Cancer Research Journal
2023; 11(2): 70-74
http://www.sciencepublishinggroup.com/j/crj
doi: 10.11648/j.crj.20231102.15
ISSN: 2330-8192 (Print); ISSN: 2330-8214 (Online)

Research Progress on the Mechanism and Treatment of Pyroptosis in Brain Glioma

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To cite this article:

Xiaohui Han, Jie Zhou, Shihua Liu, Sen Yang, Aixia Sui. Research Progress on the Mechanism and Treatment of Pyroptosis in Brain Glioma. *Cancer Research Journal.* Vol. 11, No. 2, 2023, pp. 70-74. doi: 10.11648/j.crj.20231102.15

Received: May 4, 2023; **Accepted**: May 22, 2023; **Published**: May 29, 2023

Abstract: Glioma is the most common fatal primary malignant brain tumor in the central nervous system (CNS). Currently, the main standard treatment is the combination of tumor resection, chemotherapy and radiotherapy. The World Health Organization (WHO) classifies glioma into four grades. Glioblastoma (GBM, WHO Grade 4) is the most aggressive type of glioma, characterized by cell heterogeneity, high proliferation rate, diffuse infiltration ability, and high resistance to chemotherapy drugs. Since the five-year survival rate is extremely low and the recurrence rate is high, some new effective treatment strategies are expected. Pyroptosis is an inflammatory programmed cell death mode. Compared with apoptosis, pyroptosis occurs faster and is accompanied by the release of a large number of pro-inflammatory factors. A large amount of evidence shows that pyrodeath can affect the development of tumor, and has both promoting and inhibiting effects on the development of glioma. In order to further understand the influence of pyroptosis on the glioma, this paper discussed the related studies of pyroptosis and glioma, in order to provide potential tumor treatment strategies based on pyroptosis for glioma patients.

Keywords: Glioma, Pyroptosis, Programmed Death, Molecular Mechanism

1. Introduction

Glioma is the most common primary malignant brain tumor in adults, which is usually characterized by high incidence, high recurrence rate, high mortality rate, high disability rate and low cure rate [1]. Since glioma is usually invasive and has an unclear boundary with the surrounding normal brain tissue, it is often impossible to completely cut the tumor in surgery. However, with the emergence of adverse reactions and adaptive resistance to postoperative radiotherapy and chemotherapy, the benefit degree of glioma patients, especially those with glioma recurrence, is greatly reduced. Programmed cell death such as pyroptosis and apoptosis is closely related to the development of glioma. Pyroptosis mainly mediated the activation of various caspase proteins including Caspase-1 through inflammasome, resulting in the shear and polymerization of various Gasdermin family members including GSDMD, resulting in cell perforation and cell death [2, 3]. Recent studies have found that the growth of glioma can be controlled to a certain extent by inducing pyroptosis of glioma cells. As researches have been conducted on the relationship between pyroptosis and glioma, its biological effects have become increasingly prominent. In this paper, the molecular mechanism and biological effects of pyroptosis, as well as its influence on the development of glioma, have been discussed.

2. Definition of Cell Pyroptosis and Its Associated Molecular Mechanisms

Pyroptosis is a pre-hemolytic inflammatory programmed cell death triggered by nucleotide oligomerization

domain-like receptor (NLRs) inflammatories and mediated by caspase family proteins [4]. Proinflammatory factors (IL-1β, IL-18) and cell contents are produced in the extracellular space, thus triggering inflammatory response [5]. In 2001, Cookson et al. [3] and de Vasconcelos [6] found that pyroptosis released a mass of pro-inflammatory substances and activated the natural immune response of the body. This novel cell death mode with both cell necrosis and apoptosis was named "pyroptosis". Currently, it is recognized that the pyroptosis pathway mainly includes the following two molecular mechanisms.

2.1. Classical Caspase-1-Dependent Pathway

The classical pyroptosis pathway is mediated by inflammasome, accompanied by the cleavage of Gasdermin D (GSDMD) and maturation and release of pro-inflammatory mediators [7]. On the one hand. That is, caspase-1 is recruited and activated by activating inflammatory bodies (NLRP3, NLRP4, AIM2, etc.) after cells receive extracellular stimulation (pathogen infection, cell damage, DNA damage mutation, etc.). Activated caspase-1 cleaves the GSDMD protein to form a peptide containing the GSDMD-N terminal domain (GSDMD-NT). This active peptide induces cell membrane perforation. On the other hand, mature caspase-1 shears pro-inflammatory factor precursors pro-IL-1β and pro-IL-18 to form active IL-1β and IL-18. These inflammatory factors are released into the extracellular cell along the pores in the cell membrane, causing an inflammatory response and triggering pyroptosis. GSDMD belongs to the GSDM protein family and is a universal efferent protein. Its mechanism of inducing pyroptosis is relatively clear and it plays a crucial role in pyroptosis [8].

2.2. Non-classical Approach

The non-classical pathway does not depend on the formation of inflammasome. Human caspase-4, 5 and mouse caspase-11 can be directly activated by bacterial LPS, and these activated caspase-4, 5 and 11 can shear GSDMD to form polypeptides with perforating activity and perforate the cell membrane. The activated GSDMD protein will recruit and activate the inflammatory body NLRP3 to induce the activation of caspase-1, and then cleat pro-IL-1β and pro-IL-18 to make them active and released into the extracellular cell to expand the inflammatory response.

2.3. A New Pathway of Pyroptosis Has Been Reported

Specific stimuli such as doxorubicin, 5-FU and other chemotherapy drugs can activate caspase-3 to induce GSDME cleavage and cleavage of Gsdme-C terminal domains into GSDME-CT and GSDME-NT. Among them, GSDME-NT has perforating activity, which can perforate the cell membrane and lead to pyroptosis [9]. Gasdermin E (GSDME, also known as DFNA5) is a member of the GSDM protein family, which can transform the immunologically significant "cold" tumor into the "hot" tumor recognized by the immune system, thus enhancing the phagocytosis of tumor-related macrophages on tumor cells. And the anti-tumor function of tumor infiltrating natural killer cells and CD8+T cells [10]. GSDME acted as a "converter" of apoptosis/pyroptosis downstream of caspase-3. In cells with high GSDME expression, pyroptosis morphological changes were observed after caspase-3 activation, while in cells with low GSDME expression, caspase-3 activation only showed typical apoptotic morphological changes.

Inflammatory factors and related pathways involved in pyroptosis are closely related to the occurrence and development of tumors and chemotherapy drug resistance [9, 11]. CASP5 acts on GSDMD and can cause the formation of cell membrane pores [12]. After activation, CASP5 interacts with CASP1 to promote activation, lyse IL-1/IL-18 precursor, and obtain active IL-1β/IL-18. In addition, these cytokines can be produced through the pathway produced by GSDMD-cNTs to induce pyroptosis [13]. CASP5 has been reported to be associated with cervical cancer, osteosarcoma, lung cancer, human glioblastoma and many other cancers [14-16]. CASP9 may be involved in a variety of cancers, autoimmune diseases and neurological diseases [17]. miR-23a, miR-24a and miR-582-5p have been reported to play a role in colorectal cancer and glioblastoma by regulating CASP9 [18, 19].

3. The Mechanism and Prognostic Value of Pyroptosis in Glioma

Pyroptosis can promote and inhibit the development of glioma. On the one side, pyroptosis inhibits the development of glioma by promoting inflammatory death of tumor cells. On the other side, the inflammatory mediators released by pyroptosis can promote the formation of tumor microenvironment suitable for tumor cell growth and promote the proliferation of glioma cells.

3.1. The Promoting Effect of Pyroptosis on Glioma

The GSDM family is an important regulator of pyroptosis. We found that [20] compared with non-tumor brain tissue, only GSDMD expression was up-regulated in gliomas. High expression of GSDMD was significantly associated with WHO Grade 4, IDH 1/2 wild type, mesenchymal subtype, and shorter overall survival. High GSDMD expression is associated with shorter overall survival and can be used as an independent risk factor for poor outcomes in low-grade glioma (LGG) and GBM [21]. Studies have shown that GSDMD-mediated pyroptosis may be the cause of more aggressive and worse prognosis in isocitrate dehydrogenase (IDH) wild-type glioma patients. At the same time, it may also affect the occurrence and development of tumors by affecting the process of EMT [22]. Researches show that GBM cell lines can secrete a large number of inflammatory cytokines IL-1β, IL-6 and IL-8 [23, 24] and promote the growth of glioma in an autocrine or paracrine way.

Studies [20] suggest that GSDMD expression may be involved in the regulation of macrophage infiltration and polarization. In vitro knockout of GSDMD can significantly

reduce IL-1β expression and reduce TMZ-induced pyroptosis, leading to tumor cell proliferation [25]. In addition, some studies indicate that IL-1β and other inflammatory factors released by pyroptosis of glioma cells may cause intratumoral immune inflammatory response [26], thus changing tumor microenvironment by increasing immune cell infiltration, promoting tumor cell proliferation and leading to poor prognosis of patients.

3.2. Antitumor Effect of Pyrodeath on Glioma

Caspase-1 is an important component of the classical pathway of pyroptosis, and its expression in GBM is often elevated [23]. The miR-214 showed low expression in glioma. The miR-214 could inhibit cell proliferation and migration by regulating caspase 1-mediated pyroptosis in glioma U87 and T98G cells and may provide a novel therapeutic approach for intervention in glioma. Simvastatin reduces GBM cell viability and inhibits cell migration and invasion in a dose-dependent manner. Furthermore, an inhibition of cellular pyroptosis was observed, which is characterized by caspase-1, The decreased expression of NLRP3 and IL-1β et al. However, administration of the miR-214 inhibitor reversed the inhibitory effect of simvastatin on GBM cells. Therefore, simvastatin inhibited GBM progression [27] by inhibiting caspase-1-dependent cell pyroptosis regulated by miR-214.

Hra_circ_0001836 is a circular non-coding RNA, which is often highly expressed in gliomas. It was found that glioma cells silencing Hra _circ _0001836 by [28] electron microscopy can show cell morphological changes consistent with pyroptosis.

Disulfiram (DSF) is a confirmed pyroptosis inhibitor [29], which has been well validated in preclinical studies on the treatment of glioblastoma, and has been advanced to the clinical research stage as a novel adjuvant [30, 31]. In these studies, DSF was only considered to be an acetaldehyde dehydrogenase (ALDH) inhibitor based on its classical function in the treatment of alcohol addiction, but given its new status, the function of this drug as a glioma pyroptosis inhibitor needs to be re-examined to guide the screening of suitable patients [32].

4. Clinical Application of Pyroptosis in the Treatment of Glioma

(1) Kaempferol is a kind of flavonoid widely existing in plants. Studies have shown that [33] kaempferol can increase the release of cytochrome C in mitochondria and activate caspase-3 to induce apoptosis of tumor cells. Studies have shown that kaolin inhibits glioma cell proliferation in vitro and tumor growth in vivo. High levels of ROS induce autophagy, which eventually leads to pyroptosis of glioma cells. Interestingly, when autophagy was inhibited with 3-MA, the lysed form of GSDME was also reduced, suggesting that kaempferol induces pyroptosis by regulating autophagy in glioma cells. This study showed that kaempferol has good anti-glioma cell activity by inducing ROS, which subsequently leads to autophagy and pyroptosis [34].

(2) As a natural isopentadienated chalcone compound, isobavachalcone (IBC) has been shown to inhibit GBM cell proliferation, migration, and invasion in vitro, and prevent tumor growth in vivo in subcutaneous and in situ GBM xenograft tumor models. Mechanistically, IBC may target the Pyrin-domain-containing 3 (NLRP3) transcription factor estrogen receptor alpha (ESR1 gene) of the Nod-like receptor family through network pharmacology and molecular docking analysis. Experimentally, IBC mitigated pyroptosis and inflammation associated with NLRP3 inflammasome, arrested cell cycles in G1 phase, and induced mitochondria-dependent apoptosis in GBM cells. The inhibition of NLRP3 by IBC can be saved in vitro and in vivo by the NLRP3 antagonist CY-09. These results suggest that IBC is a potential therapy for GBM and provide new insights into the treatment of GBM [35].

(3) Benzimidazole, a benzo-heterocyclic compound containing two nitrogen atoms, inhibited DNA synthesis, cell migration and invasion in a dose-dependent way, and regulated the expression of key epithelial interstitial transition (EMT) markers in U87 and U251 cells. Benzimidazole therapy also induced cell cycle stasis in the G2/M phase in a dose-dependent manner through the P53/P21/ cyclin B1 pathway. In addition, these drugs trigger pyroptosis of GBM cells via the NF-kB/NLRP3/GSDMD pathway and may simultaneously induce mitochondria-dependent apoptosis. In conclusion, benzimidazole can mediate pyroptosis of glioma cells through the NF-kB/NLRP3/caspase-1/GSDMD pathway, thereby delaying tumor development [36].

In gliomas, levels of IL-1β and IL-18 are increased, which is associated with reduced survival. Berberine targets the ERK/CASP1 signaling pathway, thereby reducing IL-1β and IL-18 secretion and inhibiting glioma cells [37]. Therefore, targeted pyroptosis is a promising strategy for tumor therapy.

The inflammatory response caused by pyroptosis promotes the infiltration of immune cells to eliminate pathogens [38-39]. However, excessive inflammatory response not merely damages normal cells, shortly reduces immune surveillance and suppresses malignant cells [40]. IL-1β is usually released from pores formed by oligomeric GSDMD [41] and has been shown to be closely associated with the formation of immunosuppressive microenvironments in several tumor types [42-44]. These studies suggest that there may be abnormal pyrogenic signaling in gliomas.

5. Conclusion

Glioma is a deadly brain tumor characterized by rapid proliferation and treatment resistance. High-grade gliomas are difficult to be completely resected due to their high proliferation rate, tumor cell heterogeneity, diffusion and infiltration. In addition, chemotherapy is resistant, leading to

treatment failure and tumor recurrence [45]. Therefore, the identification of novel biomarkers to predict treatment response and prognosis is of great clinical significance for glioma patients.

More and more evidence shows that pyroptosis plays a critical role in the development of glioma. On the one hand, pyroptosis can lead to inflammatory death of glioma cells, thus inhibiting the development of glioma. On the other hand, inflammatory mediators such as IL-1β secreted during pyroptosis may promote glioma angiogenesis and increase tumor invasiveness to a certain extent. Pyroptosis related markers (GSDMD) may be used to predict the prognosis of glioma patients and the response to TMZ treatment. However, since tumor development is a complex process of multi-factors, multi-steps and multi-genes, and pyroxis-related proteins are differentially expressed in the population, comprehensive evaluation should also be combined with other biomarkers to guide follow-up treatment. In conclusion, it is very necessary to study the correlation between pyroptosis and glioma, which can provide new ideas and clues for the targeted treatment of glioma.

Conflict of Interests

The authors declare that they have no conflict of interests.

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