Gasdermin-Mediated Pyroptosis in Cancer Immunotherapy and Pain Management: A Survey

Abstract

Gasdermin-mediated pyroptosis, a pro-inflammatory form of programmed cell death facilitated by the gasdermin protein family, has emerged as a pivotal mechanism in cancer immunotherapy. This survey paper explores the multifaceted roles of gasdermins in inducing pyroptosis, enhancing antitumor immunity, and their potential in addressing apoptosis-resistant cancer cells. The cleavage of gasdermin proteins, particularly Gasdermin D, by caspases leads to pore formation in cellular membranes, releasing pro-inflammatory cytokines like IL-1, thus potentiating immune responses against tumors. The integration of pyroptosis-inducing strategies, such as ionizing radiation and oncolytic viruses, into existing cancer therapies is discussed, highlighting their potential to improve therapeutic efficacy. Moreover, the paper delves into the intersection of immune modulation and cancer pain management, emphasizing the role of nociceptive neurons in inflammatory pain and the potential of gasdermin pathways to modulate these interactions for therapeutic benefit. The survey underscores the significance of gasdermins as biomarkers and therapeutic targets, with implications for personalized cancer treatment. Challenges such as the precise control of gasdermin activation and the optimization of delivery systems are identified, necessitating further research. The findings advocate for continued exploration into gasdermin-mediated pyroptosis to develop innovative therapies that integrate cancer treatment with pain management, ultimately enhancing patient outcomes.

1 Introduction

1.1 Concept of Gasdermin-Mediated Pyroptosis

Gasdermin-mediated pyroptosis is a pro-inflammatory form of programmed cell death driven by the gasdermin protein family [1]. This process begins with the cleavage of gasdermins, particularly Gasdermin D (GSDMD), by caspases or other proteolytic enzymes, releasing N-terminal fragments that bind to acidic phospholipids in cellular membranes to form pores, leading to cell lysis [2, 3]. The significance of this pore formation is highlighted by the role of bacterial gasdermin (bGSDM) in inducing pyroptosis [4].

Pyroptosis is crucial for the release of pro-inflammatory cytokines, such as interleukin-1 (IL-1), which are vital for the innate immune response [5]. This cell death mechanism not only exhibits bactericidal properties but also amplifies the immune response against pathogens and tumor cells [6]. The involvement of gasdermins extends to various contexts, including tumor behavior modulation and immune responses in gliomas [7], and enhancing antitumor immunity during radiation therapy through pyroptosis induced by ionizing radiation [8].

Gasdermin proteins have evolutionary importance in immune defense, promoting cytokine release essential for inflammation and host defense [9]. Their roles across diverse cellular pathways suggest they could serve as therapeutic targets, particularly in cancer treatment and immune modulation [10]. Insights into gasdermin pore formation and regulation enhance our understanding of their

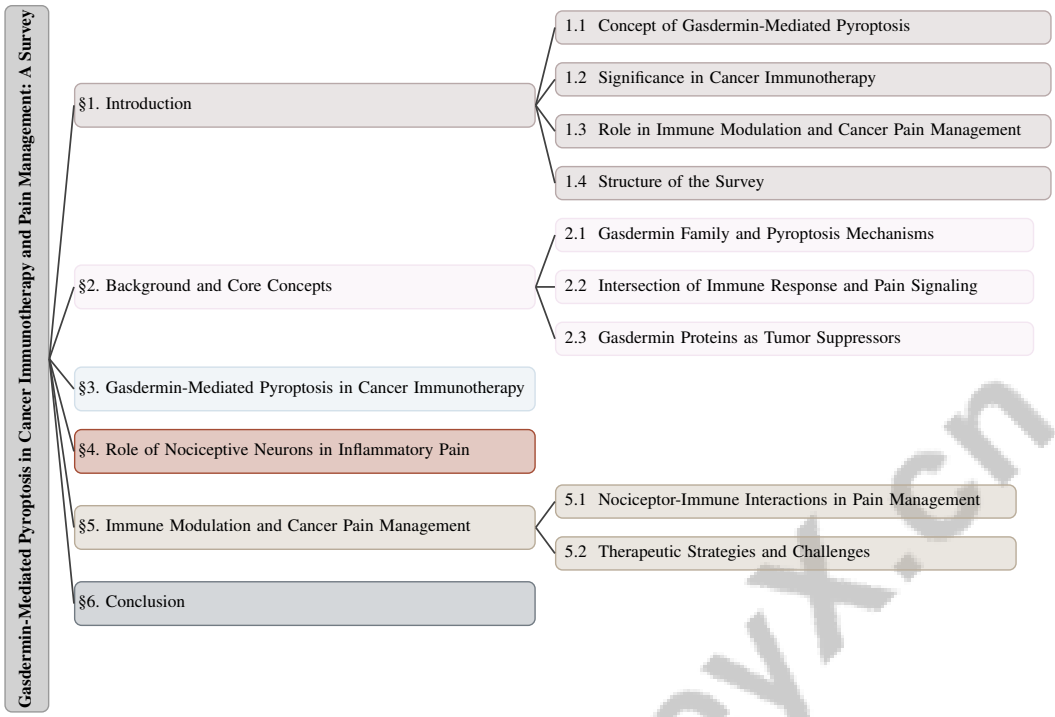

Figure 1: chapter structure

function in host defense and inflammation [11]. Beyond pyroptosis, gasdermins also regulate cellular homeostasis and responses to various stresses [12]. Thus, gasdermin-mediated pyroptosis is a critical link between cell death and immune signaling, underscoring its biological relevance in pathogen defense and cancer therapy [13].

Current research on gasdermin proteins and their microbial homologs elucidates their roles in programmed cell death, immune defense, and microbial infection, highlighting their evolutionary and functional diversity [14]. Moreover, the clinical characteristics and prognostic value of gasdermins in lung adenocarcinoma (LUAD) are explored, emphasizing their role in immune infiltration and potential in enhancing tumor immunogenicity, particularly in GSDME-low tumor cells [15, 16]. The mechanistic understanding of pyroptosis and its association with various diseases, especially cancer, further underscores its therapeutic relevance [17].

1.2 Significance in Cancer Immunotherapy

Gasdermin-mediated pyroptosis is pivotal in cancer immunotherapy, as it induces inflammatory cell death and enhances anti-tumor immunity by releasing pro-inflammatory cytokines, activating cytotoxic T cells and natural killer cells, and transforming "cold" tumors into "hot" tumors, thereby improving therapeutic efficacy. This programmed cell death mechanism, distinct from apoptosis and necroptosis, effectively circumvents resistance mechanisms that malignant cells employ to evade death, making it a promising strategy to enhance cancer treatment outcomes [7, 1, 18]. The pore formation by GSDMD is crucial for releasing cytokines like IL-1, which activate immune responses against tumor cells, facilitating not only direct cancer cell elimination but also the recruitment and activation of immune cells within the tumor microenvironment.

The ability of gasdermin-mediated pyroptosis to tackle apoptosis-resistant cancer cells is particularly noteworthy, as traditional therapies often fail against such cells [1]. For example, ionizing radiation can induce pyroptosis in tumor cells, thereby enhancing the antitumor immune response through cytotoxic T lymphocyte activation [8]. This potential integration of pyroptosis-inducing strategies into existing cancer treatments could significantly improve therapeutic efficacy.

Moreover, gasdermins have roles beyond pyroptosis, contributing to cellular homeostasis and stress responses essential for maintaining integrity and function within the tumor microenvironment [12].

The expression of gasdermin family members, including GSDMD, correlates with prognosis and immune infiltration in various cancers, such as hepatocellular carcinoma (HCC) and LUAD, indicating their potential as biomarkers for diagnosis and treatment [19]. The evolutionary perspective of gasdermins as pore-forming proteins, alongside their conserved roles in coordinating physiological responses to infection, further emphasizes their significance in cancer therapy [9]. This insight, paired with the historical evolution of cancer immunotherapy and notable breakthroughs, positions gasdermin-mediated pyroptosis as a promising avenue for future research and clinical application [20]. Continued exploration of gasdermin proteins in cancer immunotherapy reveals transformative potential, necessitating further investigations into their mechanisms and therapeutic applications [17].

1.3 Role in Immune Modulation and Cancer Pain Management

Gasdermin-mediated pyroptosis is a crucial mechanism in modulating immune responses and managing cancer-related pain, presenting promising therapeutic avenues. Recent research highlights pyroptosis's potential to enhance antitumor immunity, particularly in overcoming drug resistance in cancer cells [13]. This cell death mechanism not only aids in tumor cell elimination but also modulates the tumor microenvironment by releasing pro-inflammatory cytokines, thus enhancing immune cell infiltration and activation.

The interplay between immune modulation and pain management is particularly significant in cancer, where chronic pain poses a substantial public health challenge. Activated microglia, astrocytes, and peripheral immune cells often exacerbate chronic pain, illustrating the complex interactions between the immune and nervous systems [21]. Gasdermin-mediated pyroptosis may disrupt this cycle by modulating inflammatory pathways and reducing pain perception.

Emerging studies suggest that compounds like luteolin can induce pyroptosis, inhibiting tumor growth in colon cancer cells [22]. This indicates a dual benefit of targeting pyroptosis pathways: enhancing antitumor immunity while concurrently managing cancer-related pain. Furthermore, the activation of STING via IFN-I signaling has been identified as a critical regulator of nociception, presenting a promising target for chronic pain therapies [23]. Modulating this pathway through gasdermin-mediated pyroptosis could offer a novel approach to pain management without compromising immune function.

The dual role of nociceptors in pain and immune response modulation poses challenges in developing effective treatments [24]. However, targeting specific pathways, such as inhibiting BRD4 to reduce NLRP3 inflammasome-induced neuronal pyroptosis, may alleviate inflammatory pain while preserving immune integrity [25]. Additionally, PD-L1, known for its immune checkpoint inhibition role, also serves as an endogenous pain inhibitor capable of suppressing nociceptive neuron activity [26].

1.4 Structure of the Survey

The survey is structured to comprehensively explore gasdermin-mediated pyroptosis and its implications in cancer immunotherapy and pain management. It begins with an *Introduction* that establishes foundational concepts of gasdermin-mediated pyroptosis, highlighting its biological significance and therapeutic potential. This is followed by a detailed discussion on the *Significance in Cancer Immunotherapy*, elucidating the role of gasdermin-induced pyroptosis in enhancing anti-tumor immunity and overcoming resistance in cancer cells.

Subsequently, the survey examines the *Role in Immune Modulation and Cancer Pain Management*, exploring the intersection of immune response and pain signaling, emphasizing the dual benefits of targeting pyroptosis pathways for tumor eradication and pain alleviation. The *Background and Core Concepts* section provides an in-depth analysis of the gasdermin protein family, their mechanisms in pyroptosis, and their evolutionary significance in immune defense.

The survey further investigates the *Intersection of Immune Response and Pain Signaling*, focusing on nociceptive neurons' involvement in inflammatory pain and their relevance to cancer therapy. It scrutinizes gasdermin proteins as tumor suppressors, highlighting their implications for cancer treatment.

In the *Gasdermin-Mediated Pyroptosis in Cancer Immunotherapy* section, strategies to enhance pyroptosis for improved therapeutic outcomes are discussed, alongside an analysis of the clinical implications and therapeutic potential of targeting gasdermin-mediated pathways.

The intricate interactions between nociceptive neurons and immune cells in inflammatory pain are examined, revealing how sensory neurons detect noxious stimuli and communicate with immune cells via neuropeptides and cytokines. The dual role of macrophages in this dialogue, activating nociceptors and being influenced by them, shapes the mechanisms of acute and chronic pain. The survey emphasizes the implications of these immune signaling pathways for chronic pain development, advocating for novel therapeutic strategies targeting these interactions to alleviate inflammatory pain [27, 24, 28, 29].

Finally, the survey concludes with a synthesis of key findings, emphasizing challenges and future directions in the field. The *Conclusion* section underscores the transformative potential of gasdermin-mediated pyroptosis in cancer therapy and pain management, advocating for continued research to further elucidate its mechanisms and therapeutic applications.The following sections are organized as shown in Figure 1.

2 Background and Core Concepts

2.1 Gasdermin Family and Pyroptosis Mechanisms

The gasdermin family, comprising Gasdermin A (GSDMA), B (GSDMB), C (GSDMC), D (GSDMD), E (GSDME), and Pejvakin (PJVK), plays a crucial role in pyroptosis, an inflammatory form of programmed cell death. Pyroptosis is initiated by the cleavage of gasdermin proteins by inflammatory caspases, which are divided into canonical (caspase-1) and non-canonical (caspases-4/5/11) pathways, leading to membrane pore formation, cell lysis, and cytokine release [15]. Advances in cryo-electron microscopy (cryo-EM) have revealed the molecular architecture of gasdermin pores, enhancing the understanding of their role in pyroptosis [30]. Phylogenetic studies highlight the evolutionary significance of gasdermins, showing gene duplications and functional diversification across species, underscoring their roles in immunity.

GSDMD is pivotal in innate immunity, facilitating the release of mature interleukin-1 (IL-1) and other cytokines essential for immune responses [1]. Similarly, GSDME's activation by caspase-3 during oncolytic virus therapy highlights its role in pyroptosis, enhancing anti-tumor immunity over apoptosis [16]. Targeting gasdermin-mediated pyroptosis presents therapeutic opportunities in conditions like psoriasis, where GSDMD-mediated pyroptosis offers a novel approach beyond traditional cytokine inhibition [31]. The classification of gasdermins based on expression patterns, genetic alterations, and their associations with immune responses and drug sensitivity reveals their functional diversity in cancer biology [19]. Gasdermins are involved in various cell death pathways, including pyroptosis, apoptosis, and necroptosis [12].

Gasdermin proteins are integral to pyroptosis, crucial for immune defense against intracellular pathogens. Upon activation, gasdermins like GSDMD and GSDME form membrane pores, causing cell lysis and pro-inflammatory cytokine release. This mechanism not only eliminates infected cells but also transforms "cold" tumors into "hot" tumors, enhancing cancer therapy efficacy. Targeting gasdermin proteins represents a promising strategy to bolster immune responses and address cancer treatment resistance [1, 18, 3, 11]. Ongoing research into the structural and functional dynamics of gasdermin-induced pore formation offers promising avenues for novel treatments in cancer and inflammatory diseases.

2.2 Intersection of Immune Response and Pain Signaling

The interplay between immune response and pain signaling is complex, significantly influenced by nociceptive neurons that detect noxious stimuli and transmit pain signals to the central nervous system. This interaction is crucial for regulating inflammatory responses, highlighting the bidirectional communication contributing to acute and chronic pain development.

Nociceptors activated by inflammatory mediators during tissue injury can become hyperactive, leading to increased pain sensitivity and potentially transitioning from acute to chronic pain [21]. This transition is marked by persistent hypersensitivity even after the initial inflammation resolves, presenting a therapeutic challenge. The interaction between nociceptors and immune cells, such as macrophages and T cells, is critical, influencing both pain perception and the inflammatory environment.

Understanding how sensory neurons recognize and respond to danger signals from pathogens and damaged cells remains a primary challenge [32]. The presence of PD-1 in primary sensory neurons indicates a dual role for PD-L1 in immune regulation and pain modulation, complicating these pathways [26]. Nociceptor activation can exacerbate inflammatory responses by promoting pro-inflammatory cytokine release, creating a feedback loop sustaining pain and inflammation [33].

Gasdermin-mediated pyroptosis is a potential therapeutic target to disrupt this cycle. Inducing pyroptosis can enhance anti-tumor immunity and modulate inflammatory pathways, providing a dual benefit in cancer therapy [13]. The role of gasdermins in immune responses highlights their potential to modulate nociceptor activity and inflammatory pain.

Understanding the molecular mechanisms underlying nociceptor-immune interactions is essential for developing effective therapeutic strategies for pain and inflammation management. Targeting specific pathways, such as the STING pathway, implicated in nociception and chronic pain conditions, may alleviate chronic pain while preserving immune function [23]. This approach underscores the therapeutic potential of integrating immune modulation with pain management strategies.

2.3 Gasdermin Proteins as Tumor Suppressors

Gasdermin proteins, particularly GSDME and GSDMA3, are recognized as critical tumor suppressors, primarily through their ability to activate immune responses against tumors [3]. Their tumor-suppressive effects are mediated by pyroptosis, characterized by inflammatory programmed cell death facilitated by pore formation in the cellular membrane, predominantly through GSDMD, which preferentially releases mature IL-1 cytokines, amplifying the immune response [5].

The tumor-suppressive role of gasdermins is further illustrated by their modulation of the tumor microenvironment. For example, hypermethylation-induced downregulation of GSDME in various cancers limits pyroptosis induction and subsequent immune response, highlighting the significance of epigenetic regulation in gasdermin-mediated tumor suppression [8]. Restoring GSDME expression could potentiate pyroptosis and enhance anti-tumor immunity.

Gasdermins also serve as potential biomarkers for diagnosis and targets for immunotherapy, particularly in hepatocellular carcinoma (HCC), emphasizing their critical roles in tumor biology [34]. The engineering of bacterial gasdermins (bGSDMs) for controlled activation offers a novel therapeutic approach to harnessing their structural and functional properties for cancer therapy [4].

The intersection of gasdermin-mediated pyroptosis and immune signaling is vital for understanding chronic pain management, as immune signaling is pivotal in sustaining chronic pain states [27]. This highlights the necessity for further research into neuroimmune interactions to enhance treatment strategies, particularly in cancer therapy, where targeting the STING/IFN-I pathway could benefit both pain management and immunotherapy [23].

Despite the promising potential of gasdermin proteins in tumor suppression, challenges remain in fully elucidating the immune mechanisms and the complexities of tumor biology, which have historically impeded effective treatment [20]. Nonetheless, recognizing pyroptosis as a therapeutic target underscores its complex role in cancer and highlights the transformative potential of gasdermin proteins in cancer therapy [17]. By targeting the molecular mechanisms underlying inflammatory pain, such as through BRD4 inhibition, more effective treatment options with fewer side effects than traditional pain medications may be developed [25].

In recent years, the exploration of gasdermin-mediated pyroptosis has gained significant attention in the context of cancer immunotherapy. This emerging field underscores the intricate relationship between cell death mechanisms and therapeutic efficacy. As illustrated in Figure 2, the hierarchical structure of gasdermin-mediated pyroptosis is depicted, emphasizing key mechanisms and innovative approaches that are being developed. The figure also highlights clinical strategies and potential therapeutic outcomes, including pain management and immune modulation, which are crucial for advancing treatment protocols and improving patient outcomes. By examining these components, we can better understand the multifaceted roles that pyroptosis plays in enhancing the effectiveness of cancer therapies.

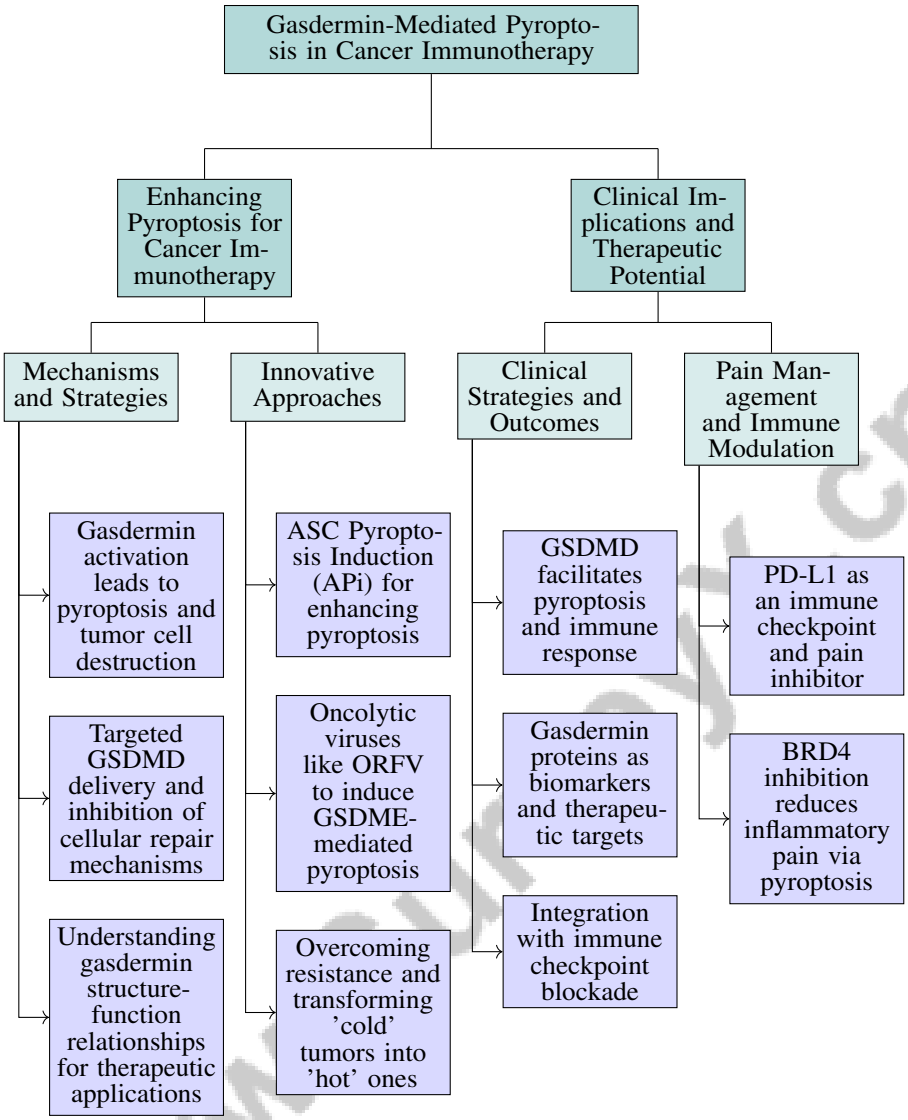

Figure 2: This figure illustrates the hierarchical structure of gasdermin-mediated pyroptosis in cancer immunotherapy, highlighting key mechanisms, innovative approaches, clinical strategies, and potential therapeutic outcomes, including pain management and immune modulation.

3 Gasdermin-Mediated Pyroptosis in Cancer Immunotherapy

3.1 Enhancing Pyroptosis for Cancer Immunotherapy

Leveraging pyroptosis through gasdermin activation presents a promising strategy to enhance cancer immunotherapy by exploiting gasdermin-mediated cell death. GSDMD plays a crucial role in this process, where its activation incites pyroptosis, leading to tumor cell destruction and heightened anti-tumor immune responses [6]. Targeted GSDMD delivery to tumor cells, coupled with inhibiting cellular repair mechanisms, has shown efficacy in sustaining cell lysis and subsequent immune activation [35].

Recent advances in structural biology have elucidated the pore-forming mechanisms of bacterial gasdermins (bGSDMs), underscoring their evolutionary significance and therapeutic potential in cancer treatment [4]. Understanding gasdermin structure-function relationships is essential for devising strategies that harness their pore-forming capabilities for therapeutic applications [14].

Innovative approaches, such as ASC Pyroptosis Induction (APi), illustrate how macrophage-derived factors can enhance pyroptosis in adipose-derived stem cells (ASCs), offering a novel cancer immunotherapy avenue [30]. Oncolytic viruses like parapoxvirus ovis (ORFV) have been employed to induce GSDME-mediated pyroptosis in tumor cells, thereby boosting anti-tumor immunity and improving cancer immunotherapy outcomes [16]. Despite the dual nature of pyroptosis posing manipulation challenges, its therapeutic potential remains significant [17].

Efforts to enhance pyroptosis in cancer therapy focus on optimizing gasdermin delivery and activation, understanding their structural mechanisms, and integrating these insights with existing immunotherapies. These strategies aim to amplify pyroptosis's immunogenic effects—marked by pro-inflammatory cytokine release and immune cell activation—addressing challenges associated with this inflammatory cell death form. By harnessing pyroptosis, these strategies seek to improve therapeutic outcomes, particularly in overcoming resistance to conventional therapies and transforming 'cold' tumors into 'hot' ones, facilitating a stronger anti-tumor immune response [35, 17, 7, 13, 1].

3.2 Clinical Implications and Therapeutic Potential

Targeting gasdermin-mediated pyroptosis in cancer treatment holds significant clinical promise, offering novel strategies to bolster anti-tumor immunity and enhance therapeutic outcomes. GSDMD is central to this process, facilitating pyroptosis by forming pores that release inflammatory cytokines, thereby augmenting immune responses against tumors [8]. This mechanism not only induces direct tumor cell lysis but also promotes immune cell infiltration and activation, such as CD8+ T lymphocytes, within the tumor microenvironment, fostering a robust anti-tumor response.

Research underscores the potential of gasdermin proteins as biomarkers and therapeutic targets. Specific gasdermin family members correlate with improved overall survival (OS) and disease-specific survival (DSS) in cancer patients, underscoring their prognostic significance [34]. In lung adenocarcinoma (LUAD), GSDM family member expression correlates with patient prognosis, indicating their utility in guiding therapeutic decisions [15].

The therapeutic potential of gasdermin-mediated pyroptosis extends beyond tumor cell destruction; it modulates the tumor microenvironment to enhance treatment efficacy, such as immune checkpoint blockade. Integrating gasdermin pathways with existing therapies could significantly improve outcomes [1]. Additionally, gasdermins' dual role in protective and pathological processes offers opportunities for targeted therapies to modulate their activity across diseases, including inflammatory conditions [9].

The intersection of immune modulation and pain management is particularly pertinent in cancer therapy. For instance, PD-L1, known for immune checkpoint inhibition, also acts as an endogenous pain inhibitor by suppressing nociceptive neuron activity, suggesting potential applications in managing cancer-related pain [26]. Moreover, BRD4 inhibition alleviates inflammatory pain by reducing NLRP3 inflammasome-mediated pyroptosis in neurons, providing a novel approach for managing chronic inflammatory pain [25].

Advancements in immunotherapy have led to significant improvements in patient outcomes, with various treatments approved for clinical use [20]. Exploring gasdermin-targeted therapies continues to reveal transformative potential, necessitating further research into their mechanisms and applications. Findings indicate that gasdermin family genes serve as potential therapeutic targets in pan-cancer, with varying roles as risk or protective factors depending on the cancer type [19]. Additionally, ORFV has been shown to sensitize immunologically 'cold' tumors to checkpoint blockade therapies, highlighting its therapeutic potential in cancer treatment [16]. Integrating these insights into clinical practice may lead to more effective cancer treatments that address both tumor progression and associated inflammatory conditions.

4 Role of Nociceptive Neurons in Inflammatory Pain

4.1 Nociceptive Neurons and Pain Sensing

Nociceptive neurons are pivotal in detecting noxious stimuli and transmitting pain signals to the central nervous system, thereby playing a crucial role in pain perception and inflammatory response modulation. These neurons serve as a critical interface between the nervous and immune systems,

directly recognizing danger signals via Toll-like receptors (TLRs), which enable rapid neuronal responses that contribute to pain and inflammation [28, 32]. In the context of cancer, nociceptive neurons not only influence tumor progression but also affect pain perception through interactions with immune cells, impacting both the tumor microenvironment and patient quality of life [28]. The activation of nociceptors by inflammatory mediators during tumorigenesis heightens pain sensitivity, complicating cancer pain management. Investigating the molecular mechanisms governing nociceptor-immune interactions is essential for identifying therapeutic targets to alleviate cancer-related pain while maintaining immune function. This understanding is vital for developing effective pain management strategies that enhance patient care and quality of life [24, 26, 28, 23, 29].

4.2 Immune-Nociceptor Interactions

The bidirectional interactions between immune cells and nociceptive neurons are fundamental to understanding pain signaling and inflammation dynamics. Nociceptors respond to inflammatory mediators and actively release substances that influence immune cell behavior, creating a feedback loop that can exacerbate or alleviate pain [24]. Shared mechanisms between sensory neurons and immune cells present potential therapeutic targets for managing chronic inflammatory pain [32]. Macrophages, for instance, engage in both pro-inflammatory and anti-inflammatory pathways, influencing pain perception through interactions with nociceptors. This regulation is mediated by microRNAs that facilitate cell communication, indicating a complex interaction network that could be targeted for therapeutic intervention [29]. Understanding these interactions is crucial for developing novel pain management strategies, especially in cancer, where chronic pain significantly impacts quality of life. By focusing on the molecular pathways governing nociceptor-immune interactions, researchers can design therapies that alleviate pain associated with tissue injury and inflammation while preserving immune responses. This dual strategy could enhance treatment efficacy for chronic pain and inflammatory diseases by leveraging the intricate crosstalk between nociceptors and immune cells [24, 28].

4.3 Chronic Pain and Immune Signaling

Chronic pain is intricately linked to immune signaling pathways, with nociceptive neurons playing a pivotal role. Persistent chronic pain often results from sustained nociceptor activation by pro-inflammatory cytokines and mediators released by immune cells, leading to heightened pain sensitivity and prolonged inflammation [21]. This highlights the bidirectional communication between the nervous and immune systems, where immune cells modulate nociceptor activity and vice versa [24]. The NLRP3 inflammasome exemplifies immune signaling's role in chronic pain, driving inflammatory responses and contributing to pain hypersensitivity [25]. NLRP3 activation in neurons can induce pyroptosis, exacerbating pain by promoting pro-inflammatory cytokine release [25]. Targeting inflammasome pathways may offer therapeutic value by alleviating chronic pain while preserving immune function. Moreover, the STING pathway, known for its role in immune responses to cytosolic DNA, has been implicated in nociception and chronic pain regulation [23]. Modulating the STING pathway could provide a novel approach to managing chronic pain, particularly in inflammation-driven conditions. By influencing immune signaling pathways, it is feasible to alter nociceptor sensitivity and reduce pain perception, presenting potential therapeutic avenues. The complex interplay between chronic pain and immune signaling pathways necessitates thorough exploration of the underlying molecular mechanisms, particularly as nociceptor-immune cell interactions significantly influence pain sensitivity and the transition from acute to chronic pain states. This relationship is critical for developing targeted therapeutic strategies that address both nociceptive and immune responses in chronic pain management, ultimately improving patient outcomes and quality of life [27, 24, 28, 23, 29].

5 Immune Modulation and Cancer Pain Management

5.1 Nociceptor-Immune Interactions in Pain Management

Nociceptor-immune interactions are central to cancer pain management, offering avenues for innovative therapies. Nociceptors, through pattern recognition receptors like Toll-like receptors, detect danger signals and modulate immune responses, influencing pain perception and inflammation [32, 24]. Targeting nociceptive signaling via immune pathways shows promise for cancer pain relief.

Activation of the STING pathway in sensory neurons is a potential strategy for modulating pain perception, presenting a novel target for chronic pain conditions [23]. Macrophages, with their dual role in pain regulation through interactions with nociceptors, are potential therapeutic targets for managing inflammation and pain [29]. Utilizing small extracellular vesicles from LPS-stimulated macrophages to deliver immunomodulatory miRNAs exemplifies a novel approach to downregulate pro-inflammatory signaling and enhance therapeutic outcomes in chronic pain [21].

Strategies inducing pyroptosis, such as using ORFV to convert immunologically 'cold' tumors into 'hot' tumors, can enhance nociceptor-immune interactions, improving pain management [16]. Gasdermin-mediated pyroptosis modulates immune responses and improves therapeutic outcomes in cancer pain management. Gasdermin proteins, beyond cell death, influence cellular stress responses and homeostasis, emphasizing their significance in developing comprehensive pain management strategies [12]. Insights from conditions like psoriasis, where gasdermin-mediated pathways are novel therapeutic targets, can complement existing treatments and refine pain management strategies for cancer patients [31]. Focusing on specific pathways and interactions, such as those involving the STING pathway or macrophage-nociceptor dynamics, can lead to targeted therapies addressing both pain and inflammation, enhancing the quality of life for cancer patients.

5.2 Therapeutic Strategies and Challenges

Incorporating pyroptosis into pain management protocols presents innovative strategies and significant challenges. Gasdermin-mediated pyroptosis, particularly through Gasdermin D (GSDMD), offers a novel approach to enhancing cancer treatment efficacy by promoting tumor cell death and modulating the tumor microenvironment [1]. However, the complexity of pyroptosis mechanisms and the varied effects of gasdermins across different cancer types complicate the development of effective therapeutic strategies [17]. Pyroptosis-inducing agents like luteolin have shown efficacy in overcoming resistance in colon cancer therapies, improving treatment outcomes [22]. Nonetheless, a major limitation is the incomplete understanding of gasdermin activation mechanisms and the potential side effects of inducing pyroptosis in normal tissues, which could lead to unintended inflammatory responses [1]. Further mechanistic studies are necessary to clarify the roles of gasdermins in various cancers and explore their potential as therapeutic targets [19].

The complexity of pyroptosis signaling pathways, which may differ significantly among sensory neuron types, presents additional challenges in developing targeted therapies that effectively manage pain without compromising immune function [32]. Identifying specific molecular targets within macrophage-nociceptor interactions could open new avenues for pain relief, underscoring the importance of understanding these interactions in pain management [29]. Evolutionary parallels in immune responses between multicellular organisms and microbes, as evidenced by gasdermin homologs in various microorganisms, provide insights into potential therapeutic applications of gasdermins [14]. However, variability in gasdermin gene expression across different cancers necessitates further research to elucidate their roles and develop targeted therapies capable of effectively modulating pyroptosis [19].

In chronic pain contexts, BRD4 inhibition has demonstrated efficacy in reducing inflammatory pain through NLRP3 inflammasome modulation in preclinical models, although further research is required to validate these findings in humans and assess the long-term effects of such treatments [25]. Novel mechanisms linking mitochondrial DNA leakage to inflammation illuminate potential therapeutic strategies, highlighting the intricate relationship between cellular stress responses and inflammatory pain [33]. While integrating pyroptosis into pain management protocols offers promising therapeutic avenues, addressing these challenges through comprehensive research and clinical evaluation is essential for developing effective and safe treatment options. Future research should focus on validating gasdermins' roles in specific cancer contexts, such as hepatocellular carcinoma (HCC), and exploring their mechanisms in tumor biology and immune response [34].

6 Conclusion

6.1 Challenges and Future Directions

Exploring the role of gasdermin-mediated pyroptosis in cancer immunotherapy and pain management unveils significant challenges and promising avenues for future research. A key challenge lies in

deepening our understanding of the mechanisms that regulate gasdermin activation and function. Current research provides limited insights into the activation pathways of gasdermins, particularly GSDMD, and how their pore-forming activities can be precisely controlled in therapeutic settings. Future investigations should prioritize elucidating these mechanisms to enhance the therapeutic potential of pyroptosis in cancer treatment.

The roles of gasdermins in non-canonical pathways also require further exploration. Understanding the molecular mechanisms that govern gasdermin functions in these alternative pathways is crucial for developing targeted therapies that exploit their unique properties. Additionally, comprehensive studies on the involvement of specific immune cells and signaling pathways in chronic pain are essential, particularly considering potential sex differences in pain responses, to develop personalized pain management strategies.

Optimizing delivery systems for gasdermin-targeted therapies presents another critical challenge. Ensuring efficient and targeted delivery, while addressing complexities in treatment preparation and storage, is vital for clinical application. Future research should focus on clarifying the molecular roles of gasdermin genes in cancer, their interactions with immune checkpoints, and potential applications in immunotherapy. Investigating the interplay between gasdermins and other cellular pathways could also reveal new therapeutic opportunities.

The therapeutic potential of small extracellular vesicles (sEVs) in modulating immune responses and managing pain represents a promising research direction. Future studies should aim to optimize the timing and dosage of sEV administration and identify the specific molecular pathways influenced by various miRNAs within sEVs. Additionally, enhancing ORFV formulations and exploring combination therapies with other immunotherapeutics could shed light on GSDME regulation in tumor cells, potentially improving the efficacy of cancer treatments.

References

[1] Mengyuan Li, Ping Jiang, Yuhan Yang, Liting Xiong, Shuhua Wei, Junjie Wang, and Chunxiao Li. The role of pyroptosis and gasdermin family in tumor progression and immune microenvironment. *Experimental hematology & oncology*, 12(1):103, 2023.

[2] Jianbin Ruan, Shiyu Xia, Xing Liu, Judy Lieberman, and Hao Wu. Cryo-em structure of the gasdermin a3 membrane pore. *Nature*, 557(7703):62–67, 2018.

[3] Caiyun Fu. Gasdermin: a novel therapeutic target for tumour treatment by activating anti-tumour immunity. *Signal transduction and targeted therapy*, 5(1):69, 2020.

[4] Alex G Johnson, Megan L Mayer, Stefan L Schaefer, Nora K McNamara-Bordewick, Gerhard Hummer, and Philip J Kranzusch. Structure and assembly of a bacterial gasdermin pore. *Nature*, 628(8008):657–663, 2024.

[5] Shiyu Xia, Zhibin Zhang, Venkat Giri Magupalli, Juan Lorenzo Pablo, Ying Dong, Setu M Vora, Longfei Wang, Tian-Min Fu, Matthew P Jacobson, Anna Greka, et al. Gasdermin d pore structure reveals preferential release of mature interleukin-1. *Nature*, 593(7860):607–611, 2021.

[6] Jinyong Wang, Kelly Deobald, and Fabio Re. Gasdermin d protects from melioidosis through pyroptosis and direct killing of bacteria. *The Journal of Immunology*, 202(12):3468–3473, 2019.

[7] Yonghua Cai, Ke Li, Jie Lin, Xianqiu Liang, Wei Xu, Zhengming Zhan, Shuaishuai Xue, Yu Zeng, Peng Chai, Yangqi Mao, et al. Lighting a fire: gasdermin-mediated pyroptosis remodels the glioma microenvironment and promotes immune checkpoint blockade response. *Frontiers in Immunology*, 13:910490, 2022.

[8] Wei Cao, Guodong Chen, Lijun Wu, KN Yu, Mingyu Sun, Miaomiao Yang, Yanyi Jiang, Yuan Jiang, Yuan Xu, Shengjie Peng, et al. Ionizing radiation triggers the antitumor immunity by inducing gasdermin e-mediated pyroptosis in tumor cells. *International Journal of Radiation Oncology* Biology* Physics*, 115(2):440–452, 2023.

[9] Diego Angosto-Bazarra, Cristina Alarcón-Vila, Laura Hurtado-Navarro, María C Baños, Jack Rivers-Auty, and Pablo Pelegrín. Evolutionary analyses of the gasdermin family suggest conserved roles in infection response despite loss of pore-forming functionality. *BMC biology*, 20(1):9, 2022.

[10] Yufu Zheng, Didi Yuan, Fei Zhang, and Renkuan Tang. A systematic pan-cancer analysis of the gasdermin (gsdm) family of genes and their correlation with prognosis, the tumor microenvironment, and drug sensitivity. *Frontiers in Genetics*, 13:926796, 2022.

[11] Chengliang Wang and Jianbin Ruan. Mechanistic insights into gasdermin pore formation and regulation in pyroptosis. *Journal of molecular biology*, 434(4):167297, 2022.

[12] Chi G Weindel, Lily M Ellzey, Eduardo L Martinez, Robert O Watson, and Kristin L Patrick. Gasdermins gone wild: new roles for gsdms in regulating cellular homeostasis. *Trends in cell biology*, 33(9):773–787, 2023.

[13] Fan Yang, Sahana N Bettadapura, Mark S Smeltzer, Hua Zhu, and Shanzhi Wang. Pyroptosis and pyroptosis-inducing cancer drugs. *Acta Pharmacologica Sinica*, 43(10):2462–2473, 2022.

[14] Shule Wang, Tingbo Ma, Xiaoyi Xia, and Leiliang Zhang. Evolutionary insights and functional diversity of gasdermin family proteins and homologs in microorganisms. *Frontiers in Immunology*, 15:1371611, 2024.

[15] Lu-Shan Peng, Sai-Li Duan, Run-Qi Li, Dan Wang, Ying-Ying Han, Tao Huang, Yu-Pei Yu, Chun-Lin Ou, and Jun-Pu Wang. Prognostic value and immune infiltration of the gasdermin family in lung adenocarcinoma. *Frontiers in Oncology*, 12:1043862, 2022.

[16] Jing Lin, Shihui Sun, Kui Zhao, Fei Gao, Renling Wang, Qi Li, Yanlong Zhou, Jing Zhang, Yue Li, Xinyue Wang, et al. Oncolytic parapoxvirus induces gasdermin e-mediated pyroptosis and activates antitumor immunity. *Nature Communications*, 14(1):224, 2023.

[17] Pian Yu, Xu Zhang, Nian Liu, Ling Tang, Cong Peng, and Xiang Chen. Pyroptosis: mechanisms and diseases. *Signal transduction and targeted therapy*, 6(1):128, 2021.

[18] Stephen B Kovacs and Edward A Miao. Gasdermins: effectors of pyroptosis. *Trends in cell biology*, 27(9):673–684, 2017.

[19] Cheng-Long Huo, Yan Deng, and Zhen-Gang Sun. A comprehensive analysis of gasdermin family gene as therapeutic targets in pan-cancer. *Scientific Reports*, 12(1):13329, 2022.

[20] Paula Dobosz and Tomasz Dzieciątkowski. The intriguing history of cancer immunotherapy. *Frontiers in immunology*, 10:2965, 2019.

[21] Renée Jean-Toussaint, Zhucheng Lin, Yuzhen Tian, Richa Gupta, Richa Pande, Xuan Luo, Huijuan Hu, Ahmet Sacan, and Seena K Ajit. Therapeutic and prophylactic effects of macrophage-derived small extracellular vesicles in the attenuation of inflammatory pain. *Brain, behavior, and immunity*, 94:210–224, 2021.

[22] Yiliu Chen, Shengsuo Ma, Dajin Pi, Yingchao Wu, Qian Zuo, Chongan Li, and Mingzi Ouyang. Luteolin induces pyroptosis in ht-29 cells by activating the caspase1/gasdermin d signalling pathway. *Frontiers in Pharmacology*, 13:952587, 2022.

[23] Christopher R Donnelly, Changyu Jiang, Amanda S Andriessen, Kaiyuan Wang, Zilong Wang, Huiping Ding, Junli Zhao, Xin Luo, Michael S Lee, Yu L Lei, et al. Sting controls nociception via type i interferon signalling in sensory neurons. *Nature*, 591(7849):275–280, 2021.

[24] Pankaj Baral, Swalpa Udit, and Isaac M Chiu. Pain and immunity: implications for host defence. *Nature Reviews Immunology*, 19(7):433–447, 2019.

[25] Tong Hua, Haowei Wang, Xiaoyi Fan, Ni An, Jian Li, Honghao Song, Erliang Kong, Yongchang Li, and Hongbin Yuan. Brd4 inhibition attenuates inflammatory pain by ameliorating nlrp3 inflammasome-induced pyroptosis. *Frontiers in immunology*, 13:837977, 2022.

[26] Gang Chen, Yong Ho Kim, Hui Li, Hao Luo, Da-Lu Liu, Zhi-Jun Zhang, Mark Lay, Wonseok Chang, Yu-Qiu Zhang, and Ru-Rong Ji. Pd-l1 inhibits acute and chronic pain by suppressing nociceptive neuron activity via pd-1. *Nature neuroscience*, 20(7):917–926, 2017.

[27] Sarah A Woller, Kelly A Eddinger, Maripat Corr, and Tony L Yaksh. An overview of pathways encoding nociception. *Clinical and experimental rheumatology*, 35(Suppl 107):40, 2017.

[28] Felipe A Pinho-Ribeiro, Waldiceu A Verri, and Isaac M Chiu. Nociceptor sensory neuron–immune interactions in pain and inflammation. *Trends in immunology*, 38(1):5–19, 2017.

[29] Ouyang Chen, Christopher R Donnelly, and Ru-Rong Ji. Regulation of pain by neuro-immune interactions between macrophages and nociceptor sensory neurons. *Current opinion in neurobiology*, 62:17–25, 2020.

[30] Cuiping Zhang, Caiqi Zhao, Xiaoyan Chen, Rujia Tao, Sijiao Wang, Guangxun Meng, Xing Liu, Changzhou Shao, and Xiao Su. Induction of asc pyroptosis requires gasdermin d or caspase-1/11-dependent mediators and ifnβ from pyroptotic macrophages. *Cell death & disease*, 11(6):470, 2020.

[31] Ni Lian, Yujie Chen, Sihan Chen, Ying Zhang, Hao Chen, Yong Yang, Heng Gu, Qing Chen, Min Li, and Xu Chen. Gasdermin d-mediated keratinocyte pyroptosis as a key step in psoriasis pathogenesis. *Cell Death & Disease*, 14(9):595, 2023.

[32] Christopher R Donnelly, Ouyang Chen, and Ru-Rong Ji. How do sensory neurons sense danger signals? *Trends in neurosciences*, 43(10):822–838, 2020.

[33] Yi-Fei Zhang, Lu Zhou, Han-Qing Mao, Fu-Hua Yang, Zhi Chen, and Lu Zhang. Mitochondrial dna leakage exacerbates odontoblast inflammation through gasdermin d-mediated pyroptosis. *Cell death discovery*, 7(1):381, 2021.

[34] Changhong Wei, Jiamin Zhou, Wenfu Tao, Lixian Qin, Keke Zhang, Jieshan Huang, Ling Gao, and Sufang Zhou. Assessment the value of pyroptosis-associated gasdermin family genes in hepatocellular carcinoma: A multi-omics comprehensive analysis. *Journal of Cancer*, 15(7):1966, 2024.

[35] Zhaoting Li, Fanyi Mo, Yixin Wang, Wen Li, Yu Chen, Jun Liu, Ting-Jing Chen-Mayfield, and Quanyin Hu. Enhancing gasdermin-induced tumor pyroptosis through preventing escrt-dependent cell membrane repair augments antitumor immune response. *Nature Communications*, 13(1):6321, 2022.

Disclaimer:

SurveyX is an AI-powered system designed to automate the generation of surveys. While it aims to produce high-quality, coherent, and comprehensive surveys with accurate citations, the final output is derived from the AI's synthesis of pre-processed materials, which may contain limitations or inaccuracies. As such, the generated content should not be used for academic publication or formal submissions and must be independently reviewed and verified. The developers of SurveyX do not assume responsibility for any errors or consequences arising from the use of the generated surveys.