is a form of regulated necrotic cell death in the absence of caspase-8 (Degterev et al., 2005; Newton et al., 2019a, b), and differs from apoptosis in morphological features (Wang et al., 2018a).

The molecular mechanisms of necroptosis began to be clarified in 2000 with the discovery of receptor-interacting

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serine/threonine kinase 1 (RIPK1), which is a regulator of Fas ligand-induced necroptosis in T cells (Holler et al., 2000). It is known that necroptosis can be triggered by multiple stimuli, including the activation of death receptors (Fas and TNF), toll-like receptors (TLR3 and TLR4), nucleic acid sensors (Z-DNA binding protein 1 (ZBP1), also known as DAI) and adhesion receptors (Vanlangenakker et al., 2012; Shindo et al., 2013; Dowling et al., 2015; Petersen et al., 2015; Arrazola and Court, 2019; Malireddi et al., 2019). Necroptosis signaling can be classified into two pathways—the canonical pathway and the noncanonical pathway. The canonical pathway is initiated by death receptors. The surface of the plasma membrane has tumor necrosis factor (TNF) receptors that can bind to TNF, and this step can activate RIPK1. RIPK1 is an essential adaptor of death receptors and contains a RIP homotypic interaction motif domain (RHIM), which activates RIPK3 via homotypic interaction, which then changes the conformation of mixed lineage kinase domain-like protein (MLKL; Chen et al., 2019; Lim et al., 2019; Baker et al., 2020). Then, phosphorylated MLKL undergoes oligomerization and translocates to the plasma membrane to change permeability, which leads to the disruption of the plasma membrane, and ultimately, cell lysis (Ofengeim and Yuan, 2013; Shan et al., 2018). The noncanonical pathway is triggered by specific pathogen recognition receptors, including TLR3, TLR4, interferon (IFN) and ZBP1. Pathogen recognition receptors contain a RHIM domain, and therefore, they can bind to RIPK3 via the RHIM domain and form a noncanonical necrosome (Huang et al., 2018; Zhang et al., 2020). Phosphorylated RIPK3 can induce the active conformation of MLKL (Moriwaki and Chan, 2017). The downstream mediators of MLKL are unclear at present. However, it is tempting to speculate that the ion channels induce plasma membrane rupture (Ding et al., 2019; **Figure 1**).

Our research group has investigated necroptosis in the nervous system for many years, from the occurrence of necroptosis in retinal neurons to a wider field, and we hope to carry out multidimensional and quantitative analysis on the research status of necroptosis within the scope of the nervous system. We found that bibliometric analysis can help us achieve this goal. Bibliometrics is the quantitative analysis of literature using mathematical and statistical methods (Zhang et al., 2017). Bibliometric analysis has emerged as one of the most useful methods to evaluate the scholarly impact, centrality, and quality of publication in a certain field (Ellegaard and Wallin, 2015; Akmal et al., 2020). Evaluation indicators include citation frequency, number of publications, times cited, H-index, impact factor and centrality (Avena and Barbosa, 2017). Benefiting from the development of visualization software, we used VOSviewer and CiteSpace to analyze the publications, which is more objective and rigorous and can provide the co-occurrence network diagram (Synnestvedt et al., 2005; Yeung et al., 2018). In this study, we retrieved and collected the research literature on necroptosis in the nervous system from the Web of Science Core Collection, and used VOSviewer and CiteSpace to analyze the publications. The objective of this bibliometric study was to identify and analyze the global output trend of necroptosis in the neuroscience field. Data analysis was performed to investigate the current hotspots in necroptosis research in the field of the nervous system and to identify future research hotspots. Our analyses will shed new light for investigators to help them plan and manage their scientific work.

Data and Methods

Data strategy and selection criteria

Literature data for this bibliometrics study were retrieved from the Web of Science Core Collection. The Web of Science Core Collection contains several important index types, including Science Citation Index Expanded (SCIE), Social Science Citation Index (SSCI) and Emerging Sources Citation Index (ESCI). To perform a systematic analysis of necroptosis in the field of neuroscience, we chose articles for visualization analysis. The term necroptosis was used in the MeSH (https://www.ncbi.nlm.nih.gov/mesh) search. The word necroptotic was used in some articles. Articles from 2007 to 2019 were selected, the language type was set to English, and type of documents was set to article and review.

The used search strategy was as follows: TS = (necroptosis OR necroptotic) refined by WEB OF SCIENCE CATEGORY (NEUROSCIENCE) AND [excluding] PUBLICATION YEARS: (2020) AND DOCUMENT TYPES: (ARTICLE OR REVIEW) AND LANGUAGES: (ENGLISH) AND WEB OF SCIENCE INDEX: (WOS. SCI), and time span of 2007 to 2019.

A total of 2239 documents were retrieved from the Web of Science Core Collection. After excluding documents published in 2020 or the published year of the documents was not clear, the 2201 documents that remained were used for visualization analysis. A flow chart of the search is given in **Figure 2**. The search was completed on April 16, 2020.

Methodology

The retrieval characteristics of necroptosis in the field of neuroscience included the distribution of publication years, countries and regions, organizations, journals, core-authors, keywords and key references. Bibliometric analysis and network visualization were performed with VOSviewer (Version 1.6.14; https://www.vosviewer.com/download#download-vosviewer) and CiteSpace (Version 5.6.R4; https://sourceforge.net/projects/citespace/files/latest/download). Microsoft Excel 2010 was used to assess the distribution of publication years. Gunn map (http://lert.co.nz/map/) online world map was used to evaluate the distribution of countries and regions. Ranking was performed using the Standard Competition Ranking method.

Outcome

We chose the keywords and key references to anticipate the research prospects and hotspots. Keywords and key reference analyses were performed with VOSviewer and CiteSpace. High-frequency terms, including key molecule and primary diseases, were used to anticipate the popular research model and research molecule. VOSviewer analysis method was Linlog/modularity and CiteSpace analysis method was LLR. Silhouette represents network homogeneity. A silhouette above 0.7 indicates that the cluster has a high reality, and above 0.5 suggests that the cluster has a credit.

Results

Distribution of publications by year

There were 1646 (74.78%) articles and 555 (25.22%) reviews among the 2201 publications. The chronological distribution of published documents is shown in **Figure 3**. From the trend line, the number of documents increased exponentially. The line chart illustrates that the number of documents increased relatively slowly from 2007 (n = 10, 0.45%) to 2017 (n = 257, 11.68%), while the number of documents rose sharply from 2017 (n = 257, 11.68%) to 2019 (n = 592, 26.90%) and reached a peak in 2019. Necroptosis acquired increasing attention in the field of neuroscience worldwide, indicating that it gradually became a research hotspot, even into the future.

Countries and regions

According to the statistical analysis, 2201 documents were published by research groups from 73 countries and regions. Some publications were the result of cooperation among multiple countries and regions, but we classified these into countries and regions. The top 10 most prolific countries and regions are shown in **Table 1**. The country with the largest number of documents was China (n = 860, 39.07%), followed by the United States (n = 635, 28.85%) and England (n =

Table 1 | Top 10 most productive countries and regions with publications on necroptosis in the field of neuroscience

Rank	Country/region	Documents	Citations	Total link strength	Links	Centrality
1st	China	860	11970	199	30	0.15
2nd	USA	635	21649	369	37	0.38
3rd	England	100	3986	156	32	0.09
4th	Germany	97	4295	121	27	0.08
5th	Italy	92	2146	94	34	0.15
6th	Canada	87	2930	103	31	0.07
7th	Japan	81	2040	61	27	0.09
8th	Republic of Korea	80	796	18	7	0.06
9th	Australia	62	2610	80	31	0.13
10th	India	61	1372	23	8	0.05

100, 4.54%). Although the number of publications from the United States was less than that from China, the citation and centrality were far higher than those from China.

The top 10 countries and regions with the strongest citation bursts are shown in **Figure 4**. India had the highest burst strength of 6.1423. The duration of burst began in 2010 and ended in 2012, indicating that there were many researchers studying necroptosis in India during 2010 to 2012. Canada had the lowest strength of 2.2056. The study of necroptosis exploded in 2013 and then ended that year.

Organizations

According to VOSviewer analysis, 2201 documents were published by 2126 different organizations, and 80 met the threshold. After excluding disjointed organizations, the remaining 76 organizations were used for the visualization map. We listed the top 10 prolific organizations in **Table 2**, and the most prolific organization was Soochow University (*n* = 70, 3.18%), followed by Zhejiang University (*n* = 52, 2.36%) and Central South University (*n* = 49, 2.23%). Among the top 10 organizations, seven are Chinese organizations and the remaining three are American organizations. However, the sum total of the citations of the seven Chinese organizations (*n* = 4126) was lower than that of Harvard University (*n* = 4387). The co-occurrence relations are shown in **Figure 5**. It is worth noting that the organizations with the highest citations included Harvard University, Ghent University, and University of California San Diego. Most were from the United States, and some were from Belgium, such as Ghent University. All evidence indicates that the United States still dominates necroptosis research in the field of neuroscience. Furthermore, the node in yellow indicates that the organization's average publishing year is 2018, and therefore, Harvard Medical University, which is represented by a yellow node, published a higher number of documents than any other organization, suggesting that it might be an emerging research organization.

Journals

It is helpful to identify core journals by analyzing the distribution of publication sources. Based on data analysis, the documents related to necroptosis in the field of neuroscience published from 2007 to 2019 are mainly distributed in 680 different journals. As shown in **Table 3**, the most prolific journal was *Cell Death & Disease* and *International Journal of Molecular Sciences*, which had 40 documents each. The range of 2019 impact factors, given in **Table 3**, is 2.274 to 6.304. The 2019 impact factor of *Cell Death & Disease* was the highest, and that of *Neuroscience Letters* was the lowest. Judging from the number of publications and the impact factor of journals, *Cell Death and Disease* might be the most influential journal.

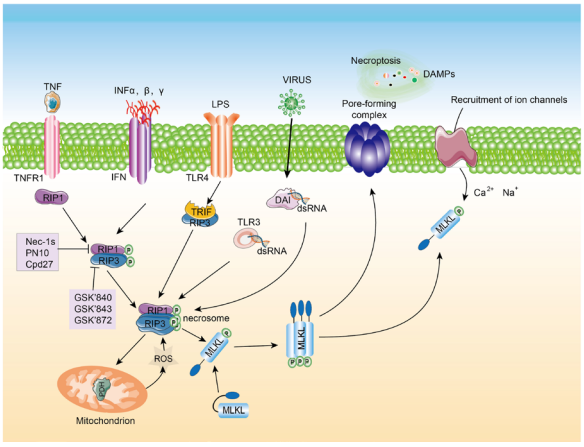

Figure 1 | Diagram of the necroptosis signaling pathway. Necroptosis can be initiated by TNF, INF, DAI and viruses.
Activated RIP1 phosphorylates RIP3 and forms a necrosis complex, the necrosome. Activated RIP3 phosphorylates MLKL, inducing oligomerization. The oligomerized MLKL translocates to the plasma membrane to form pores, causing cell death. MLKL: Mixed lineage kinase domain-like protein; RIP: receptor-interacting protein kinase; TLR: Toll-like receptor; TNF: tumor necrosis factor; TNFR1: tumor necrosis factor receptor 1.

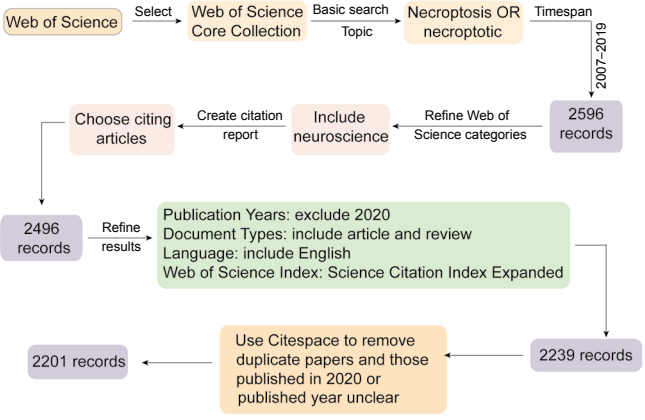

Figure 2 | Search flowchart detailing steps in the identification and screening of papers.

Authors

A total of 11,293 authors were found in 2201 documents. It is beneficial for probing the distribution of documents by analyzing core authors. The evaluation criteria of core authors included the number of published documents, the total citations and H-index. **Table 4** lists core authors of documents regarding necroptosis in the field of neuroscience from 2007 to 2019. Yuan JY ranked the first, both in the number of documents (*n* = 20) and total citations (*n* = 3335), indicating that Yuan JY is the most influential investigator of necroptosis in the field of neuroscience. Kreomer Guido had the highest H-index of 194. The core authors primarily were from the United States, Belgium, France and China, suggesting that the dominant authors were from prolific countries and organizations. **Figure 6** shows the co-authorship relations of authors. A total of 11,293 authors were found, and 229 met the threshold. After excluding unconnected authors, the remaining 137 authors were included for the visualization map. From the visualization map, we can observe that influential authors such as Yuan JY and Kreomer Guido collaborated more closely. In addition, their average published year was primarily 2013, indicating that they were the first to pay attention to this research topic. Furthermore, there are many emerging groups engaged in necroptosis research, indicating that necroptosis is still a hotspot.

Table 2 | **Top 10 most productive organizations**

Rank	Organizations	Country	Documents	Citations	Total link strength
1st	Soochow University	China	70	1394	34
2nd	Zhejiang University	China	52	641	23
3rd	Central South University	China	49	419	10
4th	Harvard University	USA	41	4387	31
4th	Shanghai Jiao Tong University	China	41	390	23
6th	Fudan University	China	33	453	30
7th	Harvard Medical School	USA	32	609	29
8th	Southern Medical University	China	29	337	15
8th	Johns Hopkins University	USA	29	853	12
10th	Nanjing Medical University	China	27	492	17

Table 3 | **Top 12 largest number of publications**

Rank	Journals	Documents	2019 impact factor
1st	*Cell Death & Disease*	40	6.304
1st	*International Journal of Molecular Sciences*	40	4.556
3rd	*Brain Research*	38	2.733
4th	*Molecular Neurobiology*	37	4.500
4th	*PLoS One*	37	2.740
6th	*Neuroscience Letter*	34	2.274
7th	*Neurochemistry International*	33	3.881
7th	*Frontiers in Cellular Neuroscience*	33	3.921
9th	*Neural Regeneration Research*	31	3.171
10th	*Neurochemical Research*	29	3.038
10th	*Scientific Reports*	29	3.998
12th	*Frontiers in Neuroscience*	26	3.707

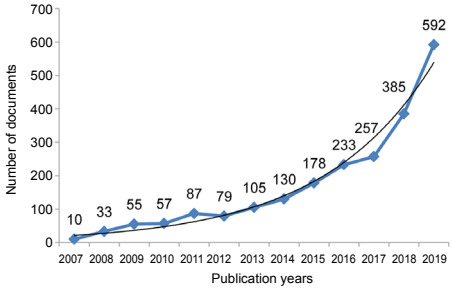

Figure 3 | **Distribution of publications on necroptosis in the field of neuroscience according to year.**
The number of publications increased relatively slowly from 2007 to 2017, while the number of publications rose sharply from 2017 onwards, to a peak in 2019.

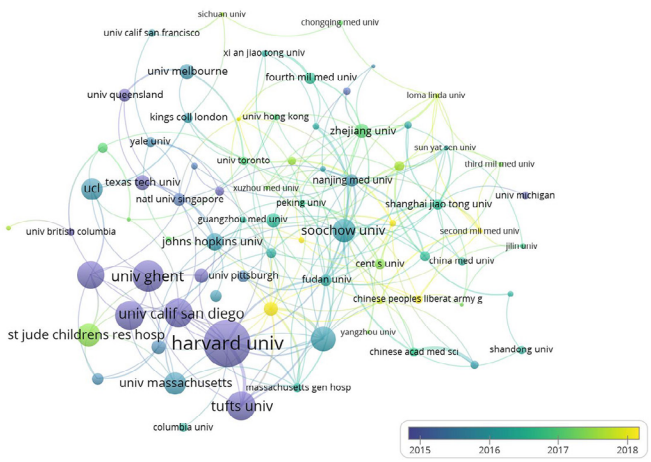

Figure 5 | **Organizations with co-occurrence relations shown as an overlay graph plotted with VOSviewer 1.6.14.**
The analysis method was Linlog/modularity. The weight was citations. Scores are the average published year. The thickness of lines indicates the strength of the relationship. The color indicates the average published year.

Keywords

A total of 9311 keywords were retrieved from 2201 documents, and 97 met the threshold. The network visualization map shows the co-occurrence relations of keywords (**Figure 7**). The size of the circle indicates the occurrence of keywords. As shown in **Figure 7**, the high-frequency keywords are apoptosis, oxidative stress, and inflammation. The average published year of these keywords, including cerebral ischemia, neuroprotection and stroke, is

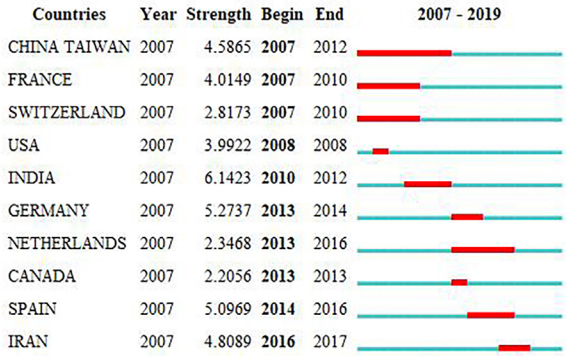

Figure 4 | **Top 10 countries/regions with the strongest citation bursts.**
A strong citation burst indicates that a variable undergoes a great change in a short period of time. Red bars indicate the duration of bursts.

2014. However, in the last 2 years, an increasing number of researchers have given attention to spinal cord injury, microglial autophagy and mitophagy, and neuroprotection by melatonin in necroptosis, indicating that the molecular mechanisms of necroptosis in the mitochondria will be the focus of future research.

Figure 8 shows the top 15 keywords with the strongest citation bursts. Cerebral ischemia had the highest burst strength of 29.8706. The burst in cerebral ischemia research in 2007 continued to 2013, suggesting that cerebral ischemia is a hotspot. In addition, ischemia had occurred five times in the top 15 keywords with the strongest citation bursts. All of this evidence suggests that ischemia is a hotspot, and many scholars have devoted themselves to researching it.

According to statistical analysis of the keywords, numerous molecules participate in the progress of necroptosis, and these molecules often suggest that some pathways and receptors also play a role in necroptosis, and different molecules or pathways also occur in different cell types. We listed the major molecules, pathways, receptors and cell types in **Table 5**. **Table 6** shows the diseases and pathological states involved in the study of necroptosis in the nervous system.

Citations

According to the citation analysis of documents, which reflects the number of times the documents were cited, we listed the top 10 highly cited documents in **Table 7**. The range of the number of citations was 431 to 1225. "Molecular mechanism of necroptosis: an ordered cellular explosion" ranked the first, which was published by Peter Vandenabeele in 2010 and was cited 1225 times. "Identification of RIP 1 kinase as a specific cellular target of necrostatins" ranked the second, and was

published by Alexei Degterev in 2008. "Regulated necrosis: the expanding network of non-apoptotic cell death pathways", ranked the third, and was cited 706 times. "Necroptosis as an alternative form of programmed cell death" ranked the last, with 431 citations among the 10 documents. It is worth noting that "Decoding ALS: from genes to mechanism" ranked sixth, but it was cited 500 times in the past 4 years. This review was likely cited so many times because it summarized the impact of the dysfunction in RNA metabolism and protein homeostasis and endoplasmic reticulum stress in ALS.

In addition to analyzing citations, co-citation analysis is also an important method of evaluating core references. As shown in **Figure 9**, the top highly-cited references were Mehta et al. (2007), Sun et al. (2012), Zhang et al. (2009), Cho et al. (2009), Degterev et al. (2008), He et al. (2009), Re et al. (2014), Vandenabeele et al. (2010) and Rosenbaum et al. (2010). Degterev et al. (2005) had the highest centrality, indicating that it was the most influential in necroptosis in the field of neuroscience. This is likely because this publication was the first to demonstrate that Nec-1 could inhibit regulated necrosis, which they termed necroptosis for the first time.

Discussion

During the preceding 12 years covered by this study, the number of annual publications increased gradually and reached a peak in 2019. The curve suggests that an increasing number of researchers became interested in necroptosis, indicating that it continues to be a research hotspot, and that publications related to necroptosis might continue to increase over the next few years. Moreover, a great majority of publications were original articles, and only a few were reviews, according to the bibliometrics, suggesting that there is a continuing need for novel investigation at this stage (Paunkov et al., 2019). However, there are still many unresolved domains in the field of necroptosis, such as clinical diseases, the upstream and downstream molecular mechanisms of necroptosis, and how to halt or slow the onset of diseases by blocking necroptosis signaling pathways (Molnar et al., 2019). The dominant countries, organizations and journals are in the West, and these countries will be in a leading position in the study of necroptosis for many years into the future.

According to our study, the core authors were from the most outstanding/productive organizations, such as Yuan JY, who worked at Harvard University in the past and is now at Harvard Medical School. Yuan JY published 235 documents from 1990 to 2020. Yuan's laboratory recently found that non-cleavable variants of RIPK1 led to an autoinflammatory response (Tao et al., 2020), and that casein kinases 1ɣ1 and 3 promote TNFα-induced necroptosis through RIPK3 (Lee et al., 2019). In addition, they found that RIPK1 activated necroptosis, and that RIPK3 deficiency and TAK1 loss could transform necroptosis into apoptosis (Naito et al., 2020). She recently published a review, "Necroptosis and RIPK1-mediated neuroinflammation in CNS diseases", which became a highly cited and hot paper in the Web of Science database just a few months ago. They cooperated with other teams from China, Canada, Republic of Korea and Germany, suggesting that international collaboration is beneficial to producing high-quality papers. Vandenabeele, Peter and Vanden Berghe, Tom, at Ghent University in Belgium, published numerous documents and had high total citations. Therefore, Belgium has occupied a place in the field of necroptosis. Xiong's laboratory from the Central South University has engaged in necroptosis research over the last few years (Huang et al., 2013; Ding et al., 2015; Chen et al., 2016; Liao et al., 2017; Shang et al., 2017; Wang et al., 2020). They are the first group to link necroptosis with methamphetamine. They found that necroptosis participated in methamphetamine-induced neurotoxicity (Xiong et al., 2016; Yang et al., 2018; Guo et al., 2020). However, from the analysis results, we can see that the main problem of Xiong's team is the lack of international communication and cooperation with other teams or institutions, which makes their research results similar to an islet, with few links with others. Moreover, the team of Tao Luyang, a group of emerging scholars, began to study necroptosis, indicating that necroptosis still garners the attention of investigators.

Taken together, 9311 keywords were retrieved from all of the documents. Stroke was the most frequent nervous system disease, indicating that stroke interests more investigators. Furthermore, Degterev et al. (2005) found that Nec-1 can

Table 4 | **Core authors of publications of necroptosis in the field of neuroscience from 2007 to 2019**

Authors	Organizations	Documents	Citations	H-index
Yuan Junying	Harvard Medical School (USA)	20	3335	81
Vandenabeele Peter	Ghent University (Belgium)	11	3079	101
Vanden Berghe Tom	Ghent University (Belgium)	8	2487	46
Degterev Alexei	Tufts University (USA)	15	2197	35
Kreomer Guido	Sorbonne University (France)	9	1866	194
Green Douglas R	St Jude Children's Research Hospital (USA)	6	838	155
Xu Xingshun	Soochow University (China)	13	495	16
Maiese Kenneth	Cellular & Mol Signaling	17	423	61
Xiong Kun	Central South University (China)	20	438	13

Table 5 | **Top 10 key molecules, pathways, cell types and receptor types involved in necroptosis in the nervous system**

Rank	Key molecules	Occurrence	Pathways	Occurrence	Cell types	Occurrence	Receptor types	Occurrence
1	Rips	295	Pi3k/AKT pathway	14	Astrocyte	104	Toll-like receptor	46
2	NF-κB	265	JNK pathway	13	Stem cells	95	NMDA receptor	35
3	Nitric oxide	117	Cell death pathway	10	Endothelial cells	91	Cb receptor (cb1/cb2)	20
4	TNFα	80	WNT pathway	8	Motor neurons	68	Glutamate receptor	20
5	Bcl-2/Beclin-1	79	AMPK pathway	7	Retinal ganglion cells	42	Chemokine receptor	10
6	Caspases	73	ERK pathway	6	Cancer cells	40	Hormone receptor	9
7	Necrostatin-1	73	MAPK pathways	6	Pc12 cells	36	Acetylcholine receptor	9
8	Cyclosporine	65	Mitochondrial pathway	6	Glial-cells	35	AMPA receptor	8
9	Glutamate	65	AKT pathway	5	Hippocampal neurons	33	Sigma 1 receptor	7
10	AMPK	48	NF-κb pathway	5	Sh-sy5y cells	31	TNF receptor	7

AKT: Protein kinase B; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor; AMPK: adenosine 5'-monophosphate (AMP)-activated protein kinase; ERK: extracellular regulated protein kinases; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; NF-κb: nuclear factor kappa-B; NMDA: N-methyl-D-aspartic acid receptor; Rips: receptor interacting protein family; TNFα: tumor necrosis factor; WNT: wingless/integrated.

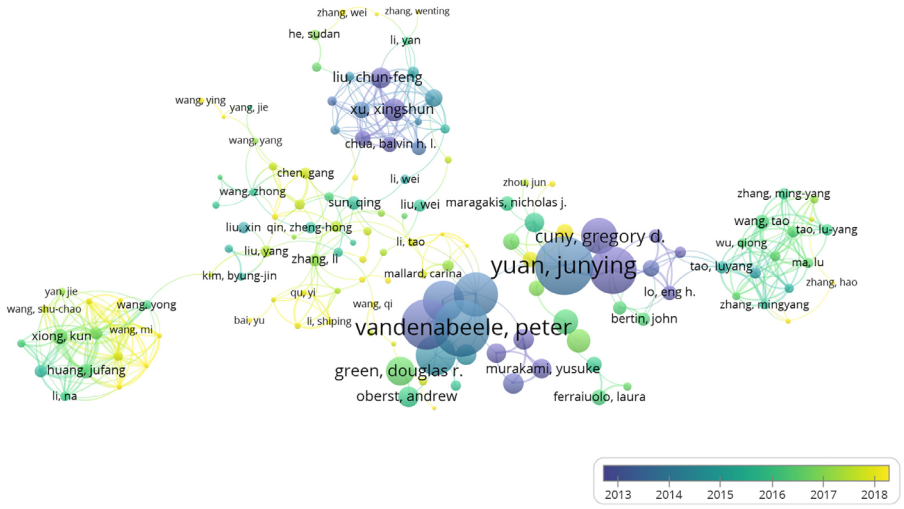

Figure 6 | Overlay visualization of co-authorship analysis of authors.
The analysis method was Linlog/modularity. The weight was citations. Scores are the average published year. The thickness of the line indicates the strength of the relationship. The color of the circle represents the average published year.

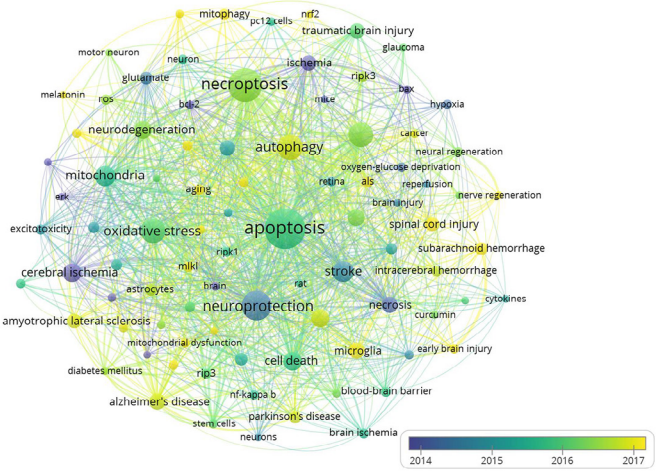

Figure 7 | Co-occurrence analysis of keywords.
The analysis method was Linlog/modularity. The weight was occurrence. The color of the circle represents the average published year.

Keywords	Year	Strength	Begin	End	2007 - 2019
cerebral ischemia	2007	29.8706	2007	2013	
focal cerebral ischemia	2007	18.3202	2008	2013	
nitric oxide	2007	11.4423	2008	2012	
apoptosis inducing factor	2007	9.2981	2008	2011	
neuroprotection	2007	9.0928	2007	2011	
ischemia	2007	8.4963	2008	2013	
stroke	2007	7.8021	2008	2012	
rat brain	2007	7.4357	2008	2013	
focal ischemia	2007	7.243	2008	2014	
bcl-2	2007	5.4302	2008	2014	
central nervous system	2007	4.7939	2008	2009	
caspase	2007	4.7623	2008	2009	
erk	2007	4.6055	2008	2013	
brain ischemia	2007	3.1669	2008	2013	
brain	2007	2.9378	2007	2010	

Figure 8 | Top 15 keywords with the strongest citation bursts.
A strong citation burst indicates that a variable undergoes a great change in a short period of time. Red bars indicate the durations of the bursts.

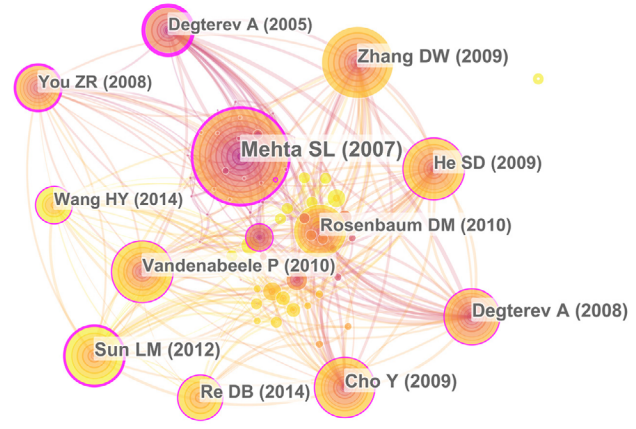

Figure 9 | Co-citation analysis of references.
The size of the circle indicates the record of documents cited. The purple part of the circle indicates the centrality of the documents.

Table 6 | The diseases and pathologies involved in the study of necroptosis

Pathology	Occurrence	Diseases	Occurrence
Ischemia	796	Stroke	330
Oxidative stress	461	Amyotrophic lateral sclerosis	209
Ischemia-reperfusion	187	Other brain injury	195
Neurodegeneration	166	Alzheimer's disease	176
Motor neuron death	77	Traumatic brain injury	130
Artery occlusion	56	Optic nerve diseases	127
DNA damage	34	Nervous cancer	109
Axonal degeneration	27	Parkinson's disease	88
Brain edema	11	Cognition dysfunction	85
Cerebral vasospasm	9	Spinal cord injury	54
Axonal regeneration	7	Subarachnoid hemorrhage	53
White matter injury	7	Multiple sclerosis	30
Anoxia	5	Huntington's disease	27

Table 7 | **Top 10 highly cited documents of necroptosis in the field of neuroscience**

Rank	Title	First author	Journals	Publication year	Total citations
1st	Molecular mechanisms of necroptosis: an ordered cellular explosion	Peter Vandenabeele	*Nature Reviews Molecular Cell Biology*	2010	1225
2nd	Identification of RIP 1 kinase as a specific cellular target of necrostatins	Alexei Degterev	*Nature Chemical Biology*	2008	1049
3rd	Regulated necrosis: the expanding network of non-apoptotic cell death pathways	Tom Vanden Berghe	*Nature Reviews Molecular Cell Biology*	2014	706
4th	Identification of a molecular signaling network that regulates a cellular necrotic cell death pathway	Junichi Hitomi	*Cell*	2008	628
5th	Necroptosis: the release of damage-associated molecular patterns and its physiological relevance	Agnieszka Kaczmarek	*Immunity*	2013	548
6th	Decoding ALS: from genes to mechanism	J. Paul Taylor	*Nature*	2016	500
7th	Neuroprotection for ischemic stroke: past, present and future	Myron D Ginsberg	*Neuropharmacology*	2008	478
8th	Necroptosis	Andress Linkermann	*New England Journal of Medicine*	2014	467
9th	Essential versus accessory aspects of cell death: recommendation of the NCCD 2015	L Galluzzi	*Cell Death and Differentiation*	2015	449
10th	Necroptosis as an alternative form of programmed cell death	Dana E Christofferson	*Current Opinion in Cell Biology*	2010	431

specifically suppress RIPK1, providing a huge contribution to ischemia/reperfusion injury research, and contributing to the cerebral ischemia and necroptosis clusters boom in 2007. Even at present, focus on ischemia/reperfusion is still very high among investigators studying diseases and pathologies associated with necroptosis. Ischemia, ischemia/reperfusion and stroke, and brain injury rank high. The number of studies on diseases and pathologies ranked high is greater than those on other types, and the number of citations is also high. From the perspective of bibliometrics, this phenomenon shows that these molecules or diseases are frequently studied as research subjects. The number of existing papers is high, and the future growth trend may tend to slow. However, new research avenues on these molecules or diseases may continue to be discovered, resulting in a second spurt of research. In contrast, diseases or pathologies that are ranked lower, such as motor neuron injury, ocular nerve disease and DNA damage, may have sufficient development room for more scholars to engage in.

The most critical necroptosis-related molecules are RIP1, RIP3 and MLKL, among which MLKL oligomerization is the executor of necroptosis. This is basically consistent with our results of keyword extraction and analysis. RIPs have the highest word frequency, which indicates that the number of publications on these molecules is the highest. However, with in-depth study of necroptosis, investigators have discovered additional molecules related to necroptosis. For example, Yuan et al. (2019) found that TAM promotes necroptosis by regulating MLKL oligomerization. TAM kinases are known for their anti-apoptotic and anti-inflammatory roles, but Najafov et al. (2019) found that they are also necessary for necroptosis, and that knocking out TAM kinases can attenuate necroptosis. The linear ubiquitination of RIPK1 can inhibit apoptosis and necroptosis, and thereby plays a critical role in cell survival. Mice with knockout of the RIPK1 gene die from caspase-8-mediated apoptosis and RIP3-mediated necroptosis (Dillon et al., 2014; Kaiser et al., 2014; Rickard et al., 2014). It is currently known that RIPK1 can promote cell survival through two mechanisms. One is by promoting cFLIP recruitment of caspase-8, causing caspase-8 inactivation (Oberst et al., 2011). The other is promoting the activation of NF-κB and pro-survival molecules, including cFLIP, A20, cIAP2 and Bcl2 family members (Micheau and Tschopp, 2003). In addition, RIPK1 can be de-ubiquitinated by zinc finger protein A20 and CYLD, causing RIPK1 downregulation and failure to activate NF-κB signaling (Ea et al., 2006). This is consistent with our keyword frequency analysis results. The statistical analyses of key molecules, pathways and receptors all indicate the importance of the NF-κB pathway in necroptosis. The ubiquitination of RIPK1 is essential for TNF activation by the NF-κB signaling pathway (Draber et al., 2015). Furthermore, the heat shock protein (HSP90)/CDC37 co-chaperone complex increases the stability of the necrosome (Li et al., 2015; Zhao et al., 2016; Wang et al., 2018b). In contrast, HSP70 enhances the stability of a necroptosis antagonist. HSP70 promotes MLKL polymerization to activate necroptosis (Johnston and Wang, 2020).

The statistical analysis of keywords suggests that we need to regard the statistical results of word frequency of keywords as a net structure. As shown in **Figure 9**, in the statistical results of these keywords representing the core content of the article, words are related to each other. For example, the word frequency of glial cells ranks high, suggesting that the role of glial cells in necroptosis is one of the research hotspots. Diseases related to necroptosis, including stroke and brain injury, are also ranked high in terms of frequency. Neuroinflammation is an important pathological state in these diseases (Yuan et al., 2019), and the important cells involved in the process of neuroinflammation are glial cells (Yang and Zhou, 2019). According to the statistical results of key molecules, the word frequencies of NO and TNF-α also ranked high, indicating that they are mainly related to glial cells in the nervous system (Yang and Zhou, 2019). The results of these reticular structures, from the perspective of bibliometrics, suggest that, on one hand, the molecules, pathways, receptors and diseases involved in the top ranked words may be one of the research hotspots, and there are many published research results, which may inhibit the growth of new directions in the future. On the other hand, the number of research results represented by the lower ranked words is relatively small, which may therefore have explosive growth potential. These results can be used as a reference when investigators select their starting point in necroptosis research.

Necroptosis as a form of necrosis has attracted increasing attention by investigators. Future research directions may focus on noncanonical pathways and subcellular structures such as mitochondria. Phosphorylated RIP3 can activate MLKL, causing MLKL oligomerization and insertion into the membrane. In addition, phosphorylated RIP3 can activate PGAM5, a mitochondrial serine/threonine protein phosphatase, which is a well-recognized major factor controlling necroptosis via multiple mechanisms (Al-Lamki et al., 2016; Couto et al., 2017). PGAM5 is able to influence mitochondrial fission by phosphorylating Drp-1, and can influence mitophagy by regulating FUNDC1 phosphorylation

(Wang et al., 2012; Chen et al., 2014). Furthermore, activated PGAM5 can regulate CypD to control mPTP opening (Zhou et al., 2018).

Numerous studies have shown that inflammation also plays an important role in the process of cell death (Pasparakis and Vandenabeele, 2015; Martin et al., 2019). For example, in immune-mediated diseases, the complex of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) plays an important role in the immune response, and this complex may be related to cell death processes (Pisetsky, 2011). DAMP, as the carrier of PAMP (Hernández-Pedro et al., 2016), plays a promoting role in inflammation (Pandolfi et al., 2016), and inflammatory factors (interleukin-1, TNFα, etc.) produced in the process of neuroinflammation participate in necroptosis (Deepa et al., 2018), suggesting that the relationship between the immune response and its associated molecules, DAMP and PAMP, and necroptosis may become a potential research hotspot in the future.

Necroptosis is not only involved in CNS diseases, but also in other pathologies (Choi et al., 2019). Numerous studies have demonstrated that necroptosis is involved in diseases of other systems, including the digestive system, circulatory system, immune system, and genital system (Zhe-Wei et al., 2018; Liu et al., 2019; Mulay et al., 2019; Ruan et al., 2019; Saeed et al., 2019). Nec-1, the top RIPK1 inhibitor in keyword analysis, can inhibit necroptosis in a variety of disease models and reduce the mortality rate of diseases (Shen et al., 2019).

According to our analysis results, it only takes about 10 years to develop programmed death in the nervous system. The collaboration between authors is not great. As seen in **Figure 6**, all the co-operators appear in the form of "islands". The center of these "islands" is a core author (the author with strong influence). The center of each "island" is surrounded by the team members of the core author. However, there are few connections between these islands. This indicates that the collaboration between core authors (or core teams) in the same research field is relatively low. Perhaps in the future, with the continuous research on programmed death and the strengthening of cooperation among authors, teams, insitutions, and countries, analysis and discussion regarding collaboration can be further carried out.

This study is the first bibliometric study using visual analysis software to analyze publications of necroptosis in the global field of neuroscience. The publications increased year by year, especially from 2017 to 2019. In the future, the amount of literature will keep increasing continuously. The leading countries were China and USA. The most influential author is Yuan Junying. Furthermore, the research prospects and hotspots might be the detailed mechanisms by which MLKL permeabilizes the membrane and the signaling pathway by which RIP3 activates downstream molecules in the mitochondria. Overall, this study provides insight into the trends and characteristics of necroptosis in the field of neuroscience, and should provide a helpful reference for further in-depth research.

Study limitations: Although this is the first bibliometric study of necroptosis in the field of neuroscience, there are some limitations, as follows: (1) The search was conducted on April 16, 2020 and included all documents up to December 31, 2019, but the Web of Science Core Collection would have been still open for documents related to 2019, and this part was omitted; (2) Only publications with the terms "necroptosis" or "necroptotic" in the title, abstract and keywords were retrieved. However, papers with these terms within the main body of the text were not retrieved for analysis; (3) Each article can only have 3–10 keywords. Because of this limitation, the author could only identify the core content with a keyword if it was present as a keyword in the publication, although it may appear elsewhere in the paper, resulting in incomplete extraction; (4) Because the search was limited to the Web of Science Core Collection indexed journals, a few documents not included in the Web of Science Core Collection were missed. These limitations have also been reported in other bibliometric studies (Wang et al., 2017; Azer and Azer, 2019; Wang et al., 2019).

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