Necroptosis

Necroptosis is a new type of programmed cell death discovered in recent years, playing an important role in various diseases. Since it was conceptualized in 2005, research on necroptosis has developed rapidly. However, few bibliometric analyses have provided a comprehensive overview of the field.

Ma et al. aimed to employ a bibliometric analysis to assess necroptosis research's current status and hotspot, highlight landmark findings, and orientate future research. A total of 3993 publications from the WoSCC were collected for this study. Multiple tools were used for bibliometric analysis and data visualization, including an online website, VOSviewer, CiteSpace, and HistCite. Publications related to necroptosis have increased significantly annually, especially in the last 5 years. Globally, the USA and Harvard University are the most outstanding countries and institutions in this field, respectively. The academic groups managed by Peter Vandenabeele and Junying Yuan both have permanent and intensive research on necroptosis. Cell Death and Differentiation is the most vital journal in this field. The molecular mechanisms of necroptosis and its role in disease are the focus of current research, while the crosstalk between programmed cell death is an emerging direction in the field. The “reactive oxygen species”, “innate immunity”, and “programmed cell death” may be potential research hotspots. The results present a comprehensive knowledge map and explore research trends. Researchers and funding agencies on necroptosis can obtain helpful references from the study [1)]

In neurosurgery

- Barcoded viral tracing identifies immunosuppressive astrocyte-glioma interactions
- PANoptosis: Cross-Talk Among Apoptosis, Necroptosis, and Pyroptosis in Neurological Disorders
- Research progress of deubiquitinating enzymes in cerebral ischemia-reperfusion injury
- Multi-omics characterization of oncosis in spinal cord injury
- A PANoptosis-Based Signature for Survival and Immune Predication in Glioblastoma Multiforme
- ZBP1 senses splicing aberration through Z-RNA to promote cell death
- Serum RIPK1, Acute Lung Injury, and Outcomes in Severe Traumatic Brain Injury: A Multicenter Prospective Study
- Mitigating Early Phosphatidylserine Exposure in a Tmem30a-Dependent Way Ameliorates Neuronal Damages After Ischemic Stroke

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Necroptosis depends on receptor-interacting serine-threonine kinase 3 (RIPK3) and mixed lineage kinase domain-like (MLKL) and displays the morphological characteristics of necrosis.

The roles of necroptosis in ICH are still not fully known. Microglia cell is the type of immune cell, plays protective roles in nerve damage, and modulates the activity of neurons through secreting exosomes. Exosome-contained miRNAs are also involved in regulating neuronal activity. However, the roles and the mechanisms of microglia-secreted exosome miRNAs in ICH neuron necroptosis need to further explore.

In a study, ICH model was constructed in rats and cells. Injury of cells in the brain was detected by PI staining. Necroptosis in rats and cells was detected by western blot and flow cytometry. The expression of miR-383-3p was detected by RT-qPCR. The roles of activated microglia-secreted

exosomes and exosome-contained miR-383-3p were detected through co-culturing medium or exosomes with neurons. The target gene of miR-383-3p was determined by luciferase assay and the expression of the target gene was detected by western blot. Rescue experiments were used to confirm the mechanism of miR-383-3p in neuron necroptosis. The miR-383-3p role was verified in vivo through injecting miR-383-3p mimic into ICH rats. Here, we found that the necroptosis of neurons was increased in ICH rats through detecting the expression of RIP1 and RIP3 and PI staining. Microglia that activated by ICH promote neurons necroptosis through secreting exosomes and transferring miR-383-3p into neurons. In mechanism, miR-383-3p negatively regulated the expression of ATF4 and then promoted the necroptosis of neurons. Overall, the results provide a novel molecular basis to neurons necroptosis in ICH and may provide a new strategy to retard the secondary brain injury of ICH [2)].

A study aimed to investigate the RIPK3-mediated necroptosis and the effects of the RIPK3 selective inhibitor GSK'872 in early brain injury following SAH. After SAH, RIPK3 expression increased as early as 6 h and peaked at 72 h. Double immunofluorescence staining revealed that RIPK3 was mainly located in neurons. Most necrotic cells were neurons, which were further confirmed by TEM. Intracerebroventricular injection of GSK'872 (25 mM) could attenuate brain edema and improve neurological function following SAH and reduce the number of necrotic cells. In addition, GSK'872 could also decrease the protein levels of RIPK3 and MLKL, and cytoplasmic translocation and expression of HMGB1, an important pro-inflammatory protein. Taken together, the current study provides the new evidence that RIPK3-mediated necroptosis is involved in early brain injury and GSK'872 decreases the RIPK3-mediated necroptosis and subsequent cytoplasmic translocation and expression of HMGB1, as well as ameliorates brain edema and neurological deficits [3)].

Regulated by receptor interacting protein kinase 1 (RIP1) and RIP3 after death signal stimulation could be specifically inhibited by necrostatin 1.

RIP1/RIP3-mediated necroptosis is an important mechanism of cell death after intracerebral hemorrhage (ICH). Through inhibiting necroptosis, necrostatin-1 plays a protective role in reducing necrotic cell death after ICH. Necrostatin-1 is a promising therapeutic agent that protects cells from necroptosis and improves functional outcome [4)].

The cell death caused by shikonin in C6 and U87 glioma cells was mainly via necroptosis. Moreover, not only RIP-1 pathway, but also oxidative stress participated in the activation of shikonin induced necroptosis [5)].

Albeit specific molecular pathways involved in glioblastoma (Glioblastoma) necroptosis is not clear and much more studies are needed to confirm the effects of therapy-induced necroptosis on Glioblastoma, it provides us with a new direction in the treatment of Glioblastoma [6)].

Curcumin attenuates necroptosis.

Necroptosis has been implicated in many pathological conditions. Genetic or pharmacological inhibition of necroptotic signaling has been shown to confer neuroprotection after traumatic brain injury and ischemic brain injury. Therefore, the necroptotic pathway represents a potential target for

neurological diseases that are managed by neurosurgeons [7].

Necroptosis-related genes

the role of necroptosis-related genes (NRGs) in glioma has not been well-uncovered. Methods: Single-cell and bulk RNA sequencing data, obtained from publicly accessed databases, were used to establish a necroptosis-related gene signature for predicting the prognosis of glioma patients. Multiple bioinformatics algorithms were conducted to evaluate the efficacy of the signature. The relative mRNA level of each signature gene was validated by quantitative real-time reverse transcription PCR (qRT-PCR) in glioma cell lines compared to human astrocytes. Results: In this predicted prognosis model, patients with a high risk score showed a shorter overall survival, which was verified in the testing cohorts. The signature risk score was positively related with immune cell infiltration and some immune check points, such as CD276 (B7-H3), CD152 (CTLA-4), CD223 (LAG-3), and CD274 (PD-L1). Single-cell RNA sequencing analysis confirmed that the glioma microenvironment consists of various immune cells with different markers. The eight NRGs of the signature were detected to be expressed in several immune cells. QRT-PCR results verified that all the eight signature genes were differentially expressed between human astrocytes and glioma cells. Conclusion: The eight NRGs correlate with the immune microenvironment of glioma according to our bioinformatics analysis. This necroptosis-related gene signature may evaluate the precise methodology of predicting prognosis of glioma and provide a novel thought in glioma investigation [8].

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