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Pyroptosis: A New Strategy for Oncolytic Virus Therapy of Cancer

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Abstract:

In recent years, pyroptosis, as a form of proinflammatory programmed death, has been found to play a key role in the anti-tumor mechanism of OVs. This article systematically reviews the molecular mechanism of pyroptosis and tumor immune regulation, summarizes novel therapeutic strategies such as genetic engineering of OVs to enhance pyroptosis and combined with immune checkpoint inhibitors (ICIs), and analyzes their effects on tumor microenvironment (TME) immune remodeling. The results showed that OVs mainly induced pyroptosis by activating the caspase-3/GSDME pathway, releasing inflammatory factors (such as IL-18, HMGB1) and damage-associated molecular patterns (DAMPs), recruiting CD8+ T cells and natural killer (NK) cell infiltration, and thus transforming "cold tumors" into "hot tumors". OVs can be transformed to express GSDM proteins, regulate mitochondrial dysfunction, and target tumor immune components to promote the treatment of tumors through pyroptosis. This article provides a theoretical basis for the clinical transformation of OVs and suggests that pyroptosis-based combination therapy may become an important direction for future tumor im-munotherapy.

Keywords:-oncolytic virus; immunotherapy; pyroptosis; tumor microenvironment; gasdermin

I. Introduction

Oncolytic viruses (OVs) have become a research hotspot in cancer treatment because of their ability to selectively kill tumor cells and activate anti-tumor immunity. OVs have shown the dual advantages of selectively killing tumor cells and activating immune responses in cancer treatment, but their clinical efficacy is still limited by tumor heterogeneity, immunosuppressive microenvironment and viral resistance of some tumors. Traditional OVs mainly exert their efficacy by inducing apoptosis or necrosis, but these forms of death have weak immu-nogenicity and are difficult to stimulate lasting anti-tumor immunity. In recent years, cell pyroptosis, as a programmed death mode accompanied by a strong inflammatory response, has become a new direction for enhancing the efficacy of OVs due to its characteristics of releasing damage-associated molecular patterns (DAMPs) and cytokines (such as IL-1β, IL-18). In 2015, the U.S.

Food and Drug Administration (FDA) approved T-VEC for the treatment of some melanoma patients. Subsequently, T-VEC was approved in the European Union, Canada, Australia, Switzerland and other countries. In 2023, Japan approved Delytact (HSV-1 modified virus) for the treatment of recurrent glioblastoma. Oncolytic virus therapy has become a new paradigm for tumor immunotherapy. It significantly improves anti-tumor immune response by combining engineered viruses with immunotherapy, radiotherapy and other strategies. Currently, many trials have verified the potential of OVs to fight tumors through pyroptosis, and continued breakthroughs have been made in precise and safe delivery, combined therapy, etc., accelerating clinical transformation. However, the specific mechanism of how OVs accurately induce tumor cell pyroptosis and regulate the immune microenvironment has not been systematically elucidated.

This article focuses on the mechanism of OVs reshaping the tumor micro-environment (TME) through pyroptosis and the latest progress in treating tumors, and explores the application prospects of innovative strategies such as combined immunotherapy and nanodelivery systems, in order to provide ideas for optimizing OVs design and clinical practice.

II. Molecular mechanism of pyroptosis and tumor immune regulation

Previous studies describe four distinct pyroptosis signaling pathways. Comprehensive analysis of its triggers – classical and non-classical in-flammasome pathways, apoptotic caspase-mediated pathways, and granzyme-based pathways– requires assessment of molecular signatures. In the final stage of pyroptosis, proteolytic cleavage of gasdermin (GSDM) enables pore formation in the plasma membrane, releasing cytokines, alarm proteins, and DAMPs [1].

Inflammatory caspases (e.g., human caspase-1/4/5; murine caspase-11) initiate pyroptosis through two principal routes: the canonical pathway re-quiring inflammasome assembly and the inflammasome-independent non-canonical pathway. Notably, caspase-1 activation is strictly inflammasome-dependent. Inflammasomes in the classical pathway typically comprise pattern recognition receptors (PRRs), adaptor proteins, and pro-caspase-1. Different inflammasomes respond to various stimuli. When PRRs are stimulated, inflammasomes produce mature caspase-1. Human caspase-4/5 (murine caspase-11) bypass inflammasomes, directly activated by Gram-negative bacterial lipopolysaccharide (LPS). Ac-tivated caspases cleave full-length GSDMD, liberating its pore-forming N-terminal fragment (GSDMD-NT) that inserts into the plasma membrane, while the C-terminal fragment (GSDMD-CT) exerts autoinhibition. Canonical inflam-masome-induced pyroptosis represents a host defense mechanism against pathogens. Conversely, specific Gram-negative bacteria exploit the non-canonical pathway (caspase-4/5/11→GSDMD axis) to trigger pyroptotic cell death.

Some apoptotic caspases can also trigger pyroptosis. For example, chemotherapeutic drugs can “reprogram” apoptosis to pyroptosis by inducing the cleavage of GSDME by caspase-3. The chemotherapeutic 5-FU exemplifies this mechanism by activating caspase-3 to process GSDME [2]. Similarly, during Yersinia infection, caspase-8 cleaves GSDMD to initiate pyroptosis, while apoptosis-executing caspases-3/6/7 proteolyze GSDMB.

Beyond pathogen responses, some cytotoxic lymphocytes exploit perfor-in-granzyme pathways to deliver proteases into malignancies. Granzymes A/B then proteolyze specific gasdermins (e.g.GSDMB, GSDME), directly instigating ne-oplastic cell pyroptosis as an anti-tumor strategy [1].

Pyroptosis exhibits context-dependent duality in oncology: Chronic in-duction within TME fosters cancer progression through sustained cytokine release (e.g., IL-1β). This perpetuates a pro-tumorigenic niche via MDSC recruitment, M2 macrophage polarization, CAF activation, and upregulation of immune checkpoints (PD-1/LAG-3) On the other hand, acute and massively activated pyroptosis not only induces the death of a large number of cancer cells but also activates immunosurveillance to cause a large number of immune cells to in-filtrate and inhibit tumor growth [3,4]. The anti-tumor immunity of pyroptosis first releases DAMPs and inflammatory mediators, regulating the innate immune response to promote the recruitment of adaptive immune cells and increase antigen presentation, thereby leading to widespread immune activation. Molecules such as IL-1β, HMGB1, and IL-18 released by pyroptosis can induce the maturation of dendritic cells (DCs), activate CD8+ T cells, and inhibit the differentiation of immunosuppressive T regulatory cells, reversing the “cold tumor” microenvironment.

III. Pyroptosis-inducing strategies for OVs

A. Modification of Virus to Express GSDM Protein and Modification of Virus Packaging

The GSDM protein family is a key protein in cell pyroptosis. Genetically engineered OVs to express GSDM proteins, promote pyroptosis and reshape TME, and promote lymphocyte infiltration. For instance, armed M1

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OVs were generated by integrating full-length murine GSDME (mGSDME-FL) or its N-terminal fragment (mGSDME-NT). Western blotting confirmed stable expression of these transgenes. Cell morphological analysis found that they significantly induced cell py-roptosis in EMT-6 breast cancer cells, accompanied by significantly elevated extracellular HMGB1, ATP, and LDH release ($p < 0.01$), increasing CD8+T cells in the TME to 25% (5% in the control group) and NK cell infiltration to 8% (2.5% in the control group). The median survival of mice in the treatment group was significantly prolonged ($p < 0.01$), and the long-term survival rate (>60 days) reached 80%, which was twice that of the M1 group [5].

Although GSDM-NT can elicit potent anti-tumor immunity, it has a strong anti-tumor potential. However, since its broad cytotoxicity to mammalian cells, a suitable packaging strategy must be developed to enable its efficient production and delivery to cancer cells. For example, the Schwann cell-specific promoter has been used to control the expression of GSDMD-NT during adeno-associated virus (AAV) packaging, which may be specifically used for the treatment of schwannoma [6]. A recent study used a mammalian-specific promoter to drive GSDMD-NT expression and packaged this recombinant adeno-associated virus (rAVV) virus in the Sf9 insect cell system. This approach can significantly reduce the toxicity during virus preparation [7]. In another approach, the double-flocculated GSDMD-NT was inverted and cloned into a rAAV vector, which can be reversed by co-infection with rAAV-Cre during treatment, thereby obtaining high titer rAAV-P1 and rAAV-P2 viruses [7]. In the glioblastoma model, rAAV-P2 significantly reduced tumor volume and prolonged the survival of rats (50-day survival rate 50%, control group 0%), and Evans Blue staining showed that rAAV-P2 temporarily opened the blood-brain barrier and promoted T cell infiltration, while flow cytometry revealed elevated $CD8^+$ T and NK cell populations in tumors [7]. Therefore, modifying OVs to express GSDM protein can promote the induction of pyroptosis in tumor cells. However, it is necessary to use methods such as selective promoters and vector cells to effectively produce and deliver the modified OVs to cancer cells to avoid excessive damage to normal cells and reduce efficacy.

B. OVs Capable of Inducing Pyroptosis

While OVs traditionally induce immunologically silent apoptosis, this fails to explain the highly inflammatory TME observed during OV therapy. Some studies on the potential pro-inflammatory mechanisms of OVs have shown that some OVs can induce tumor cell pyroptosis. For example, oncolytic parapoxvirus (ORFV) and its recombinant therapeutic derivatives have been shown to trigger tumor cell pyroptosis through GSDME, stabilizing GSDME protein by reducing ubiq-uitination even in GSDME-low cells, and subsequently triggering elevated GSDME cleavage and cell pyroptosis [8]. Studies have shown that vesicular stomatitis virus (VSV) elicits GSDME-mediated pyroptosis in tumor cell lines, tissues, and patient-derived colon cancer models, activating and recruiting cytotoxic T lymphocytes (CTLs) associated with pyroptosis [9]. Reovirus (EV-D68) protease 3C inactivates GSDMD function, while viral protease 2A initiates GSDME-dependent pyroptosis [10]. Studies have shown that some OVs can trigger GSDME-mediated cell pyroptosis, which may help explain the mechanism by which OVs promote the inflammatory transformation of TME.

C. Mitochondrial Dysfunction and Regulation of ROS Signaling

BAK/BAX-mediated mitochondrial outer membrane permeabilization (MOMP) not only executes apoptosis but also releases pyroptosis-promoting factors like reactive oxygen species (ROS) [11]. Recombinant measles virus rMV-Hu191, which induces pyroptosis in esophageal squamous cell carcinoma (ESCC) via BAK/BAX-dependent caspase-3/GSDME activation [12]. Because a large number of inflammatory pathways were activated in ESCC cells treated with rMV-Hu191, severe mitochondrial damage was induced.

ROS are critical molecules that stimulate caspase-3/GSDME cleavage, driving pyroptosis [13]. Studies have found that ROS plays a key role in pyroptosis induced by Coxsackievirus group B3 (CVB3). Colon cancer infection with CVB3 significantly elevates ROS levels, activating caspase-3/GSDME-mediated pyroptosis in colon cancer cell lines [14]. BAK and BAX, as upstream effectors, may become new targets for regulating pyroptosis, which may activate caspase-3/GSDME pathway-induced apoptosis by increasing ROS in tumor cells.

D. 2.4 Targeting TME Components

Some OVs can selectively inhibit some cancers but show low cytotoxicity to other tumors. Although they have low toxicity to tumors, they may have a higher affinity for the corresponding TME components and inhibit tumor growth by changing the TME to promote immune cell infiltration. For example, recombinant human adenovirus type 5 (H101) is an oncolytic virus used to treat nasopharyngeal carcinoma. Although H101 has been shown to show low cytotoxicity to B16F10 melanoma cells, endothelial cells are more sensitive to H101 treatment. H101 induces caspase-1/GSDMD-dependent pyroptosis in endothelial

cells, signifi-cantly increasing the proportion of CD45+, CD3+, and CD8+ T cells in tumors ($P<0.01$) and significantly reducing the proportion of CD206+ M2 macrophages ($P<0.05$), indicating that the immune microenvironment has shifted from tumor promotion to anti-tumor, inhibiting the growth of B16F10 melanoma in mice [15]. The study found that H101 induced B16F10 cell death in vitro only at high doses (2×105 MOI), suggesting that its anti-tumor effect in vivo mainly depends on immune regulation and endothelial pyroptosis rather than direct oncolysis. In addition to targeting tumor cells, OVs can also change the TME by targeting TME components, reprogramming immunosuppressive cells, and inhibiting tumor an-giogenesis.

E. Nano Delivery System

The clinical application of OVs faces problems such as low delivery ef-ficiency, rapid immune clearance, and poor targeting. Nanodelivery systems can protect viruses from immune clearance, enhance tumor penetration, and can also cooperate with other prodrugs to form combined therapies to assist in activating pyroptosis and regulating TME. A study constructed ROS/pH-responsive magne-to-plasmonic nanoparticles (MPNPs) which deliver STAT3 inhibitor niclosamide(NI) with enhanced bioavailability. Combined with ICP34.5/ICP47-deficient HSV-1, they induce GSDME-dependent pyroptosis, converting immunologically "cold" to "hot" tumors while eliminating immunosuppressive cells and therapy-evading cancer stem cells [16,17]. The combination induced a large amount of gasdermin E (GSDME)-dependent cell pyroptosis and transformed immune "cold" tumors into immune "hot" tumors, promoting T cell infiltration and effectively killing tumor stem cells and immunosuppressive cells that evaded OVs monotherapy. In addition, the use of MPNPs also minimized systemic toxicity.

Another study combined ACNPs, a dual-reaction DNA methyltransferase in-hibitor nano prodrug, with oncolytic herpes simplex virus (oHSV). The epigenetic inhibitor 5-azacytidine (5-Aza) upregulated GSDME expression at the genetic level, while oHSV stabilizes GSDME protein by suppressing ubiquitination and degradation [18]. This dual intervention concertedly enhances pyroptosis. Both systems demonstrate reduced systemic toxicity while potentiating OV efficacy through pyroptotic activation.

IV. Combination therapy strategies

Immune checkpoint inhibitors (ICIs) have been successfully used in clinical treatment. However, they have limited efficacy for certain types of cancer, possibly due to unique immunosuppressive TME and other reasons [16]. Combining OVs with immune checkpoint inhibitors may enhance efficacy. H101 combined with PD-L1 antibody treatment of mouse melanoma found that compared with the use of either therapy alone, the combined therapy further reduced tumor volume and weight ($P<0.001$). It significantly increased CD8+ T cells and further reduced CD206+ M2 macrophages that promote tumor growth ($P<0.01$), significantly en-hancing the oncolytic effect [15]. rAAV-P2 combined with anti-PD-L1 antibody further inhibited tumor growth, with tumor weight reduced to 0.1 g (0.3 g in the rAAV-P2 group alone) [7]. With VSV pre-conditioning, PD-1 antibodies could further significantly prolong the survival of B16 tumor-bearing mice ($P<0.001$), while PD-1 antibodies alone did not significantly improve the survival [9]. Similarly, ORFV reversed the immunosuppressive microenvironment and made unresponsive tumors sensitive to PD-1 therapy. In addition, Adjuvants like low-dose etoposide further amplified this effect by enhancing ORFV-induced GSDME cleavage and cytotoxic lymphocyte recruitment [8].

V. Discussion

There are still many mechanisms by which OVs regulate cell pyroptosis that have not been elucidated, which may suggest new regulatory targets and treatment strategies. Cell pyroptosis is a double-edged sword. Although it enables innovative tumor eradication strategies, excessive activation may induce detrimental inflammation and tissue damage [19]. The safety of some OVs still needs to be improved. For example, CVB3 can also infect normal cells and cause myocarditis, etc., and the tropism for cardiac tissue needs to be reduced by viral capsid modification (such as VP1 mutants); at the same time, the long-term safety of toxic proteins such as GSDME expressed by the modified virus remains to be observed. The systemic expression of GSDM protein may damage normal epithelial cells, and the use of tumor-specific promoters can limit its ex-pression range. The risk of inflammatory storm of OVs cannot be ignored. In clinical trials, some patients showed high fever, hypotension, and respiratory distress. Early warning can be provided by detecting plasma IL-6 and HMGB1 levels through microfluidic chips, and improving the phased drug delivery strategy may reduce the incidence of inflammatory storms. Drug interventions such as glucocorticoids and tocilizumab can also be used.

In addition, OVs can be genetically modified to improve tumor targeting, such as by modifying them with tumor-specific hypoxia-inducible factor (HIF)-responsive promoters [20]. Computer simulation and AI design also have great prospects in viral gene design. The delivery efficiency of some OVs still needs to be improved. Ultra-

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sound/microbubble-assisted delivery has been proven to be effective in adenoviruses and may be extended to other OVs.

Previous studies have shown that some OVs only require partial fragments to work, and the effects and advantages can be verified by constructing plasmids containing different fragments. Due to the high mutation rate of viruses, it is also feasible to screen for viruses with new beneficial mutations. Some viruses, such as ORFV, can reduce virulence genes in the viral genome without changing tropism, replication, pyroptosis-promoting properties, and anti-tumor ability. This feature makes it possible to carry larger and more foreign genes in the future.

VI. Conclusion

This article explores the molecular mechanism of pyroptosis, which is mediated by GSDM protein pore formation and activated by four major pathways. Pyroptosis has a dual role in tumor promotion and anti-tumor regulation in tumor immunoregulation. This article also systematically explores the anti-tumor mechanism and treatment strategy of OVs-induced cell pyroptosis. Genetically engineering OVs to express GSDM-NT can promote tumor cell pyroptosis, and strategies such as insect cell packaging or double flocculation gene design can reduce the intracellular toxicity of GSDM-NT. Some natural OVs also have pyroptosis potential and have been shown to trigger GSDME-mediated cell py-roptosis in different ways. OVs can also activate GSDME-mediated pyroptosis through the BAK/BAX-ROS-caspase-3 axis. Targeting the TME such as endothelial cells can reshape the TME, reprogram immunosuppressive cells, and induce anti-tumor immunity. Nanodelivery systems improve the delivery efficiency and targeting of OVs while synergizing with other nano prodrugs to promote tumor pyroptosis. Oncolytic therapy in conjunction with certain immunosuppressants has been shown to both enhance the pyroptosis oncolytic effect and make tumors more sensitive to immunosuppressants.

During clinical transformation, oncolytic virus therapy will also face problems such as insufficient targeting, lack of efficacy biomarkers, and design of combined dosing regimens. These studies and findings emphasize the potential of OVs as an effective therapeutic agent for cancer using cell pyroptosis as a strategy, but there are still certain defects in clinical transformation and treatment efficiency and safety. Further research on the mechanism and wider application of pyroptosis induction of these OVs may pave the way for more effective cancer immunotherapy.

References

[1] Z. Rao, Y. Zhu, P. Yang, Z. Chen, Y. Xia, C. Qiao, W. Liu, H. Deng, J. Li, P. Ning, and Z. Wang, "Pyroptosis in inflammatory diseases and cancer," *Theranostics*, vol. 12, no. 9, pp. 4310–4329, May 2022.

[2] Y. Wang, B. Yin, D. Li, G. Wang, X. Han, and X. Sun, "GSDME mediates caspase-3-dependent pyroptosis in gastric cancer," *Biochem. Biophys. Res. Commun.*, vol. 495, pp. 1418–1425, 2018.

[3] J. Hou, J. M. Hsu, and M. C. Hung, "Molecular mechanisms and functions of pyroptosis in inflammation and antitumor immunity," *Mol. Cell*, vol. 81, no. 22, pp. 4579–4590, Nov. 2021.

[4] T. Du, J. Gao, P. Li, Y. Wang, Q. Qi, and X. Liu et al., "Pyroptosis, metabolism, and tumor immune microenvironment," *Clin. Transl. Med.*, vol. 11, e492, 2021.

[5] X. Y. Chen, Y. Liu, W. B. Zhu, S. H. Li, S. Wei, J. Cai, Y. Lin, J. K. Liang, G. M. Yan, L. Guo, and C. Hu, "Arming oncolytic M1 virus with gasdermin E enhances antitumor efficacy in breast cancer," *iScience*, vol. 27, no. 11, 111148, Oct. 2024.

[6] S. G. Ahmed, A. Abdelanabi, M. Doha, and G. J. Brenner, "Schwannoma gene therapy by adeno-associated virus delivery of the pore-forming protein Gasdermin-D," *Cancer Gene Ther.*, vol. 26, pp. 259–267, 2019.

[7] Y. Lu, W. He, X. Huang, Y. He, X. Gou, X. Liu, Z. Hu, W. Xu, K. Rahman, S. Li, S. Hu, J. Luo, and G. Cao, "Strategies to package recombinant Adeno-Associated Virus expressing the N-terminal gasdermin domain for tumor treatment," *Nat. Commun.*, vol. 12, 7155, Dec. 2021.

[8] J. Lin, S. Sun, K. Zhao, F. Gao, R. Wang, Q. Li, Y. Zhou, J. Zhang, Y. Li, X. Wang, L. Du, S. Wang, Z. Li, H. Lu, Y. Lan, D. Song, W. Guo, Y. Chen, F. Gao, Y. Zhao, R. Fan, J. Guan, and W. He, "Oncolytic Parapoxvirus induces Gasdermin E-mediated pyroptosis and activates antitumor immunity," *Nat. Commun.*, vol. 14, 224, Jan. 2023.

[9] J. Lin, F. Liu, F. Gao, Y. Chen, R. Wang, X. Wang, Y. Li, Q. Li, S. Sun, Z. Li, Y. Lan, H. Lu, W. Guo, L. Du, F. Gao, D. Song, K. Zhao, J. Guan, and W. He, "Vesicular stomatitis virus sensitizes immunologically cold tumors to checkpoint blockade by inducing pyroptosis," *Biochim. Biophys. Acta Mol. Basis Dis.*, vol. 1868, no. 12, 166538, Dec. 2022.

[10] S. Shen, H. Guo, Y. Li, L. Zhang, Y. Tang, H. Li, X. Li, P.-H. Wang, X.-F. Yu, and W. Wei, "SARS-CoV-2 and oncolytic EV-D68-encoded proteases differentially regulate pyroptosis," *J. Virol.*, vol. 98, no. 2, e0190923, Feb. 2024.

[11] L. Hu, M. Chen, X. Chen, C. Zhao, Z. Fang, H. Wang, and H. Dai, "Chemotherapy-induced pyroptosis is mediated by BAK/BAX-caspase-3-GSDME pathway and inhibited by 2-bromopalmitate," *Cell Death Dis.*, vol. 11, no. 4, 281, Apr. 2020.

[12] A. Wu, Z. Li, Y. Wang, Y. Chen, J. Peng, M. Zhu, Y. Li, H.

Song, D. Zhou, C. Zhang, Y. Lv, and Z. Zhao, "Recombinant measles virus vaccine rMV-Hu191 exerts an oncolytic effect on esophageal squamous cell carcinoma via caspase-3/GSDME-mediated pyroptosis," *Cell Death Discov.*, vol. 9, no. 1, 171, May 2023.

[13] C. Rogers, T. Fernandes-Alnemri, L. Mayes, D. Alnemri, G. Cingolani, and E. S. Alnemri, "Cleavage of DFNA5 by caspase-3 during apoptosis mediates progression to secondary necrotic/pyroptotic cell death," *Nat. Commun.*, vol. 8, 14128, 2017.

[14] Y. Zhang, T. Xu, H. Tian, J. Wu, X. Yu, L. Zeng, F. Liu, Q. Liu, and X. Huang, "Coxsackievirus Group B3 has oncolytic activity against colon cancer through Gasdermin E-mediated pyroptosis," *Cancers (Basel).*, vol. 14, no. 24, 6206, Dec. 2022.

[15] Z. M. Wang, M. K. Li, Q. L. Yang, S. X. Duan, X. Y. Lou, X. Y. Yang, Y. Liu, Y. W. Zhong, Y. Qiao, Z. S. Wang, L. Sun, and F. Qian, "Recombinant human adenovirus type 5 promotes anti-tumor immunity via inducing pyroptosis in tumor endothelial cells," *Acta Pharmacol. Sin.*, vol. 45, no. 12, pp. 2646–2656, Dec. 2024.

[16] A. Salmaninejad et al., "PD-1/PD-L1 pathway: basic biology and role in cancer immunotherapy," *J. Cell Physiol.*, vol. 234, pp. 16824–16837, 2019.

[17] W. Su, W. Qiu, S. J. Li, S. Wang, J. Xie, Q. C. Yang, J. Xu, J. Zhang, Z. Xu, and Z. J. Sun, "A dual-responsive STAT3 inhibitor nanoprodrug combined with oncolytic virus elicits synergistic antitumor immune responses by igniting pyroptosis," *Adv. Mater.*, vol. 35, no. 11, e2209379, Mar. 2023.

[18] Y. Y. Wang, J. Wang, S. Wang, Q. C. Yang, A. Song, M. J. Zhang, W. D. Wang, Y. T. Liu, J. Zhang, W. M. Wang, Z. Xu, and Z. J. Sun, "Dual-responsive epigenetic inhibitor nanoprodrug combined with oncolytic virus synergistically boost cancer immunotherapy by igniting Gasdermin E-mediated pyroptosis," *ACS Nano*, Jul. 2024.

[19] S. M. Man, R. Karki, and T.-D. Kanneganti, "Molecular mechanisms and functions of pyroptosis, inflammatory caspases and inflammasomes in infectious diseases," *Immunol. Rev.*, vol. 277, pp. 61–75, 2017.

[20] S. L. Longo, C. Griffith, A. Glass, E. J. Shillitoe, and D. E. Post, "Development of an oncolytic herpes simplex virus using a tumor-specific HIF-responsive promoter," *Cancer Gene Ther.*, vol. 18, pp. 123–134, 2011.