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Extensive Cross Linking for Pyroptosis, Apoptosis and Necroptosis (Panoptosis): A Bibliometric Analysis

Qi Chen[1], Jia-xuan Li[2], Wei Zhang[2], Chang-Liang Xia[1], Jun-Nan Ma[1], Shuan-Ji Ou[3], Yang Yang[3], Yong Qi[*1] and Chang-Peng Xu[*1]

[1]Department of Orthopaedics, Guangdong Second Provincial General Hospital, Guangzhou, Guangdong, P.R. China; Jinan University, Guangzhou 501632, China

[2]Department of Orthopaedics, Guangdong Second Provincial General Hospital, Guangzhou, Guangdong, P.R. China; The Second School of Clinical Medicine, Southern Medical University, Guangzhou, China

[3]Department of Orthopaedics, Guangdong Second Provincial General Hospital, Guangzhou, Guangdong, P.R. China

[*]**Corresponding author:** Yong Qi, Department of Orthopaedics, Guangdong Second Provincial General Hospital, Guangzhou, Guangdong, P.R. China; Jinan University, Guangzhou 501632, China, E-mail: gd2hqy@163.com

Chang-Peng Xu, Department of Orthopaedics, Guangdong Second Provincial General Hospital, Guangzhou, Guangdong, P.R. China; Jinan University, Guangzhou 501632, China, E-mail: gd2hxcp@163.com

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Abstract

Background: The crosstalk between the three modes of death: pyroptosis, apoptosis, and necroptosis (PANoptosis) are a hot and emerging area of research in recent years. Understanding and analyzing the research progress and direction of PANoptosis will be a hint and guidance for scholars to carry out related research in the future. Our study summarized the knowledge structure and identify emerging trends and potential hotspots in PANoptosis from a scientometric perspective.

Methods: Publications related to PANoptosis were retrieved from Web of Science Core Collection. The search strategies were: TS ="Pyroptosis" AND "Apoptosis" AND "Necroptosis" OR "PANoptosis" OR "PANoptosome" OR "PAN-optosis". Microsoft Excel, VOS viewer, and CiteSpace software were used to analyze and conduct the study.

Results: Finally, we have selected 370 relevant articles for analysis. The total number of references regarding PANoptosis has a distinct increased year by year. The documents we obtained come from 51 different countries and 711 institutions. The United States of America (USA) is the most published country, total of 1903 authors were involved, Kanneganti Thirumala-Devi has the highest number of published literatures, and R K Subbarao Malireddi was the author co-cited most often. The journal with the most studies was Cell death and Differentiation, and Nature was the most commonly cited journal. In our outcome of PANoptosis, the most common keywords are pyroptosis, necroptosis, apoptosis, PANoptosis, caspase-8, inflammasome, caspase-1, panoptosome, and ripk3. These words can reflect current hot spot and developing areas of study.

Conclusion: The research of PANoptosis will continue to be the hotspot. Several outstanding scientists have emerged who are steadily moving the field forward. Closer national and inter-institutional communication and cooperation may facilitate the flourishing of PANoptosis. The focus of current research and developmental trends in the future are the related pathway mechanism of PANoptosis, the discovery and the role of PANoptosis in various diseases.

Keywords: Panoptosis, Pyroptosis, Apoptosis, Necroptosis, Bibliometrics, Vosviewer, Citespace, Programmed Cell Death

Introduction

Programmed cell death (PCD) is a genetically regulated process of cell suicide. It is important to the development of homeostasis and the integrity of prokaryotic and eukaryotic cells [1]. Today more than ten types of death have been identified and defined, pyroptosis, apoptosis, and necroptosis as three important and well-defined PCD which has intricated molecular machinery responsible for the initiation, transduction, and implementation of cell death. Their hypothesis of a molecular mechanism has been established and is widely accepted [2]. In 1972, Apoptosis was characterized as an inherently programmed phenomenon based on the morphological characteristics of apoptosis, which was one of the first identified forms of PCD [3], Apoptosis was characterized as an inherently programmed phenomenon based on the morphological characteristics of apoptosis, which was one of the first identified forms of PCD[3], caspases are central during carrying out the programmed dismantling of cellular components for cellular homeostasis. Caspase8 and caspase9 respectively act as initiators of exogenous and endogenous apoptosis [4-5], initiating the caspase cascade that drives activation of caspase-3/-6/-7/-9/-10, leading to robust execution of apoptosis [6-7]. In 2001, Cookson BT first introduced the concept of pyroptosis a caspase 1-dependent pro-inflammatory PCD pattern [8]. The classical inflammasome complex consists of a cytosolic sensor (which can be either a nucleotide binding domain and leucine-rich-repeat- containing (NLR) protein or a member of the AIM2 like receptor (ALR) family), an adaptor protein ASC and an effector caspase pro-caspase-1 [9], what's more, the inflammasome activation is currently believed by caspase-1/-4/-5 in humans and caspase-1/11 in mice [10]. The formation of plasma membrane pores and impairment of membrane integrity is the character morphology of pyroptosis. Pyroptosis is a form of regulated cell death mediated by gasdermin family proteins. In humans, the gasdermin family consists of six members: GSDM-A, -B, -C -D, -E (also called DFNA5), and DFNB59. Mice lack GSDMB but express three GSDMAs (mGSDMA1–3) and four GSDMCs (mGSDMC1–4). Structurally, all gasdermin family members except DFNB59 have an N-terminal pore-forming domain, a C-terminal autoinhibitory domain, and a loop domain that links the N- and C-terminal domains. Protease-mediated cleavage within the linker loop releases the N-terminal domain, which then oligomerizes to form nonselective pores at the plasma membrane and causes membrane permeability changes, cell swelling and membrane rupture [11]. The term necroptosis was first to be described in 2005 when the inhibitor of necroptosis necrostatin-1was found to target RIPK1 [12]. In TNF-a-induced necroptosis, RIPK1 and RIPK3 play key roles [13-14]. The necrosome phosphorylates the pseudo kinase MLKL, which damages the cell membrane and causes cell necrosis [15]. As soon as individual PCD pathways were thought to be non-interfering with each other in molecular, but in recent years, studies have increasingly demonstrated the mutual scramble and linkage between the three PCD pathways in the context of infection, and cancer [16-17]. PANoptosis was first discovered in 2019 by Kuriakose T and Malireddi RKS, who discovered ZBP1 mediated IAV NP and PB1 proteins and utilizes RIPK1 to simultaneously activate apoptosis, necroptosis, and pyroptosis in IAV-infected cells [18]. PANoptosis is the emerging mode of death under the combination of the three modes of death so it is composed of the initial's parts of the "pyroptosis", "apoptosis" and "necroptosis", and the common part of the three words "optosis". During PANoptosis, an inflammatory cell death occurred through the collective activation of pyroptosis, apoptosis, and necroptosis and weakened pathogen immune evasion effect. The PANoptosome consists of molecules in the cell death pathway that form a single molecular complex, from pyroptosis, apoptosis, and necroptosis, through the interaction of homogeneous and heterogeneous structures [19].

PANoptosis plays an important role in regulating the immune and inflammatory responses of the body, in addition to its involvement in the development and progression of various diseases, infectious diseases and cancers are currently the most common diseases found in Panoptosis [12,18,20,21]. The role of PANoptosis in infection is a hot area of current research. During infection, cells can eliminate replicating viruses through cell death, an antiviral immune response. However, exaggerated cell death may also lead to severe clinical disease and host death. Many pathogens target multiple host PCD pathways through virulence factors to maximize host damage [22]. PANoptosis has

been helpful in better blocking the survival and transmission of viruses and provides better molecular targeting direction for clinical infection treatment.

Bibliometrics was first proposed by American bibliographers in 1969. Bibliometric analysis aims knowledge in the literature, such as the distribution of countries/regions, authors, and research areas of journals. After qualitative and quantitative analysis of bibliometrics, we can visualize the hot spots and directions of related fields through graphs and tables [23-24].

In this paper, a bibliometric approach was used to present and decode the literature on basic research and clinical diseases by analyzing the literature about PANoptosis. Our study focused on the volume of publications, author, country, and institution interaction, keywords, and highly cited literature.

Materials and Methods

Data collection

The Web of Science Core Collection database (WoSCC) Science Citation Index extension (SCI-Expanded) data were used in this study. WoSCC is an authoritative database in the field of science. Considering that PANoptosis is an emerging death mode in which three death modes of pyroptosis, apoptosis, and necroptosis occur simultaneously, and the research on the cross-linking of the three death modes never stopped before the concept of PANoptosis was proposed, so we used a search strategy of TS ="Pyroptosis" AND "Apoptosis" AND "Necroptosis" OR "PANoptosis" OR "PANoptosome" OR "PAN-optosis". We obtain 408 articles, removing the literature types of book chapters, online publications, and editorial material. After removing the types of literature as book chapters, online publications, editorial materials, conference abstracts, conference proceedings papers, and letters, 370 articles were obtained. We used the WoSCC export information function to download the author, affiliation, title, abstract, keywords, journal, year of publication, WoSCC classification, and citations for each article.

After reading the titles, abstracts, and author keywords, we concluded that all 370 articles contained pyroptosis, apoptosis, necroptosis, or PANoptosis, so we used all 370 articles retrieved for data analysis.

Data analysis route

The txt files obtained from WoSCC, Microsoft Excel, VOSviewer, CiteSpace, and Scimago Graphica were mainly used for graphing.

We chose Microsoft Excel to analyze and graph the annual number of articles and citations downloaded from WoSCC. Microsoft Excel was also used for some data management and some form of production. We used VOSviewer and CiteSpace which are two common and mature bibliometric analysis software to generate network visualization maps for bibliometric and visual analysis. We focused on the main authors, countries, institutions, keywords, citation analysis, and co-citation analysis. In the network visualization map, each node corresponds to a parameter, such as country, institution. The size of the node has a diameter roughly proportional to the number of publications, citations, or occurrences in software [25]. In VOSviewer, if two articles are more closely cited, they will be automatically assigned to a cluster with the same color, we mainly analyze the clusters characteristics and node connections. Degree is an indicator that reveals the extent to which nodes are connected in the network; higher degree in a node suggests that more information interacts through this node. In CiteSpace, we focus on the degree and the linkage of the nodes. We used Scimago Graphica to depict the amount of contribution and linkage of different countries around the world to the literature.

Results

Publications and citations analysis

Using the search terms given earlier, a total of 370 documents were obtained from the database using the search strategy in Figure 1. The annual number of articles published and the total number of the quilt for each year of publication from 2008 to 2022 are shown in Figure 1. The annual number of articles published and the total quilt for each year of publications from 2008-2022 are shown in Figure 1. Studies on pan-apoptosis showed a slowly increasing trend from 2014-2018 and a rapidly increasing trend from 2019 onwards, with 48 publications in 2019, 79 in 2020, 114 in 2021, and 32 in 2022 (as of 25 April) (Figure 2). The cumulative total citation frequency of all publications, after removing self-citations, is 16,763 and 15,688 respectively (average citation frequency per entry: 45.31). 2021 is not only the peak year for publications but also the peak year for citations, suggesting that articles published in 2021 are highly referenced and therefore widely cited in the research process.

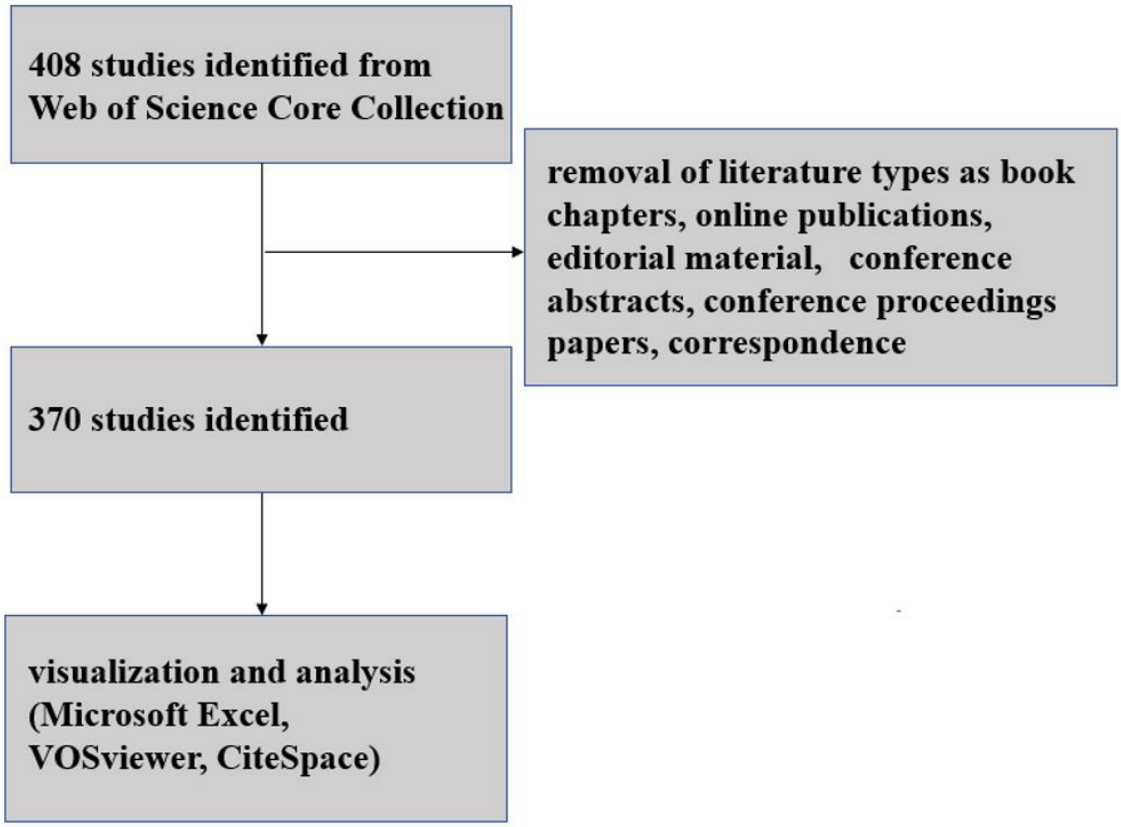

Figure 1: Flowchart of literature selection

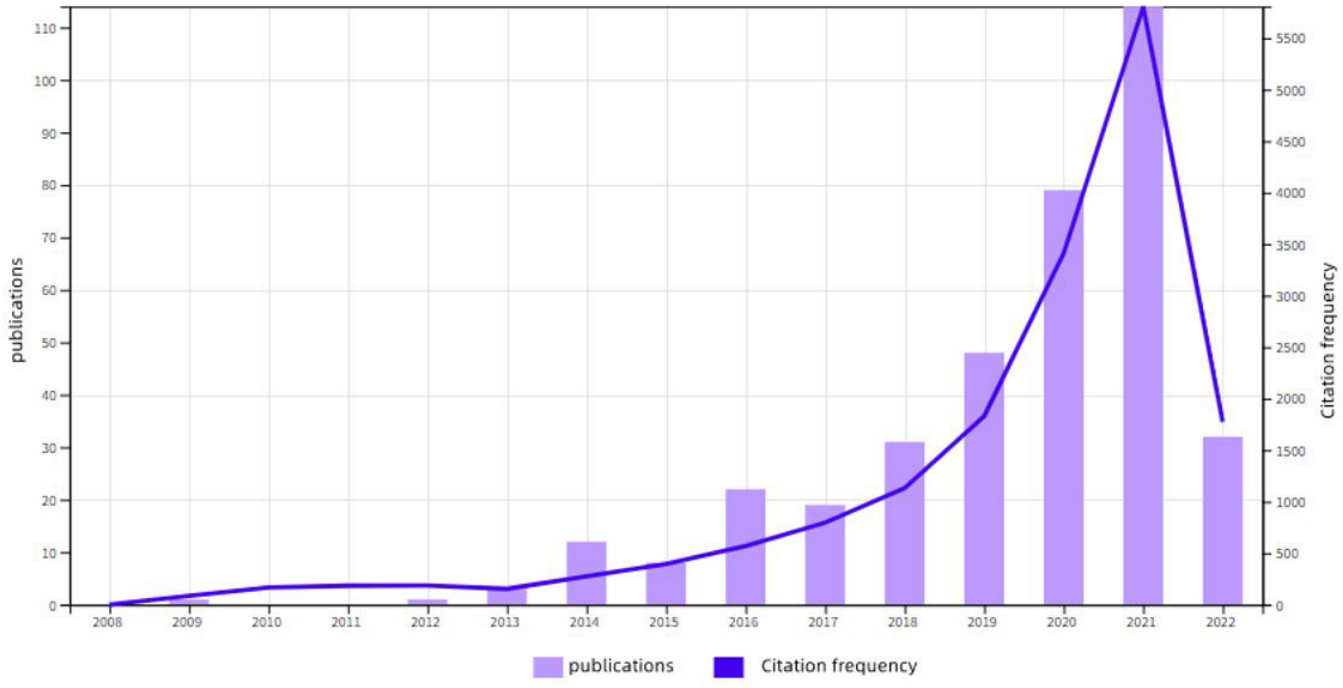

Figure 2: Analysis of publications and frequency of citations

Figure 3 A: Global spatial distribution of the references. B. Country co-occurrence analysis graph. Size of Label is measured by the number of co-occurring articles in to figures

Country and institution analysis

We use CiteSpace to analyze the country co-occurrence. The 370 published papers came from 51 different countries and 711 institutions. As can be seen from Table 1, China (130 publications, 34.9%) and USA (126 publications, 33.8%) have the highest number of publications, much higher than the other countries by more than three times. Country co-occurrence analysis through CiteSpace shows that USA (22 publications) and China (17 publications) are also the two countries with the most collaborations with other countries. The USA also has some collaboration visible with Germany and Australia. Suggesting that the USA is the leading driving force, and still dominates in this research field. The most published institutions are ST JUDE Children's Research Hospital (34 articles, 9.1%) from USA, followed by the League of European Research Universities Leru (22 articles, 5.9%) from Europe and Central South University (17 articles, 5.9%) from China.

The institution co-occurrence graph directly reflects the degree of collaboration and communication between institutions (Figure 4). In terms of author partnerships, the most publications are produced by the University of Massachusetts, which also has several affiliations with other organizations. Walter & Eliza Hall Inst Med R and Univ Massachusetts not only has the high volume of publications but also has a wide range of associations with other institutions.

Table 1: Analysis of author and co cited author

Author	Count	Institution	Author	Co-count	Total link strength	Institution
Kanneganti TD	25	St. Jude Children's Research Hospital	Malireddi RKS	65	2992	St. Jude Children's Research Hospital
Malireddi RKS	12	St. Jude Children's Research Hospital	Newton K	56	2860	Genentech
Karki R	10	St. Jude Children's Research Hospital	Kayagaki N	44	2399	Genentech
Green Dr	8	St. Jude Children's Research Hospital	Shi JJ	43	2108	Institute Of Chinese Medical Sciences
Linkermann A	8	University Hospital Carl Gustav Carus At Technische Universität Dresden	Gurung P	40	1941	St. Jude Children's Research Hospital
Vogel P	8	St. Jude Children's Research Hospital	Man SM	38	1758	St. Jude Children's Research Hospital
Zheng M	8	St. Jude Children's Research Hospital	Karki R	36	1649	St. Jude Children's Research Hospital
Kesavardhana S	7	St. Jude Children's Research Hospital	Dondelinger Y	31	1563	Vib Inflammation Research Center
Place De	7	St. Jude Children's Research Hospital	Kesavardhana S	30	1478	St. Jude Children's Research Hospital
Zhang J	7	Eye & Ent Hosp	Galluzzi L	26	1449	Weill Cornell Medical College

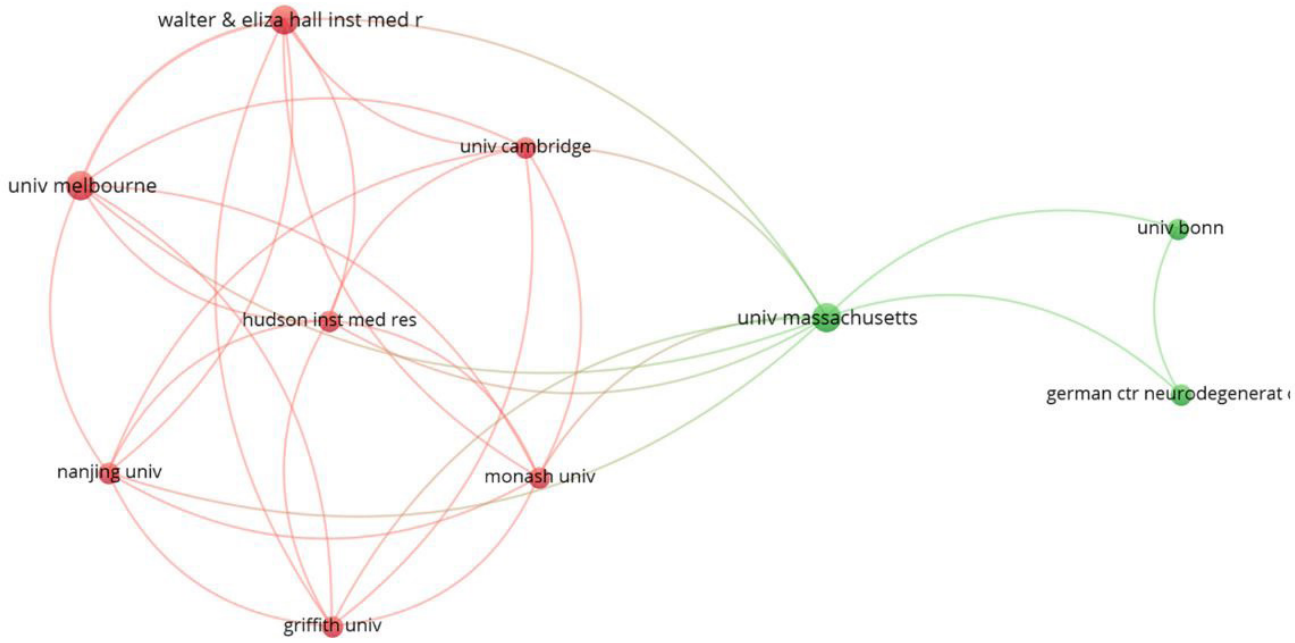

Figure 4 A: Institution citation analysis by VOSviewer. B co-institutional analysis by VOSviewer. (Minimum number of documents of an institution > 2)

Authors and co-cited authors analysis

1923 authors and 370 publications were involved. The top 10 authors in terms of the number of papers in PANoptosis are shown in Table 1, from which it can be seen that the author who has the most published papers are Kanneganti TD (n =25), followed by Malireddi RKS (n =12), Karki Rajendra (n =10) all of them were from St. Jude Children's Research Hospital, and we found that half of the top 10 authors with the highest number of citations were from Jude Children's Research Hospital in the U.S. It shows that under the leadership of Kanneganti TD, the researchers of this institution have made important contributions in the field of PANoptosis. Furthermore, we note that Malireddi RKS, Karki R among the 10 highly productive authors are also among the top 10 co-authors indicating that these two investigators have a high international reputation in the field.

Distribution of journals

As shown in Table 3, the top three most prolific journals were Cell Death and Differentiation (IF =12.067), Cell Death & Disease (IF =9.685), and frontiers in Immunology (IF =8.786). Here, the number of times a journal is co-cited which reflects whether the journal has had a significant impact in a particular area of research was used to measure the influence of the journal. The top three journals with the highest co-citation frequencies were Nature (Citation =440), Cell (Citation =285) and P Natl Acad Sci USA (Citation =240) (Table 2). In table 2, we can see that 80% percent of journals are from Q1. According to the 2022 Journal citation reports (JCR), except for International Journal of Radiation Oncology Biology Physics and Journal of Immunology, the remainder of the top 10 co-cited journals were in Q1, showing that reputable journals are still concentrating on research in the area of PANoptosis.

Analysis of highly cited references

Table 3 presents a summary of the highly cited reference. The most frequently cited papers "Classification of cell death: recommendations of the Nomenclature Committee on Cell Death 2009" (Citation =2198) and "Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018" (Citation =2198) are both from the Cell Death Committee. In these papers, the Nomenclature Committee on Cell Death defines apoptotic necrosis morphologically, while PANoptosis is not explicitly mentioned, demonstrating that PANoptosis as a mode of death and its research is in its infancy; “Old, new and emerging functions of The third most cited paper, Old, new and emerging functions of caspases”, is a review paper in which the authors summarize the main functions of caspases, and in this 2015 paper, the authors have summarized the dual role of caspase-8 in cell death, mediating both receptor-mediated apoptosis and necrotic apoptosis in its absence, suggesting that the link between apoptosis and necrosis has been established through caspase-8 at this time. In addition to general summaries of several different forms and mechanisms of death, there are also articles addressing the changes that occur in the plasma membrane during programmed death, programmed death inflammation, and infection that have a high citation frequency. These articles provide important references for further studies on the pathways and molecules of cell death, including apoptosis, focal necrosis, and other forms of death.

Table 2: Top 10 countries, co-cited countries and institutions analysis

Rank	Country	Count	Percentage	Co-Country	Count	Percentage	Degree	Affiliations	Count	Percentage
1	China	130	34.9%	Usa	22	34.4%	7	St Jude Children S Research Hospital	34	9.1%
2	USA	126	33.8%	China	17	26.6%	4	League Of European Research Universities Leru	22	5.9%

3	Germany	38	10.2%	Germany	6	9.4%	4	Central South University	17	4.5%
4	Australia	27	7.2%	Australia	4	6.3%	5	Institute National De La Sante Et De La Recherche Medicale Inserm	16	4.3%
5	France	20	5.3%	Belgium	2	3.1%	2	University Of Melbourne	15	4.0%
6	Japan	19	5.1%	Greece	1	1.6%	3	Chinese Academy Of Sciences	14	3.7%
7	England	17	4.5%	Pakistan	1	1.6%	2	Udice French Research Universities	12	3.2%
8	Spain	12	3.2%	Ukraine	1	1.6%	2	Walter Eliza Hall Institute	12	3.2%
9	Belgium	11	2.9%	Hungary	1	1.6%	2	Flanders Institute For Biotechnology Vib	9	2.4%
10	India	10	2.6%	France	1	1.6%	1	Ghent University	9	2.4%

Table 3: Analysis of the number of journal articles and co-citations

Journal	Count	IF	JCR	Journal	Citation	IF	JCR
Cell Death and Differentiation	14	12.067	Q1	Nature	440	69.504	Q1
Cell Death & Disease	14	9.685	Q1	Cell	285	66.85	Q1
Frontiers in Immunology	13	8.786	Q1	Proceedings Of the National	240	12.779	Q1
International Journal of Molecular Sciences	11	6.208	Q2	Cell Death and Differentiation	178	12.067	Q1
Frontiers In Cell and Developmental Biology	8	6.081	Q2	International Journal of Radiation Oncology Biology Physics	160	8.013	Q2
Cells	6	7.666	Q1	Science	160	63.714	Q1
Viruses Basel	6	5.818	Q2	Immunity	158	43.474	Q1
Cell	5	66.85	Q1	Immunology	137	7.215	Q2
Cell Death Discovery	5	7.109	Q2	Journal of Experimental Medicine	118	17.579	Q1

Analysis of co-cited literature

Co-citations were defined as two or more articles being cited by one or more papers at the same time according to the references, and a co-citation study is used to measure the degree of association between articles. Among the 370 co-cited articles retrieved, the top 10 co-cited articles are listed in Table 4, with the most frequently cited article is "Caspase-11 cleavage of gasdermin D for non-classical inflammasome signaling", TAK1 restricts spontaneous NLRP3 activation and cell death to control myeloid proliferation and "Pathogen blockade of TAK1 triggers caspase-8 dependent cleavage of gasdermin D and cell death". Degree Centrality is the most direct measure of node centrality in network analysis. The greater the node degree of a node (the more nodes connected to it) means the higher the degree of centrality of the node and the more important the node is in the network. "Caspase-11 cleavage of gasdermin D for non-classical inflammasome signaling" and "TAK1 restricts spontaneous NLRP3 activation and cell death to control myeloid proliferation", we can observe that both of these references have high degrees, indicating that they have high reference values. "Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death" has the highest degree, it means the findings of this article have important linkages in the findings of three PCD ways.

Tabel 4: Analysis of TOP 10 cited reference and

Rank	Title	Authors	Degree	Journal	Publication Year	DOI
1	Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling	Kayagaki N	29	Nature	2015	10.1038/nature 15541
2	TAK1 restricts spontaneous NLRP3 activation and cell death to control myeloid proliferation	Malireddi RKS	26	J Exp Med	2018	10.1084/jem. 20171922
3	Pathogen blockade of TAK1 triggers caspase-8 dependent cleavage of Gasdermin D and cell death	Orning P	9	Science	2018	10.1126/science. aau2818
4	Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death.	Shi J	31	Nature	2015	10.1038/nature 15514
5	ZBP1/DAI is an innate sensor of influenza virus triggering the NLRP3 inflammasome and programmed cell death pathways.	Kuriakose T	11	Sci Immunol	2016	10.1126/ sciimmuno l.aag2045
6	Caspase-8 induces cleavage of gasdermin D to elicit pyroptosis during Yersinia infection	Sarhan J	22	P Natl Acad Sci Usa	2018	10.1073/ pnas.1809548115
7	ZBP1 and TAK1: Master Regulators of NLRP3 Inflammasome/Pyroptosis, Apoptosis, and Necroptosis (PAN-optosis).	Malireddi R	21	Front Cell Infect Mi	2019	10.3389/ fcimb.2019.00406
8	Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin.	Wang Y	17	Nature	2017	10.1038/nature 22393
9	Caspase-6 Is a Key Regulator of Innate Immunity, Inflammasome Activation, and Host Defense.[13]	Zheng M	16	Cell	2020	10.1016/j. cell.2020.03.040
10	RIPK1 inhibits ZBP1-driven necroptosis during development.	Newton K	20	NATURE	2016	10.1038/nature 20559

Keyword analysis

The co-occurrence of keywords provides an understanding of the research hotspots and research directions in the field. We extracted 112 keywords with VOSviewer. Because negative-stranded RNA virus, positive-strand RNA virus are all studies on RNA virus, we combined these words. The keyword density graph (Figure 6A) visually shows these high-frequency keywords and the graph that the yellow highlighted areas are the words that have a high frequency. As shown in Figure 5B, we extracted the words with a high frequency of keyword occurrences, it includes pyroptosis, necroptosis, apoptosis, PANoptosis, caspase-8, inflammasome, caspase-1 panoptosome, and ripk3. Since our search strategy included thermal apoptosis, necrosis, apoptosis, and PANoptosis, it is normal for these four keywords to appear more frequently, and the remaining keywords indicate research hotspots related to three PCD ways. We performed a network clustering analysis of these keywords using VOSviewer. Cluster analysis was conducted on the basis of keywords, and finally, nine color clusters were formed (Figure 7), representing the nine research directions and research areas. The largest cluster is cluster 1 (red), followed by cluster 2 (green), cluster 3 (blue), cluster 4 (yellow), cluster 5 (dark purple), cluster 6 (light blue) cluster 7 (orange), cluster 8 (reddish-brown) and cluster 9 (light purple).

Cluster 1 has 20 keywords, including ASC, burkholderia thailandensis, caspase-1, caspase-11, caspase-3, caspase-7, caspase-8, cell fusion, gasdermin d, gasdermin e, mitochondria, MLKL, NLRP3, PANoptosome, RIPKl, RIPK3, t6ss, type six secretion system, vgrg5, virulence. Cluster 2 has 20 keywords including anticancer immunity, astragaloside-iv, bimetallic nanoparticles, cancer, cd4+, cells, cerebral, ischemia, reperfusion, combination, ferroptosis, gold, hiv, humanized, mice, molecular, mechanism, necroptosis, osteoarthritis, panax, notoginseng, saponions, phosphorylation, pyroptosis, signal pathway. Cluster 3 had 12 keywords including aspergillus fumigatus, candida albicans, coronavirus, fungi, host defense, infectious diesease, infectious disease, influenza, influenza virus, microbiology, mouse hepatitis virus, rna virus. Cluster 4 has 11 keywords, including apoptosis, apoptotic bodies, apoptotic cell disease, autophagy, cell clearance, efferocytosis, necrosis, netosis, phagocytosis, rheumatoid, arthritis, therapy-resistant, tumors. Cluster 5 has 10 keywords including brain, central nervous system, ischemia/reperfusion, middle cerebral artery, non-apoptotic regulated cell death, oral infectious diseases, oral microbiomes, oxygen and glucose deprivation, PANoptosis, regulated cell death. Cluster 6 has 10 items and contains keywords cell death switch, immunotherapy, inflammasome, inflammation, innate immunity, non-apoptotic programmed cell death, survival, TLR priming, virus infection, ZBP1. Cluster 7 has 8 items and contains immunology, mechanism, membrane pore, morphology, and plasma membrane. Cluster 8 has 8 items containing keywords such as macrophages, myeloid cells, pathogens, and proteolysis. Cluster 9 has 8 items and contains keywords such as irf8, naip, nlr, nlrc4, and nod-like receptors. In addition, we also obtained a keyword network with PANoptosis as the central node. This network can be observed to be composed of clusters of 4 main colors. The main cluster is among cluster 1, it contains caspase-1, caspase-11, caspase-3, caspase-7, caspase-8, gasdermin d, gasdermine, mitochondria, mlkl, nirp3, panoptosome, ripkl, ripk3, t6ss, vgrg5, virulence. The next cluster contains infectious diesease, infectious disease, influenza, influenza virus, microbiology, mouse hepatitis virus, rna virus. The third cluster has central nervous system, brain, oral infectious diseases, oral microbiomes, oxygen, and glucose deprivation. While certain representative terms, such as pyroptosis, necroptosis, apoptosis, and programmed cell death, also appear in the network.

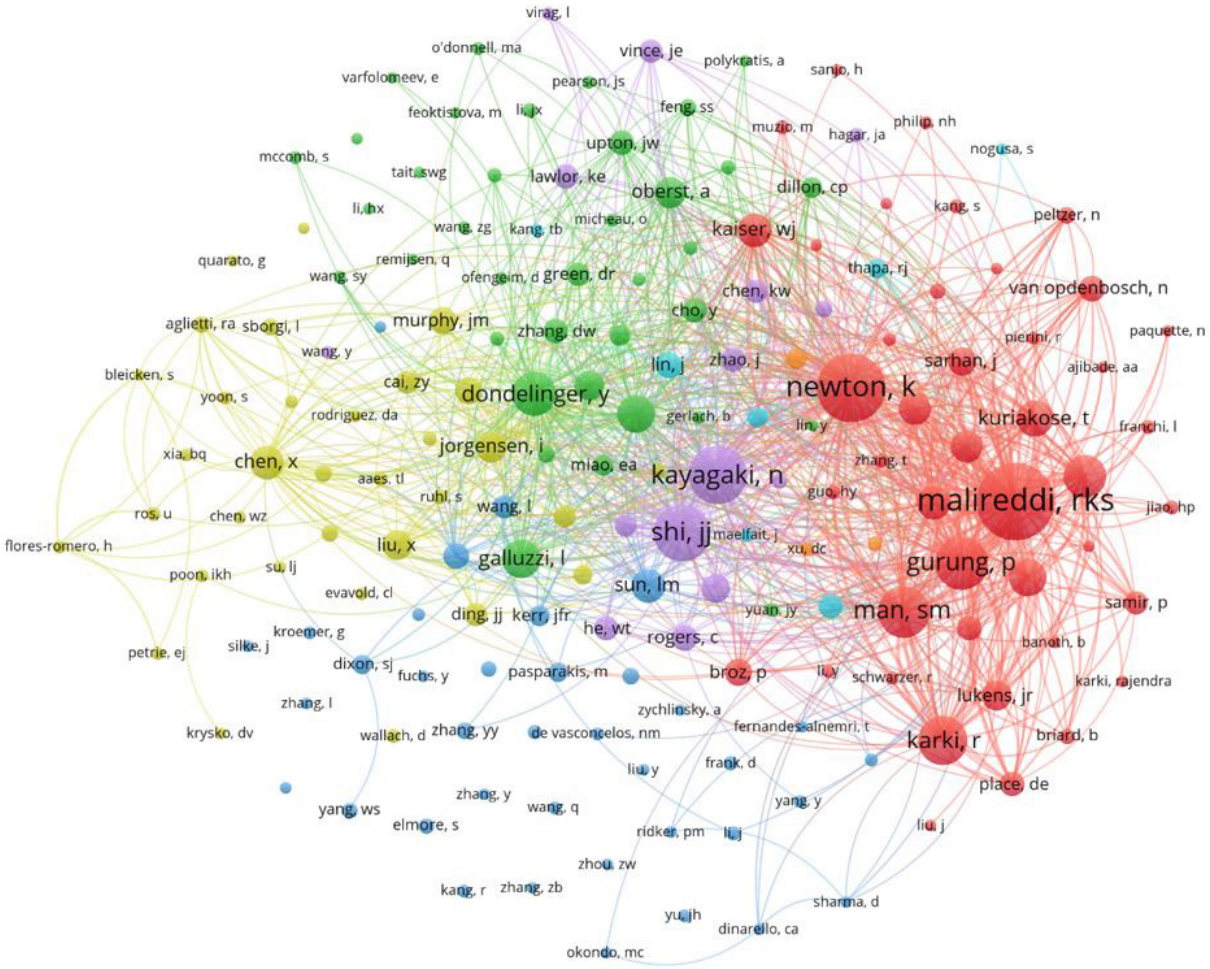

Figure 5: Author co-occurrence analysis of the literature we obtained by VOSviewer. (Minimum number of documents of an author > 1)

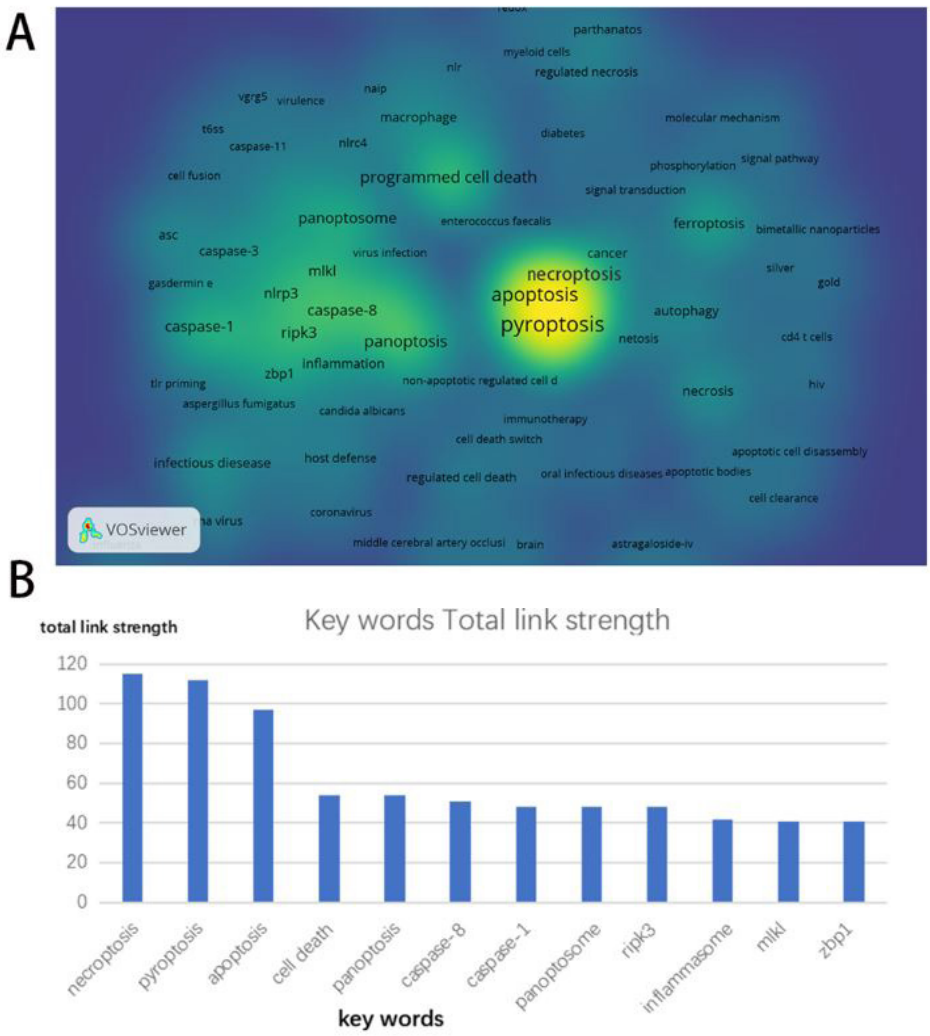

Figure 6 A: VOSviewer visualization map of keywords density graph.

B. The top 12 keywords in keywords occurrence frequency

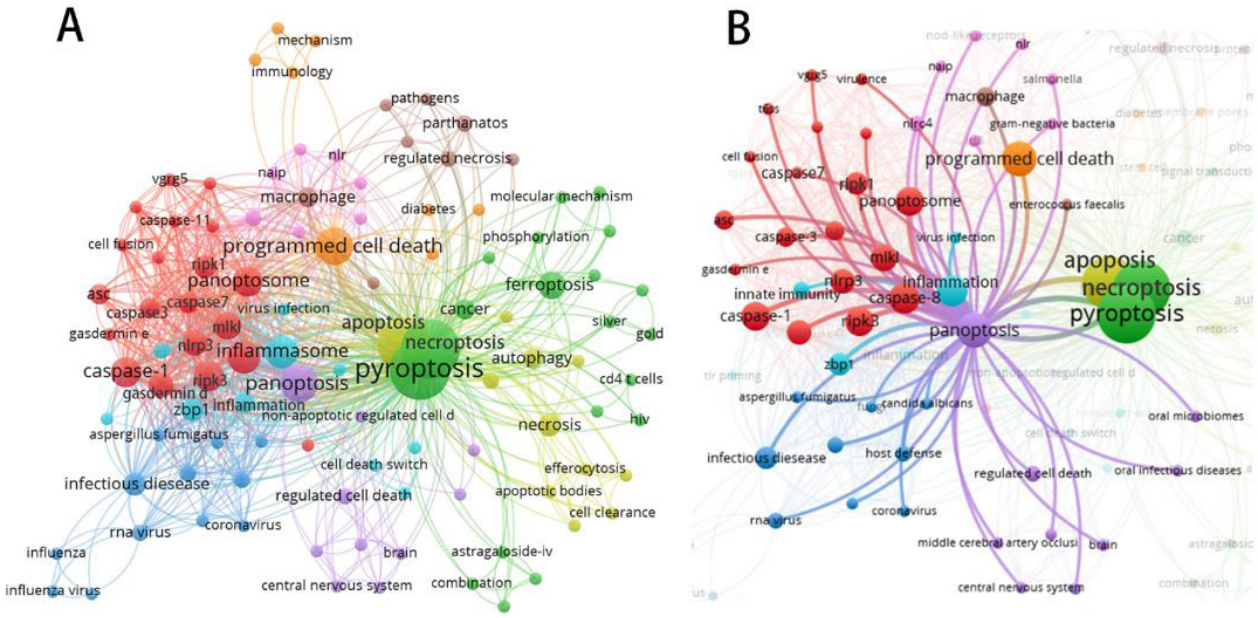

Figure 7: VOSviewer visualization map of keywords clustering analysis related to PANoptosis

Top 10 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2009 - 2022
Galluzzi L, 2012, CELL DEATH DIFFER, V19, P107, DOI 10.1038/cdd.2011.96, DOI	2012	9.01	2013	2016	
Sun L, 2012, CELL, V148, P213, DOI 10.1016/j.cell.2011.11.031, DOI	2012	11.97	2014	2017	
Murphy J, 2013, IMMUNITY, V39, P443, DOI 10.1016/j.immuni.2013.06.018, DOI	2013	9.07	2014	2018	
Kaczmarek A, 2013, IMMUNITY, V38, P209, DOI 10.1016/j.immuni.2013.02.003, DOI	2013	7	2014	2018	
Vanden B, 2014, NAT REV MOL CELL BIO, V15, P134, DOI 10.1038/nrm3737, DOI	2014	8.8	2015	2019	
Wang H, 2014, MOL CELL, V54, P133, DOI 10.1016/j.molcel.2014.03.003, DOI	2014	10.85	2016	2019	
Dondelinger Y, 2014, CELL REP, V7, P971, DOI 10.1016/j.celrep.2014.04.026, DOI	2014	8.03	2016	2019	
Shi J, 2015, NATURE, V526, P660, DOI 10.1038/nature15514, DOI	2015	7.81	2016	2020	
Kayagaki N, 2015, NATURE, V526, P666, DOI 10.1038/nature15541, DOI	2015	7.37	2016	2020	
Shi J, 2014, NATURE, V514, P187, DOI 10.1038/nature13683, DOI	2014	7.33	2016	2019	

Figure 8: Top 10 keywords with the strongest citation bursts

The keyword burst graph (Figure 6) by CiteSpace provides a clear view of emerging keywords and topics in relation to trends over time, predicts the direction of cutting-edge research, and reveals emerging research directions. The red segment on the blue timeline indicated the burst duration. From 2014-2018, the fields of protein, mixed lineage, and tumor necrosis factor were cited with higher heat and longer duration years. Programmed cell death was the keyword with the highest burst intensity among the burst terms, with strong bursts in 2015-2018. Rip1 kinase, captoror interaction protein, gasdmermin d, and apoptoc cells also had varying degrees of bursts. In the last two years, inflammasome and nlrp3 have been the hot spots of attention and research in the field of the research of three classical PCD ways.

Timeline viewer (Figure 9) by CiteSpace is based on the interaction and mutation relationship between keywords in a certain field, through the distribution and connection of different clustering keywords on the timeline, we can see the development process of PANoptosis more intuitively. From 2014 to 2016, the research focused on the essential proteins in programmed cell death, the main words are programmed necrosis (necroptosis), domain like protein, rip1 kinase, activation, autophagy, and mixed lineaged kinase. From 2016 to 2019, the research focused on several modes of death and their key proteins, the main words are nlrp3 inflammasome, pyroptosis, gasdermin d, serine protease, mixed lineage kinase, necroptosis. The number of keywords in the main research has significantly increased between 2019 and 2022. The most typical keywords are those that relate to mechanisms, such as innate, aim 2 inflammasome, caspase-1, caspase-3, cd4 t cell, and fas-induced apoptosis, as well as diseases, such as cancer, collagen-induced arthritis and i/r injury.

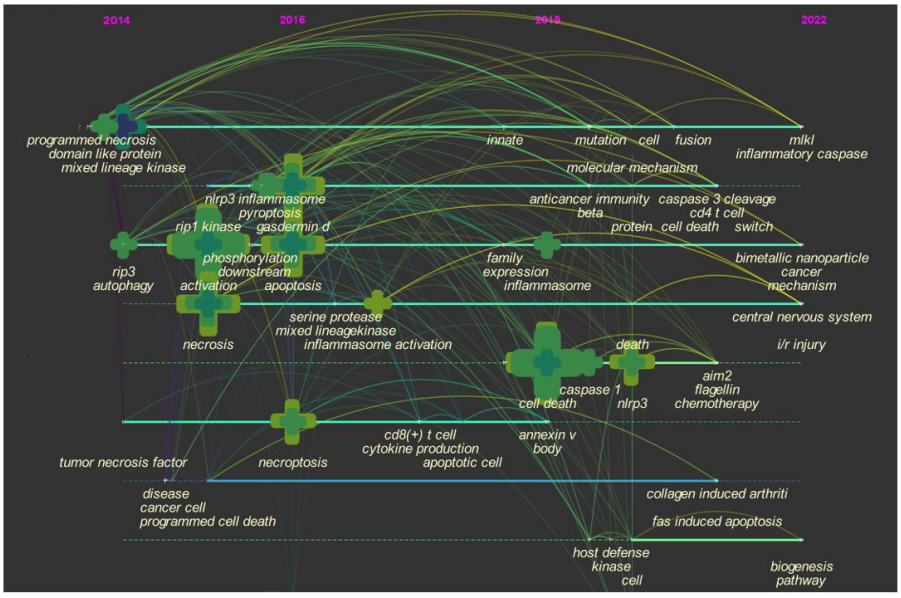

Figure 9: CiteSpace visualization map of timeline viewer related to PANoptosis

Discussion

General Information

The yearly number of documents can also reflect the extent of global scholarly interest in this field. It shows that the total number of publications is rising. From 2014 to 2018, the amount of relevant literature is rising at a slow rate (Figure 2). In particular, after 2019, the amount of literature showed steady growth. It might be because, in 2019, the concept of PANoptosis was formally introduced and the innate immune sensor ZBP1 and the essential cell survival kinase TAK1 were presented to play an important regulatory role in PANoptosis [26], since then, the number of PANoptosis studies has increased dramatically. It is worth noting that the number of publications in the literature on PANoptosis exceeded one hundred in 2021, it reflects that the research related to PANoptosis is in the hot study direction these two years and has a grateful development trend in the future.

Table 1 shows the distribution of countries, co-cited countries, and institutions analysis. USA has the highest number of publications, which means the USA is the leading countries PANoptosis research. Degree centrality is the most direct measure of node centrality in network analysis. Analyzing the node degree is important to help understand the importance of nodes in the network. We can see USA (degree 7) has the highest degree in the top 10 co-cited countries, which means it acted as a bridge in connecting the worldwide network and played an important role. Meanwhile, Australia (degree 5), China (degree 4) and Germany (degree 4) have a higher degree, suggesting that they also have some impact on the cooperation. Generally, 370 published papers came from 51 different countries, but the cooperation between 51 countries does not have strong country-to-country ties (Figure 3). Therefore, there is necessary for the USA to strengthen cooperation and linkages with institutions in other countries to promote the progress in the research of PANoptosis.

After the analysis of authors and co-cited authors, Kanneganti TD (n =25) has the highest number of publications, followed by Malireddi RKS (n =12), Karki R (n =10), Green Dr (n =8), Linkermann A (n =8). It is noteworthy that Kanneganti TD was rewarded as the most highly cited researcher in the world (Clarivates/Web of Science) in 2020 and 2019. She has been devoted to understanding how the innate immune system, as a founding member of the inflammasome field, she and her lab pioneered the concept of PANoptosis and describe its implications in health and disease. In the research she led, she and her team member Teneema Kuriakose published in 2016 that the ZBP1-mediated expression of NP and PB1 was confirmed, and the RIPK1-RIPK3-Caspase-8 axis was used to induce cell death and inflammatory responses, formally linking pyroptosis, apoptosis (key component caspase-8) and necroptosis (key components RIPK1, RIPK3) [18]. This study was the first to identify ZBP1 as an innate immune sensor that can activate molecules from pyroptosis, apoptosis, and necroptosis. After this discovery, people began to seek more evidence for the occurrence of PANoptosis and continue to contribute to the construction of its molecular mechanism. Malireddi, R.K. is the highest co-cited author (Total link strength =2992), Newton K is as followed (Total link strength =2860), they all have close cooperation or affiliation with the Kanneganti TD team.

Table 3 shows journals and co-cited journals, the journal with the most articles about PANoptosis was Cell Death and Differentiation (IF =12.067), followed by Cell death & Disease (IF =9.685), Frontiers in Immunology (IF =8.786). In addition, the three journals with the highest co-citation frequencies were Nature (IF =69.504), Cell (IF =66.85) and P Natl Acad Sci USA (IF =12.779). Journals among the top ten co-cited almost belong to Q1, which are all high-impact journals, showing the attention and importance of PANoptosis in important international journals.

Table 5 shows the top 10 co-cited references we acquired, half of the literature is about the protein GSDMD and the other half is about the two Master Regulators ZBP1 and TAK1. Kayagaki N's research [27], which is the most co-cited one, The main description of the process of pyroptosis: GSDMD as a rigorous target of caspase-11. Malireddi RKS research [28] is the second co-cited, they identified a critical role for TAK1 in NLRP3 inflammasome quiescence and maintenance of cellular homeostasis and survival, providing additional important evidence for the cross-linking of apoptosis and necrosis l. Pontus Orning's research [29] is the third most cited article in total, TAK1 inhibition induces GSDMD-dependent cleavage of RIPK1 and caspase-8, a finding that serves as important experimental evidence for PANoptosis cross-linking. The 4th co-cited research by Shi J [30] found that the specific cleavage of GSDMD in Caspase-1/-4/-5/-11 provides an important experimental basis for re-understanding and redefining scorch death. Kuriakose T's reference [18] is the first study of simultaneous cross-linking of apoptosis, necroptosis, and pyroptosis, and the first biological evidence of PANoptosis. Up to date, ZBP1 and TAK1 are two identified molecules that can under specific stimuli molecules that trigger a response to PANoptosome assembly [26], AIM2

has also been found to play an important role in regulating pyrin and ZBP1 to drive the onset of PANoptosis [31]. Understanding the pathways and modes of action of ZBP1 and RIPK1 in PANoptosis is significant for understanding PANoptosis.

Table5: Analysis of the TOP 10 co-cited references

Rank	Title	Authors	Degree	Journal	Publication Year	DOI
1	Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling	Kayagaki N	29	Nature	2015	10.1038/nature15541
2	TAK1 restricts spontaneous NLRP3 activation and cell death to control myeloid proliferation	Malireddi RKS	26	J Exp Med	2018	10.1084/jem.20171922
3	Pathogen blockade of TAK1 triggers caspase-8 dependent cleavage of Gasdermin D and cell death	Orning P	9	Science	2018	10.1126/science.aau2818
4	Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death.	Shi J	31	Nature	2015	10.1038/nature15514
5	ZBP1/DAI is an innate sensor of influenza virus triggering the NLRP3 inflammasome and programmed cell death pathways.	Kuriakose T	11	Sci Immunol	2016	10.1126/sciimmunol.aag2045
6	Caspase-8 induces cleavage of gasdermin D to elicit pyroptosis during Yersinia infection	Sarhan J	22	P Natl Acad Sci Usa	2018	10.1073/pnas.1809548115
7	ZBP1 and TAK1: Master Regulators of NLRP3 Inflammasome/Pyroptosis, Apoptosis, and Necroptosis (PAN-optosis).	Malireddi R	21	Front Cell Infect Mi	2019	10.3389/fcimb.2019.00406
8	Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin.	Wang Y	17	Nature	2017	10.1038/nature22393
9	Caspase-6 Is a Key Regulator of Innate Immunity, Inflammasome Activation, and Host Defense.[13]	Zheng M	16	Cell	2020	10.1016/j.cell.2020.03.040
10	RIPK1 inhibits ZBP1-driven necroptosis during development.	Newton K	20	NATURE	2016	10.1038/nature20559

The Hotspots and Frontiers

Based on the co-occurrence analysis of keywords in the literature, including hotspot density map, clustering map, timeline map, and burst map, the research hotspots and directions of PANoptosis and three PCD pathways cross-linking are visualized. Cluster analysis was conducted on the basis of keywords, and nine colored clusters represent the nine research directions and research areas. We get the following hints from the information in the picture above:

Hot vocabulary interpretation

Figure 6 shows 10 keywords with high occurrence frequency: pyroptosis, necroptosis, apoptosis, PANoptosis, caspase-8, inflammasome, caspase-1, Panopto some, and ripk3. These 10 keywords are the current hot spots and directions of PANoptosis and its related research. Pyroptosis now considered to be caspase-1 or caspase-11/4/5 induced, then performed molecularly GSDMD was cleaved, and the N-terminal domain can oligomerize to form pores in the cell membrane, inducing cell membrane rupture [11,20]. Caspase8 which acts as a typical protein that needs to be activated during apoptosis, was found to regulate NLRP3 inflammasome activation in 2014, and it was found to suppresse necroptosis mediated by the kinase RIPK3 and the pseudokinase MLKL [4,32,33]. Caspase-3/-7 specifically block pyroptosis by cleaving GSDMD at a distinct site from the inflammatory caspases [34].

Necroptosis has both passive and active pro-inflammatory functions, it can detect pathogens and promote tissue repair, while can be activated when apoptosis was inhibited. When some death receptors like Fas /Fas ligand (FasL), 4 Toll-like receptors (TLR4 and TLR3), and cytosolic nucleic acid sensors such as RIG-I and STING were active, type I interferon (IFN-I) and TNFα generate effects and promote necroptosis. Caspase-8 was in response to pharmacological, RIPK1 and RIPK3 can interact with each other through their RIP homotypic interaction motif (RHIM) and form the necrosome, a cytosolic complex. Pseudo-kinase mixed lineage kinase domain-like (MLKL) was phosphorylated by necrosome and activated MLKL plays a corresponding role in mediating cell death [35-38].

As the earliest and the most well-studied form of cell death, apoptosis was originally considered immunologically silent, and was thought to be the only way to die procedurally, played a major role in the homeostatic development of eukaryotes and prokaryotes. Two ways: extrinsic or intrinsic pathways can both initiate apoptosis. Signals from outside the cell initiate the extrinsic pathway, like Fas L, TNF, and TNF-related apoptosis-inducing ligand (TRAIL), fas-associated death domain (FADD), and pro-caspase-8, through homotypic interactions, activate caspase-8 and produces apoptosis-related cellular effects [39]. Intrinsic apoptosis was derived by caspase-9/-3/-7. cytochrome C bind to the apoptotic peptidase activated factor 1 (APAF1) in the cytoplasm prompts apoptosome formation, leading to the activation of initiator caspase-9 to induce activation of caspases-3/-7 to drive intrinsic apoptosis [5].

NOD-like receptor Protein 3 (NLRP3) inflammasome activation leads to the secretion of cytokines, IL-1β and IL-18, and induction of pyroptosis [40]. TAK1 activation drives RIPK3-dependent necroptosis and inhibits apoptosis. TAK1 acts as a switch between apoptosis and necroptosis [41]. In recent years, the lack of TAK1 in macrophages has been found to induce spontaneous activation of NLRP3 inflammatory vesicles without toll-like receptor (TLR) initiation and subsequent activation signals, thus cross-linking pyroptosis, apoptosis, and necroptosis [21,28].

PANoptosome assembling and envisioning

PANoptosome is the main part that performs PANoptosis [42]. In different microbial infections, different proximal sensor molecule(s) can activate the protein complexes named the PANoptosome. PANoptosome is a mechanism of action that can induce pyroptosis (e.g. ASC and caspase-1), apoptosis (caspase-8), and necroptosis (RIPK3, RIPK1) [19]. In the course of IVA infection, the molecular mechanism of PANoptosis has been largely established, so it is the most established model of PANoptosis. In this model, the sensor of IAV is ZBP1, which acts as a master regulator of cell death during IAV infection. ZBP1 contains an RHIM domain to mediate cell death and also a Zα domain which binds Z-nucleic acids. Currently, it is widely known that pyroptosis, apoptosis, and necroptosis are induced by inflammasomes, apoptosomes and necrosomes. In inflam-

masomes, sensors (such as NLRP3, AIM2, or Pyrin), the adaptor protein ASC and CASP1 can be assembled together through PYD-PYD or CARD-CARD interactions. In apoptosome, death receptors (such as Fas) and adaptor protein (such as FADD) interact by a DD domain, CASP8, FADD and pro-CASP8 through DED-DED interactions forms complex-II in the cytosol and leads to the initiation of extrinsic apoptosis [5]. Necrosomes are formed when RIPK3 and RIPK1 through RHIM-RHIM combined and CASP8 activity is inhibited [38,42,45]. ZBP1 binds IAV viral ribonucleoproteins (vRNPs) and through RHIM forms a complex called the ZBP1-dependent PANoptosome consisting of RIPK3, RIPK1, caspase-6, caspase-8, ASC, NLRP3, and caspase-1 [18,45]. RIPK1 having the RHIM domain, also has the chance to act as the center of the PANoptosome [46]. Similarly, a protein TRIF, which also contains the RHIM structural domain, could act on RIPK1 and RIPK3. RIPK1 and RIPK3 possibly interact with and induce PANoptosis. This assumption has been confirmed after TLR3 activation and cystathionin inhibition [47].

So far, ZBP1 and RIPK1 as two upstream molecules have been identified. In some specific stimuli, they can trigger the assembly of the PANoptosome. Current models of ZBP1 PANoptosome assembly during IAV infection are centered on known homotypic/heterotypic interaction (such as RHIM, DD, DED, PYD, and CARD). These intermolecular interactions may be responsible for PANoptosome skeleton formation.

Therefore, at present, the assembly mechanism of PANoptosome mainly relies on the hypothesis and experimental proof by researchers, and the homotypic and heterotypic structural interactions among three PCD pathways (e. g. RHIM, DD, CARD) will become the theoretical support and important development direction and hot spot for the assembly mechanism of PANoptosome.

PANoptosis and disease

Although IAV was the first infection found to trigger PANoptosis. The role of viruses such as MHV and SARS-CoV-2 in triggering PANoptosis has also been reported in recent years [21,48], besides cross-linking between the three PCD pathways had been found in Vesicular stomatitis virus, Vaccinia virus, Respiratory syncytial virus and the possibility of PANoptosis during their infection should be a concern [49]. A mature model of bacterial infection PANoptosis is in Yersinia infection, with its effector YopJ inhibiting TAK1. The role of Salmonella typhi and Listeria monocytogenes in triggering PANoptosis has been reported also. However, in bacterial infections, scholars have focused more on the cross-linking of pyroptosis and apoptosis, whether necrosis also exists with the cross-linking of pyroptosis and apoptosis leading to PANoptosis is less studied de part in the study of bacterial infections. Fungi, one of the three major pathogen types that infect hosts, have also been shown to trigger PANoptosisb [42].

PANoptosis is a form of inflammatory programmed death that induces inflammation and blocks intracellular signaling of pathogens and becomes an important component of the body's immune defense [17]. in Burkholderia infections,-PANoptosis-deficient mice have a higher mortality rate than pyroptosis-deficient mice, which reflected an important role of PANoptosis in limiting the virulence of pathogens [50]. MCMV-encoded viral inhibitor of RIP activation (vIRA) contains RHIM domain, that can target ZBP1, RIPK3, and RIPK1 to restrict PANoptosome formation to Inhibit PANoptosis [51]. This suggests that although PANoptosis was seen as an evolved model of death, there are still pathogens that can manipulate the PANoptosis pathway to evade the host's immune effect on them.

It has been found that the presence of markers of cell scorching, apoptosis, and necrotizing apoptosis are present in inflammatory cells recruited in the airways after STING agonist activation in mice. This predicts the feasibility of PANoptosis activation by STING as a therapeutic strategy for local cancer metastasis or infection [52]. In addition, PANoptosis can be found to be applicable in tumor treatment. During the treatment of melanoma, combining interferons (IFNs) and nuclear export inhibitors (NEIs) can activate ZBP1-dependent pyroptosis, apoptosis, and necroptosis (PANoptosis) in melanoma cells, limiting tumor growth and development [53]. The roles in infection, autoinflammatory disease, inflammation and cancer are widely followed, PANoptosome components may implicate in many other pathophysiological settings through cell death. For example, many central nervous system diseases involve the death of nerve cells, so the phenomenon of PANoptosis in cerebral ischemia has been noticed by scholars [54]. Exploring and discovering the case physiological mechanism of PANoptosis in other diseases and understanding the application of programmed death in various diseases in a systematic and diversified way will be beneficial to providing a molecular basis and therapeutic direction for disease targeting.

Future perspectives

Host-pathogen struggle determines disease progression and regression, bacteria are constantly adapting to their hosts and developing new virulence strategies, while new ways of dying have been evolved by the hosts to better defend themselves immunologically [22]. Therefore, a new cell death pathway presented with the stronger mechanistic activity would provide a higher chance of eliminating infected cells and play an important role in the innate immune defense. During infection, microbial components can target the PANoptosis pathway, leading to cell death [17]. This plasticity in the activation of the PANoptosis is mediated by the PANoptosome, in which blocking key molecules from pyroptosis, apoptosis, or necroptosis alone cannot stop cell death. Thus, PANoptosis arose from the evolution of pathogens towards a better strategy of resistance to the virulence of pathogens. While, identifying specific upstream sensor molecules (e.g., ZBP1) to clarify the involvement of PANoptosis in disease pathogenesis is currently an important direction for molecular targeting of diseases. Comparing the large figure containing the three PCD pathways to the small figure with PANoptosis in Figure 7, we see clear overlap with a large portion of non-overlap. The non-overlapping part represents all the keywords shown in the three PCD cross-linking processes and may contain the future direction of PANoptosis. So, revisiting the occurrence of PANoptosis in pathogenic infections, cancer, and other diseases involving cell death, and identifying key sensing factors to provide an important basis for targeting disease therapy will be the future development hotspots and research directions in the field of PANoptosis.

Limitation

The following are the limitations of this study. Firstly, the information retrieved only in the WoSCC database does not fully reflect the existing information in the field. Secondly, the WoSCC database is continuously updated and non-English citations were removed, and we only analyzed literature selected with a screening strategy up to March 30, 2022. Finally, since studies related to the intersection of the three death modes of scorching, apoptosis, and necrosis have been in progress, and the biological event of simultaneous occurrence of the three is defined as PANoptosis is lagging behind, we included scorching apoptosis necrosis as a key search term in the keyword search. However, at the same time, although the completely irrelevant part of the literature was manually eliminated, the less relevant parts were still visible in the keyword display chart, reducing the overall suggestiveness of the chart.

Conclusion

The research of PANoptosis will continue to be the hotspot. Several outstanding scientists have emerged who are steadily moving the field forward. Closer national and inter-institutional communication and cooperation may facilitate the flourishing of PANoptosis. The focus of current research and developmental trends in the future are the related pathway mechanism of PANoptosis, the discovery, and the role of PANoptosis in various diseases.

Abbreviations

PCD: Programmed cell death

WoSCC: Web of Science Core Collection database

GSDMD: Gasdermin family protein D

GSDME: Gasdermin family protein E

USA: United States

IAV: influenza A virus

TAK1: transforming growth factor-β-activated kinase 1

RIPK3: receptor-interacting serine/threonine-protein kinase 3

MLKL: mixed lineage kinase domain-like pseudo kinase

ZBP1: Z-DNA-binding protein 1

RHIM: RIP homotypic interaction motif

FADD: fas-associated death domain

TRAI: TNF-related apoptosis-inducing ligand

IKK: IκB kinase

TLR: toll-like receptor

Disclosure

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References

1. Ameisen JC (2002) On the origin, evolution, and nature of programmed cell death: a timeline of four billion years. Cell death and differentiation 9: 367-93.

2. Galluzzi L, Vitale I, Aaronson SA et al. (2018) Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell death and differentiation 25: 486-541.

3. Kerr JF, Wyllie AH, Currie AR (1972) Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. British journal of cancer 26: 239-57.

4. Kruidering M, Evan GI (2000) Caspase-8 in apoptosis: the beginning of "the end"? IUBMB life 50: 85-90.

5. Li P, Nijhawan D, Budihardjo I et al. (1997) Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade. Cell 91: 479-89.

6. Kroemer G, Galluzzi L, Vandenabeele P et al. (2009) Classification of cell death: recommendations of the Nomenclature Committee on Cell Death 2009. Cell death and differentiation 16: 3-11.

7. Wang J, Zheng L, Lobito A et al. (1999) Inherited human Caspase 10 mutations underlie defective lymphocyte and dendritic cell apoptosis in autoimmune lymphoproliferative syndrome type II. Cell 98: 47-58.

8. Cookson BT, Brennan MA (2001) Pro-inflammatory programmed cell death. Trends Microbiol 9: 113-4.

9. Rathinam VA, Fitzgerald KA (2016) Inflammasome Complexes: Emerging Mechanisms and Effector Functions. Cell 165: 792-800.

10. Shi J, Gao W, Shao F (2017) Pyroptosis: Gasdermin-Mediated Programmed Necrotic Cell Death. Trends in biochemical sciences 42: 245-54.

11. Zhang JY, Zhou B, Sun RY et al. (2021) The metabolite α-KG induces GSDMC-dependent pyroptosis through death receptor 6-activated caspase-8. Cell Res 31: 980-97.

12. Degterev A, Hitomi J, Germscheid M et al. (2008) Identification of RIP1 kinase as a specific cellular target of necrostatins. Nat Chem Biol 4: 313-21.

13. Cho YS, Challa S, Moquin D et al. (2009) Phosphorylation-driven assembly of the RIP1-RIP3 complex regulates programmed necrosis and virus-induced inflammation. Cell 137: 1112-23.

14. Liu Y, Liu T, Lei T et al. (2019) RIP1/RIP3-regulated necroptosis as a target for multifaceted disease therapy (Review). International journal of molecular medicine 44: 771-86.

15. Sun L, Wang H, Wang Z et al. (2012) Mixed lineage kinase domain-like protein mediates necrosis signaling downstream of RIP3 kinase. Cell 148: 213-27.

16. Koren E, Fuchs Y (2021) Modes of Regulated Cell Death in Cancer. Cancer Discov 11: 245-65.

17. Place DE, Lee S, Kanneganti TD (2021) PANoptosis in microbial infection. Curr Opin Microbiol 59: 42-9.

18. Kuriakose T, Man SM, Malireddi RK et al. (2016) ZBP1/DAI is an innate sensor of influenza virus triggering the NLRP3 inflammasome and programmed cell death pathways. Sci Immunol 1.

19. Samir P, Malireddi RKS, Kanneganti TD (2020) The PANoptosome: A Deadly Protein Complex Driving Pyroptosis, Apoptosis, and Necroptosis (PANoptosis). Front Cell Infect Microbiol 10: 238.

20. Malireddi RKS, Gurung P, Kesavardhana S et al. (2020) Innate immune priming in the absence of TAK1 drives RIPK1 kinase activity-independent pyroptosis, apoptosis, necroptosis, and inflammatory disease. J Exp Med 217.

21. Zheng M, Williams EP, Malireddi RKS et al. (2020) Impaired NLRP3 inflammasome activation/pyroptosis leads to robust inflammatory cell death via caspase-8/RIPK3 during coronavirus infection. J Biol Chem 295: 14040-52.

22. Lacey CA, Miao EA (2020) Programmed Cell Death in the Evolutionary Race against Bacterial Virulence Factors. Cold Spring Harb Perspect Biol 12.

23. Cooper ID (2015) Bibliometrics basics. J Med Libr Assoc 103: 217-8.

24. Gao Y, Wang Y, Zhai X et al. (2017) Publication trends of research on diabetes mellitus and T cells (1997-2016): A 20-year bibliometric study. PLoS One 12: e0184869.

25. Zhao J, Yu G, Cai M et al. (2018) Bibliometric analysis of global scientific activity on umbilical cord mesenchymal stem cells: a swiftly expanding and shifting focus. Stem Cell Res Ther 9: 32.

26. Malireddi RKS, Kesavardhana S, Kanneganti TD (2019) ZBP1 and TAK1: Master Regulators of NLRP3 Inflammasome/Pyroptosis, Apoptosis, and Necroptosis (PAN-optosis). Front Cell Infect Microbiol 9: 406.

27. Kayagaki N, Stowe IB, Lee BL et al. (2015) Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. Nature 526: 666-71.

28. Malireddi RKS, Gurung P, Mavuluri J et al. (2018) TAK1 restricts spontaneous NLRP3 activation and cell death to control myeloid proliferation. J Exp Med 215: 1023-34.

29. Orning P, Weng D, Starheim K et al. (2018) Pathogen blockade of TAK1 triggers caspase-8-dependent cleavage of gasdermin D and cell death. Science 362: 1064-69.

30. Shi J, Zhao Y, Wang K, et al. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. Nature 526: 660-5.

31. Lee S, Karki R, Wang Y, Nguyen LN, Kalathur RC et al. (2021) AIM2 forms a complex with pyrin and ZBP1 to drive PANoptosis and host defence. Nature 597: 415-9.

32. Gurung P, Anand PK, Malireddi RK et al. (2014) FADD and caspase-8 mediate priming and activation of the canonical and noncanonical Nlrp3 inflammasomes. Journal of immunology (Baltimore, Md : 1950) 192: 1835-46.

33. Newton K, Wickliffe KE, Maltzman A et al. (2019) Activity of caspase-8 determines plasticity between cell death pathways. Nature 575: 679-82.

34. Taabazuing CY, Okondo MC, Bachovchin DA (2017) Pyroptosis and Apoptosis Pathways Engage in Bidirectional Crosstalk in Monocytes and Macrophages. Cell Chem Biol 24: 507-14. e504.

35. Bertheloot D, Latz E, Franklin BS (2021) Necroptosis, pyroptosis and apoptosis: an intricate game of cell death. Cell Mol Immunol 18: 1106-21.

36. Lalaoui N, Boyden SE, Oda H et al. (2020) Mutations that prevent caspase cleavage of RIPK1 cause autoinflammatory disease. Nature 577: 103-08.

37. Newton K, Wickliffe KE, Dugger DL et al. (2019) Cleavage of RIPK1 by caspase-8 is crucial for limiting apoptosis and necroptosis. Nature 574: 428-31.

38. Orozco S, Yatim N, Werner MR et al. (2014) RIPK1 both positively and negatively regulates RIPK3 oligomerization and necroptosis. Cell death and differentiation 21: 1511-21.

39. Dickens LS, Boyd RS, Jukes-Jones R et al. (2012) A death effector domain chain DISC model reveals a crucial role for caspase-8 chain assembly in mediating apoptotic cell death. Mol Cell 47: 291-305.

40. Sharma D, Kanneganti TD (2016) The cell biology of inflammasomes: Mechanisms of inflammasome activation and regulation. J Cell Biol 213: 617-29.

41. Morioka S, Broglie P, Omori E et al. (2014) TAK1 kinase switches cell fate from apoptosis to necrosis following TNF stimulation. J Cell Biol 204: 607-23.

42. Banoth B, Tuladhar S, Karki R et al. (2020) ZBP1 promotes fungi-induced inflammasome activation and pyroptosis, apoptosis, and necroptosis (PANoptosis). J Biol Chem 295: 18276-83.

43. Peterson LW, Philip NH, DeLaney A et al. (2017) RIPK1-dependent apoptosis bypasses pathogen blockade of innate signaling to promote immune defense. J Exp Med 214: 3171-82.

44. Vanden Berghe T, Hassannia B, Vandenabeele P (2016) An outline of necrosome triggers. Cell Mol Life Sci 73: 2137-52.

45. Zheng M, Karki R, Vogel P, Kanneganti TD (2020) Caspase-6 Is a Key Regulator of Innate Immunity, Inflammasome Activation, and Host Defense. Cell 181: 674-87. e613.

46. Malireddi RKS, Kesavardhana S, Karki R, Kancharana B, Burton AR et al. (2020) RIPK1 Distinctly Regulates Yersinia-Induced Inflammatory Cell Death, PANoptosis. Immunohorizons 4: 789-96.

47. Kaiser WJ, Sridharan H, Huang C et al. (2013) Toll-like receptor 3-mediated necrosis via TRIF, RIP3, and MLKL. J Biol Chem 288: 31268-79.

48. Karki R, Sharma BR, Tuladhar S et al. (2021) Synergism of TNF-α and IFN-γ Triggers Inflammatory Cell Death, Tissue Damage, and Mortality in SARS-CoV-2 Infection and Cytokine Shock Syndromes. Cell 184: 149-68. e117.

49. Wang Y, Kanneganti TD (2021) From pyroptosis, apoptosis and necroptosis to PANoptosis: A mechanistic compendium of programmed cell death pathways. Computational and structural biotechnology journal 19: 4641-57.

50. Place DE, Christgen S, Tuladhar S, Vogel P, Malireddi RKS et al. (2021) Hierarchical Cell Death Program Disrupts the Intracellular Niche Required for Burkholderia thailandensis Pathogenesis. mBio 12: e0105921.

51. Upton JW, Kaiser WJ, Mocarski ES (2019) DAI/ZBP1/DLM-1 Complexes with RIP3 to Mediate Virus-Induced Programmed Necrosis that Is Targeted by Murine Cytomegalovirus vIRA. Cell host & microbe 26: 564.

52. Messaoud-Nacer Y, Culerier E, Rose S et al. (2022) STING agonist diABZI induces PANoptosis and DNA mediated acute respiratory distress syndrome (ARDS). Cell death & disease 13: 269.

53. Karki R, Sundaram B, Sharma BR et al. (2021) ADAR1 restricts ZBP1-mediated immune response and PANoptosis to promote tumorigenesis. Cell reports 37: 109858.

54. Yan WT, Yang YD, Hu XM et al. (2022) Do pyroptosis, apoptosis, and necroptosis (PANoptosis) exist in cerebral ischemia? Evidence from cell and rodent studies. Neural regeneration research 17: 1761-8.