Cancer Neurobiology and Ion Channels: A Survey

Abstract

Cancer neurobiology, an interdisciplinary field bridging oncology and neuroscience, offers significant insights into tumor behavior and treatment modalities through the study of ion channels, neurotransmitter signaling, and tumor-nerve interactions. This survey examines the multifaceted roles of these components in cancer progression, metastasis, and pain mechanisms. Ion channels, particularly mechanosensitive ones like Piezo1 and TRP channels, modulate cancer cell dynamics and present promising therapeutic targets. Neurotransmitter signaling influences tumor-nerve crosstalk, impacting cancer cell plasticity and adaptability. The neuro-cancer interface underscores the importance of neural elements in tumor progression, while cancer pain mechanisms reveal complex interactions between cancer cells and the nervous system, necessitating innovative pain management strategies. The survey highlights the potential of targeting ion channels and neurotransmitter pathways to disrupt cancer progression and improve therapeutic outcomes. Future research directions include exploring the roles of specific ion channels in immune modulation, understanding the impact of neurotransmitter dynamics on tumor biology, and developing advanced models to study cancer pain. By integrating mechanobiology, ion channel modulation, and personalized medicine, this field holds promise for advancing therapeutic strategies and improving patient outcomes.

1 Introduction

1.1 Relevance of Cancer Neurobiology

Cancer neurobiology is a vital interdisciplinary field that merges oncology and neuroscience, providing insights into cancer mechanisms and treatment strategies. This area focuses on neurotransmitter systems, which are implicated in cancer progression and therapeutic approaches [1]. The interplay between neurotransmitter signaling and circadian rhythms is significant, as disruptions in these cycles can affect cognitive functions and contribute to psychiatric disorders, ultimately influencing cancer outcomes [2].

The resting membrane potential (RMP) plays a crucial role in cancer cell behavior, presenting potential therapeutic targets [3]. Additionally, mechanotransductive receptors like Piezo1 are explored for their dual functions in cancer and neurological disorders, offering new avenues for treatment [4]. The neuro-cancer interface is essential for understanding tumor-nerve interactions, illustrated by the expression of neuroligin 1 (NLGN1) in prostatic and pancreatic cancers, which highlights the importance of these interactions in cancer progression and potential therapeutic targets [5].

Moreover, cancer cell plasticity is critical, particularly in aggressive forms like pancreatic ductal adenocarcinoma (PDA), where it contributes to disease progression and treatment resistance [6]. The influence of neural activity on tumor progression is evident in lethal cancers such as triple-negative breast cancer (TNBC) and melanoma, emphasizing the need to understand neural impacts on metastasis [7]. The role of ubiquitination in regulating inflammatory cell death offers further insights into the ubiquitin-proteasome system (UPS) in cancer, suggesting new therapeutic directions [8].

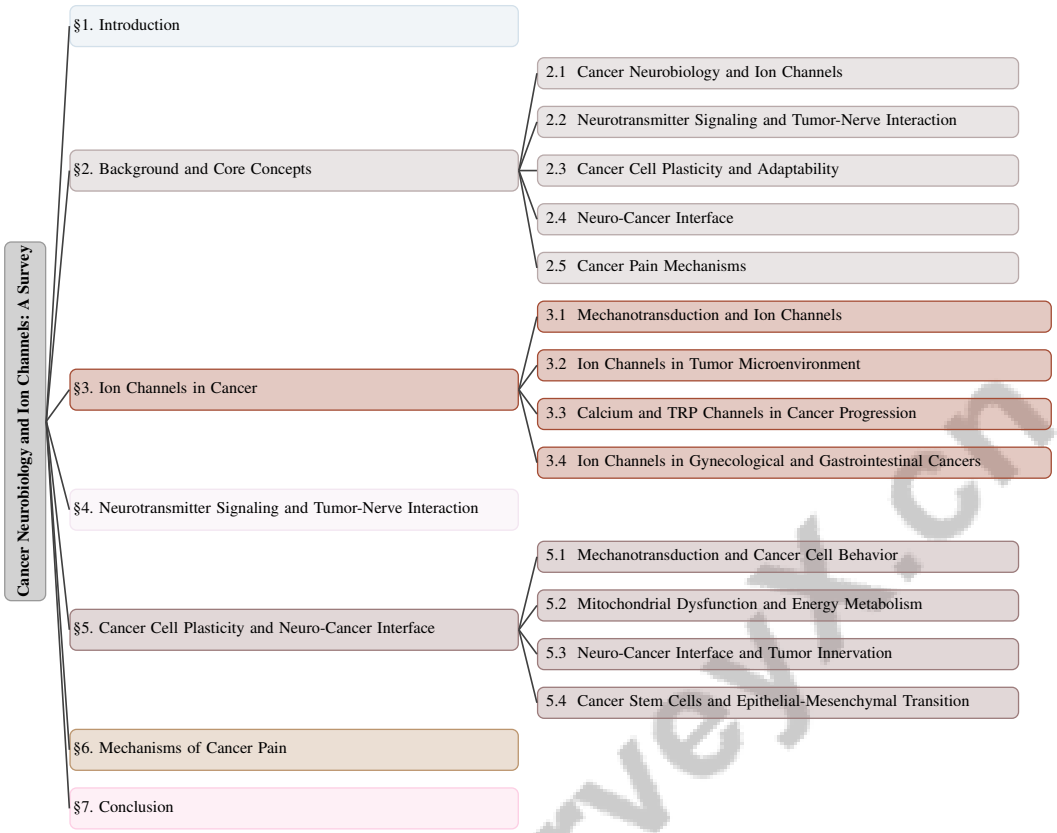

Figure 1: chapter structure

In colorectal cancer (CRC), the mechanistic view of tumor-nerve interactions underscores the critical role of nerves in cancer development and progression [9]. The study of Catechol-O-Methyltransferase (COMT) enhances our understanding of its physiological and pathological roles, including in cancer contexts [10]. These insights collectively emphasize the importance of cancer neurobiology in advancing our understanding of cancer progression and treatment, opening new research and clinical opportunities.

1.2 Interdisciplinary Nature of the Field

Cancer neurobiology exemplifies an interdisciplinary approach that synthesizes insights from both neuroscience and oncology, enhancing comprehension of tumor behavior and progression. This field integrates diverse research areas, as demonstrated by the exploration of Piezo1's significance in neurological conditions and cancer biology [4]. The investigation of semiconducting photothermal nanoagonists further illustrates this interdisciplinary convergence, as these agents can induce apoptosis in cancer cells via TRPV1 channel activation, bridging materials science and biological research [11].

The survey addresses the complex interplay between nerves and various cancer types, including pancreatic, colon, rectal, prostate, head and neck, and breast cancers, highlighting the necessity of merging neuroscience with oncology to fully understand tumor-nerve interactions [12]. Additionally, research organized by neurotransmitter types—such as dopamine, serotonin, and norepinephrine—and their circadian regulation underscores the importance of interdisciplinary approaches in elucidating these biochemical interactions [2].

In colorectal cancer, the integration of neurobiology and oncology is crucial for exploring nerve involvement, revealing how neural elements influence tumor development [9]. The impact of neural activity on tumor behavior, particularly in aggressive cancers like triple-negative breast cancer and melanoma, further exemplifies the interdisciplinary nature of cancer neurobiology, where insights from both fields are essential [7].

AI-generated, for reference only.

Furthermore, the mechanisms of ubiquitination and its regulatory enzymes, along with the consequences of dysregulation in inflammatory responses and cell death, are examined within this interdisciplinary framework, providing a comprehensive understanding of cancer progression and potential therapeutic targets [8]. This multifaceted approach enriches our knowledge of cancer biology and opens new avenues for innovative therapeutic strategies.

1.3 Structure of the Survey

This survey is meticulously structured to encompass the multifaceted dimensions of cancer neurobiology, highlighting the intricate interactions between the nervous system and cancer cells. Initially, the survey introduces the relevance and interdisciplinary nature of cancer neurobiology, setting the stage for a comprehensive exploration of its core concepts. The subsequent section delves into the background and core concepts, providing an overview of fundamental topics such as ion channels, neurotransmitter signaling, tumor-nerve interactions, cancer cell plasticity, the neuro-cancer interface, and cancer pain mechanisms.

Following this foundational overview, the survey examines the role of ion channels in cancer development and progression, exploring their influence on cancer cell behavior and the tumor microenvironment. The discussion then transitions to neurotransmitter signaling and tumor-nerve interactions, analyzing their impact on tumor progression and metastasis. Further sections are dedicated to exploring cancer cell plasticity and the neuro-cancer interface, emphasizing their contributions to cancer adaptability and treatment resistance.

The survey also addresses the mechanisms underlying cancer pain, focusing on the nervous system's role in its development and management challenges. Finally, the concluding sections summarize the key findings, discuss therapeutic implications, and propose future research directions, underscoring the importance of continued exploration in this dynamic field.The following sections are organized as shown in Figure 1.

2 Background and Core Concepts

2.1 Cancer Neurobiology and Ion Channels

Cancer neurobiology, melding oncology and neuroscience, scrutinizes the interplay between cancer cells and the nervous system, focusing on how tumor-associated nerves influence cancer progression. Perineural invasion, associated with adverse outcomes in cancers like pancreatic and breast, exemplifies this interaction, as tumors can initiate their own innervation, underscoring the need for targeted therapeutic strategies [13, 12, 14]. Ion channels, pivotal membrane proteins, regulate ion movement crucial for cancer cell proliferation, migration, and apoptosis, rendering them prime therapeutic targets. Dysregulated calcium signaling, often via calcium-permeable channels, is a cancer hallmark, driving unchecked proliferation, apoptosis resistance, and enhanced metastatic potential, with the transient receptor potential (TRP) ion channel family playing a significant role in calcium influx [15]. Acid-sensing ion channels (ASICs), overexpressed in acidic tumor microenvironments like breast cancer, further promote cancer cell proliferation and migration [16].

Mechanosensitive ion channels, including Piezo and TRP families, are central to mechanotransduction, influencing cellular responses to mechanical stimuli in both physiological and pathological contexts, including cancer. Piezo1, for instance, affects immune cell behavior and cancer development, highlighting its therapeutic potential. Ubiquitination's role in regulating inflammatory cell death offers insights into the ubiquitin-proteasome system (UPS) in cancer, suggesting new therapeutic avenues [8]. Innovative strategies targeting ion channels, such as semiconducting polymer nanoparticles for precise cancer treatment through photothermal-responsive carriers, demonstrate cancer neurobiology's interdisciplinary nature [15]. Additionally, a novel radiomics interpretation pipeline leveraging generative adversarial networks (GANs) with deep learning enhances brain tumor diagnosis and prognosis, integrating computational approaches in cancer treatment.

Exploring ion channels within cancer neurobiology elucidates cancer progression mechanisms and opens promising avenues for targeted therapies. Understanding cellular mechanotransduction and mechanosensitive ion channels, like Piezo and TRP, can identify knowledge gaps and lead to novel therapeutic strategies aimed at improving cancer treatment outcomes by targeting these channels as biomarkers and therapeutic targets [17, 3, 18, 19].

2.2 Neurotransmitter Signaling and Tumor-Nerve Interaction

Neurotransmitter signaling plays a pivotal role in the interactions between the nervous system and cancer cells, significantly influencing tumor progression and metastasis. This interdisciplinary field uncovers how neurotransmitter dynamics affect cancer development [1]. Perineural invasion (PNI) involves complex tumor-nerve interactions and modifications in the tumor microenvironment (TME) that facilitate cancer cell migration along nerve pathways [20]. Interactions between Schwann cells, the central nervous system (CNS), and the peripheral nervous system (PNS) are crucial in tumorigenesis, as these cells can influence cancer cell behavior and contribute to the tumor milieu [21]. In breast cancer, interactions with sensory neurons highlight the need to understand mechanisms influencing nerve growth and associated pain exacerbated by cancer progression [22].

Neurotransmitters and neurotrophic factors are key in tumor-nerve interactions, particularly in colorectal cancer, where they modulate tumor growth and nerve invasion [9]. The role of neuroligin 1 (NLGN1) in mediating interactions between cancer cells and nerves is crucial for understanding tumor invasion and metastasis, further emphasizing the interdisciplinary nature of this research [5]. Advanced techniques for neurotransmitter detection, such as in vivo sampling, imaging, and electrochemical methods, are essential for exploring these interactions and their implications in cancer biology [23]. These methods allow researchers to monitor neurotransmitter signaling dynamics within the TME, providing valuable data for therapeutic strategies.

Investigating intrinsic hippocampal functional connectivity (FC) networks offers insights into cognitive impairments experienced by breast cancer survivors post-chemotherapy, suggesting alterations in neurotransmitter signaling may contribute to these deficits [24]. Collectively, these studies underscore the importance of neurotransmitter signaling in tumor-nerve interactions and highlight potential therapeutic targets for disrupting these pathways to impede cancer progression and metastasis.

2.3 Cancer Cell Plasticity and Adaptability

Cancer cell plasticity enables dynamic adaptation to varying microenvironmental conditions, significantly contributing to treatment resistance and metastasis. This adaptability is linked to remodeling calcium signaling pathways, which play a critical role in tumor progression and therapeutic resistance [25]. Reversible cell plasticity among cancer cells facilitates phenotypic state switching in response to environmental cues, crucial for understanding treatment resistance [26]. In pancreatic cancer, Gas6 promotes metastasis through interactions with tumor cells and natural killer (NK) cells, exemplifying how cellular plasticity influences treatment resistance and disease progression [6]. Additionally, cancer cells exhibit metabolic flexibility, adapting their pathways to thrive under diverse conditions, essential for sustained growth in hostile tumor microenvironments [27].

The tumor microenvironment (TME) is a critical determinant of cancer cell plasticity, influencing epithelial/mesenchymal transitions that alter immune checkpoint ligand profiles and interactions with immune cells [28]. This adaptability is further complicated by perineural invasion in colorectal cancer, where nerve interactions impact tumor progression and prognosis [9]. Ubiquitination processes play a pivotal role in modulating cancer cell plasticity. The complexity of ubiquitin signaling pathways and the functional relevance of ubiquitinated proteins present challenges in targeting dysregulated ubiquitination in cancer [8]. The influence of the TME on cancer cell plasticity, although not fully elucidated, remains a focal point for identifying factors driving metastasis and tumor recurrence, thus increasing patient mortality [29].

Addressing the challenges posed by cancer cell plasticity, particularly in metastatic breast cancer where traditional therapies often fail, is essential for developing effective strategies against tumor progression and resistance [27, 30]. Advancing our understanding of these mechanisms can lead to targeted interventions that improve patient outcomes.

2.4 Neuro-Cancer Interface

The neuro-cancer interface is pivotal in cancer progression, emphasizing the interactions between tumors and the nervous system. This interface illustrates that tumors engage in extensive communication with their microenvironment, including neural components. Processes like neo-neurogenesis and neo-axonogenesis facilitate new neural connections that support tumor growth and metastasis [14]. Mechanotransduction plays a significant role at the neuro-cancer interface, with mechanosensitive

ion channels, such as Piezo channels and integrins, translating mechanical stimuli into biochemical signals that influence cancer cell behavior [19]. These channels are crucial in the gastrointestinal (GI) tract, modulating cellular responses to mechanical changes in the TME [31]. The immunoregulatory effects of Piezo1 on immune cells, including macrophages and T cells, illustrate its role in inflammation and cancer, highlighting its potential as a therapeutic target [17].

Schwann cells, often overlooked in cancer biology, facilitate tumor progression by creating a supportive microenvironment that enhances cancer cell survival and dissemination [21]. Their role in forming a favorable niche underscores the need to consider neural elements in treatment strategies. Perineural invasion (PNI) is a critical mechanism within the neuro-cancer interface, where cancer cells invade surrounding nerves, leading to increased dissemination and reduced survival [32]. Understanding the nervous system's role in the TME and the mechanisms underlying PNI is essential for improving patient outcomes.

Exploring ferroptosis in brain diseases provides insights into unique mechanisms and potential therapeutic approaches, suggesting parallels that may inform cancer research [33]. Elucidating interactions at the neuro-cancer interface can uncover novel therapeutic targets and strategies to disrupt these pathways, ultimately enhancing cancer treatment and patient survival.

2.5 Cancer Pain Mechanisms

Cancer pain mechanisms are complex, involving interactions between cancer cells, the nervous system, and the tumor microenvironment. Understanding these interactions is crucial for addressing cancer-related pain, which significantly impacts quality of life. Peripheral sensory neurons (PSNs) are sensitized by tumor-derived factors, heightening pain perception [34]. The tumor microenvironment exhibits a unique metabolic profile, with cancer cells relying on aerobic glycolysis, known as the Warburg effect [35]. This altered metabolism supports rapid growth and produces byproducts that sensitize PSNs, exacerbating pain.

Programmed cell death (PCD) mechanisms are intricately linked to cancer pain, posing challenges in determining their contributions to pain, as defects may be primary causes or secondary effects of neurological changes [36]. Understanding these mechanisms is vital for developing effective pain management strategies. Neuropeptides, key immune response modulators, also influence cancer pain mechanisms by affecting the TME and immune cell activity, further contributing to pain perception [34]. The bidirectional communication between the nervous and immune systems underscores cancer pain's complexity and highlights potential therapeutic targets for alleviating pain.

Investigating cancer pain mechanisms, including the roles of peripheral and central nervous system pathways, can lead to targeted strategies addressing diverse pain experiences in cancer patients. This tailored approach aims to enhance pain management and improve overall quality of life, especially as cancer-related pain prevalence rises with an aging population and more effective treatments. Understanding biochemical pathways influenced by interventions, such as resistance training, may offer additional pain relief avenues, emphasizing the need for personalized pain management strategies [37, 38, 39].

In recent years, the role of ion channels in cancer biology has garnered significant attention, particularly in understanding their involvement in various cellular processes. Figure 2 illustrates the hierarchical structure of ion channels' roles in cancer, categorizing their involvement in mechanotransduction, tumor microenvironment, calcium and TRP channel signaling, and specific cancer types such as gynecological and gastrointestinal cancers. This figure encapsulates key concepts, including mechanosensitive ion channels, therapeutic strategies, and the influence of ion channels in cancer progression and metastasis. By delineating these relationships, the figure provides a comprehensive overview that enhances our understanding of the multifaceted roles ion channels play in cancer pathology and treatment.

3 Ion Channels in Cancer

3.1 Mechanotransduction and Ion Channels

Mechanotransduction, the conversion of mechanical stimuli into biochemical signals, is critical in regulating cancer cell behaviors, including proliferation, migration, and apoptosis. Mechanosensitive

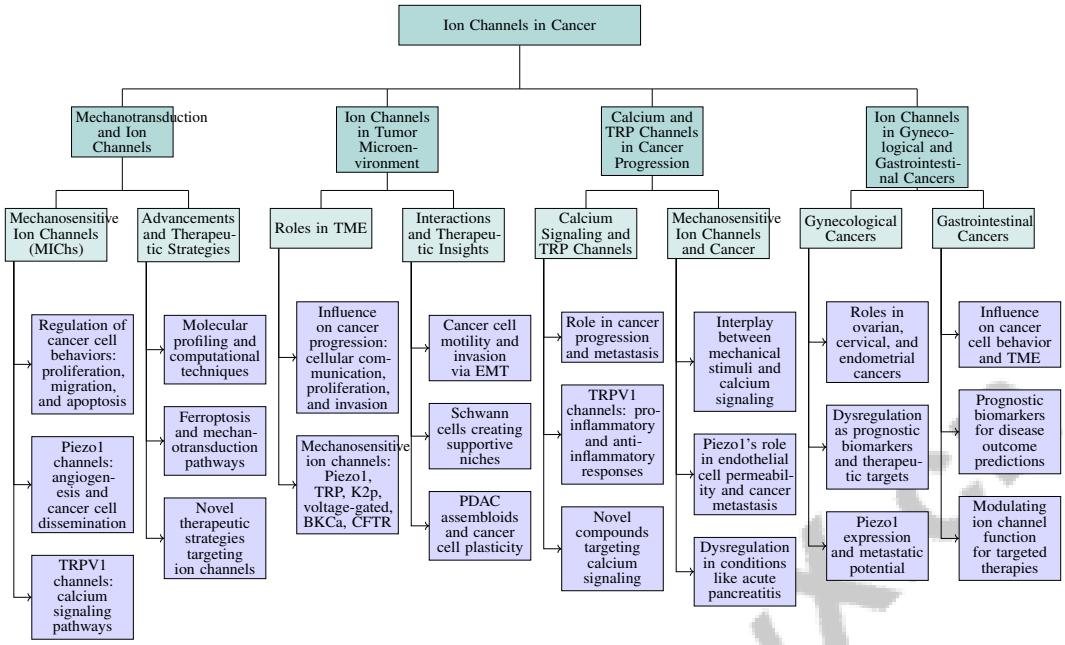

Figure 2: This figure illustrates the hierarchical structure of ion channels' roles in cancer, categorizing their involvement in mechanotransduction, tumor microenvironment, calcium and TRP channel signaling, and specific cancer types such as gynecological and gastrointestinal cancers. Key concepts include mechanosensitive ion channels, therapeutic strategies, and the influence of ion channels in cancer progression and metastasis.

ion channels (MIChs) are pivotal in these processes, significantly impacting cancer dynamics [18]. Piezo1 channels, for instance, facilitate angiogenesis around tumors, enhancing nutrient supply and enabling cancer cell dissemination, marking them as vital therapeutic targets [40]. Similarly, TRPV1 channels influence calcium signaling pathways, affecting cancer cell behavior and presenting additional therapeutic opportunities [41]. The overexpression of acid-sensing ion channels (ASICs), particularly ASIC1a, in acidic tumor microenvironments further promotes cancer cell proliferation and invasion, as demonstrated by studies using siRNA and pharmacological inhibition in breast cancer models [42].

Advancements in molecular profiling and computational techniques, such as deep learning models and GANs, have enhanced the understanding of ion channels' roles in cancer, improving diagnostic and prognostic accuracy [13]. Research into ferroptosis and its intersections with mechanotransduction pathways suggests that neural activity patterns may influence aggressive tumor behavior [33, 7].

As illustrated in Figure 3, the hierarchical structure of mechanotransduction and ion channels in cancer research highlights key mechanosensitive ion channels, computational techniques, and therapeutic strategies. Targeting mechanotransduction pathways and associated ion channels offers novel therapeutic strategies to modulate cancer cell behavior, paving the way for improved treatment outcomes [8].

3.2 Ion Channels in Tumor Microenvironment

Ion channels are essential in the tumor microenvironment (TME), influencing cancer progression through their roles in cellular communication, proliferation, and invasion. The TME, composed of cancer cells, immune cells, stromal cells, and extracellular matrix components, relies on ion channels for mediating interactions and signal transduction. Mechanosensitive ion channels, including Piezo1, TRP channels, K2p channels, voltage-gated ion channels, BKCa channels, and CFTR, are integral to the mechanotransductive processes within the TME, responding to mechanical stimuli and modulating cancer cell behavior [31].

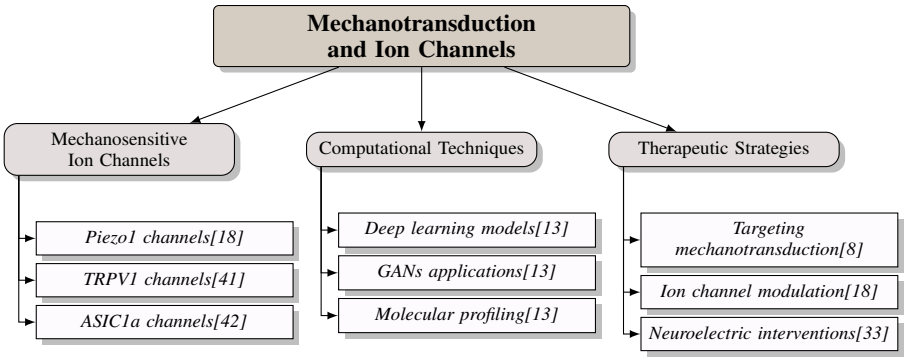

Figure 3: This figure illustrates the hierarchical structure of mechanotransduction and ion channels in cancer research, highlighting key mechanosensitive ion channels, computational techniques, and therapeutic strategies.

Piezo1, in particular, enhances cancer cell motility and invasion via epithelial-to-mesenchymal transition (EMT) mechanisms, promoting angiogenesis and nutrient supply [40, 43]. Schwann cells within the TME also play a significant role, interacting with neuronal and tumor cells to create supportive niches that promote tumor growth [21]. The use of PDAC assembloids, derived from organoid cultures of ductal cancer cells co-cultured with endothelial and immune cells, provides insights into cancer cell plasticity and the dynamic nature of the TME [44].

These channels facilitate complex interactions between cancer cells and their environment, influencing proliferation, migration, invasion, and EMT, ultimately contributing to tumor progression [20, 45, 46, 16, 18]. Understanding these roles can lead to novel therapeutic targets and strategies to disrupt cancer progression, improving patient outcomes.

3.3 Calcium and TRP Channels in Cancer Progression

Calcium signaling plays a crucial role in cancer progression and metastasis, with transient receptor potential (TRP) channels, particularly TRPV1, significantly regulating calcium influx and influencing cancer cell behaviors such as proliferation, invasion, and therapy resistance [15]. TRPV1 mediates both pro-inflammatory and anti-inflammatory responses, indicating its complex role in cancer progression [41]. Activation of TRPV1 channels induces rapid ion influx, triggering apoptosis in TRPV1-positive cancer cells, highlighting its therapeutic potential [11].

Novel compounds, including those derived from scorpion venom, show promise in targeting ion channels involved in calcium signaling for cancer treatment [47]. Beyond TRP channels, store-operated calcium channels (SOCs) contribute to dysregulated calcium homeostasis, supporting tumorigenic processes [16]. These channels' aberrant expression and function facilitate cancer cell proliferation and metastasis, creating opportunities for targeted interventions.

Mechanosensitive ion channels, such as Piezo1, demonstrate the interplay between mechanical stimuli and calcium signaling in cancer [18]. Piezo1 enhances endothelial cell permeability, aiding cancer cells in bloodstream navigation, a critical metastatic step. Its role varies across cancer types, exhibiting protumorigenic effects in breast and gastric cancers, while inhibition in lung cancer promotes metastasis, illustrating the nuanced roles of MIChs in cancer [18]. Dysregulation of ion channels and metal ion signaling in conditions like acute pancreatitis can lead to cellular damage, potentially progressing to pancreatic cancer, emphasizing the broader implications of ion channel dysregulation in cancer [45].

The involvement of calcium and TRP channels in cancer progression highlights the intricate mechanisms by which ion channels contribute to tumorigenesis and metastasis. Advancing the understanding of these channels can reveal novel therapeutic targets to disrupt cancer progression and improve patient outcomes [8].

3.4 Ion Channels in Gynecological and Gastrointestinal Cancers

Ion channels play critical roles in the pathophysiology of gynecological cancers, including ovarian, cervical, and endometrial cancers, influencing tumor biology aspects such as proliferation, migration, and invasion [46]. Dysregulation of specific ion channels in these malignancies contributes to cancer progression and presents potential prognostic biomarkers and therapeutic targets. For instance, Piezo1 expression is associated with facilitating cancer cell dissemination, underscoring its relevance in the metastatic potential of gynecological tumors [40].

In gastrointestinal (GI) cancers, ion channels similarly influence cancer cell behavior and the TME. Dysregulated ion channel activity in GI cancers can serve as prognostic biomarkers, aiding in disease outcome predictions and therapeutic decisions [16]. Modulating ion channel function holds promise for targeted cancer therapies, offering new avenues to disrupt cancer progression and enhance patient prognosis.

Exploring ion channels in gynecological and gastrointestinal cancers highlights their critical roles in tumorigenesis and metastasis. By deepening the understanding of cancer cell plasticity and metabolic adaptability, particularly in breast and gynecological cancers, researchers can devise innovative therapeutic strategies targeting the mechanisms driving tumor progression, therapeutic resistance, and metastasis. This approach aims to enhance existing treatment efficacy and significantly improve patient outcomes by addressing the complexities of malignant behavior in these diseases [42, 27, 46, 13, 30].

4 Neurotransmitter Signaling and Tumor-Nerve Interaction

This section delves into how neurotransmitter signaling affects tumor-nerve interactions and cancer biology, particularly in modulating tumor behavior and the tumor microenvironment. Understanding these dynamics is essential for grasping their implications in cancer progression. The subsequent subsections will explore the mechanisms of neurotransmitter signaling in cancer, emphasizing key pathways and interactions that contribute to tumor development and progression.

4.1 Mechanisms of Neurotransmitter Signaling in Cancer

Neurotransmitter signaling plays a critical role in cancer development by influencing tumor-nerve interactions and reshaping the tumor microenvironment. Monitoring neurotransmitter dynamics is crucial to understanding their roles in cancer progression [1]. The neuromedin B-induced Schwann Cell Reprogramming (NMB-SCR) method exemplifies how neurotransmitter signaling can affect these interactions and tumor development [48]. In pancreatic ductal adenocarcinoma (PDAC), neurotransmitter signaling induces specific transcriptomic and functional repair signatures in peripheral neuroglia, suggesting that neuroglial cells may create a supportive niche for cancer cells [49]. The complexity of neurotransmitter roles is further compounded by interactions between mechanical stimuli and ion channels within the tumor microenvironment, an area that remains inadequately understood [31].

To illustrate these mechanisms, Figure 4 presents a comprehensive overview of neurotransmitter signaling in cancer, focusing on tumor-nerve interactions, monitoring techniques, and cognitive implications. This figure highlights specific methods and findings from recent studies, emphasizing their role in understanding cancer progression and identifying potential therapeutic targets. Additionally, functional connectivity analysis of hippocampal networks reveals the influence of neurotransmitter signaling on cognitive performance and cancer-related outcomes, underscoring the broader implications of neurotransmitter dynamics in cancer biology [24]. These findings highlight the necessity for advanced methodologies to effectively monitor and modulate neurotransmitter signaling.

4.2 Tumor-Nerve Crosstalk and Perineural Invasion

Tumor-nerve crosstalk and perineural invasion (PNI) are pivotal in cancer progression, influencing tumor behavior and patient prognosis. PNI, where cancer cells invade the perineural space, is linked to increased local recurrence and metastasis in PDAC, with prevalence rates in surgical specimens ranging from 70.8% to 93% [49, 50]. Understanding tumor cell interactions with the nerve microenvironment is a major challenge in treating cancers exhibiting PNI [20]. Pathways such

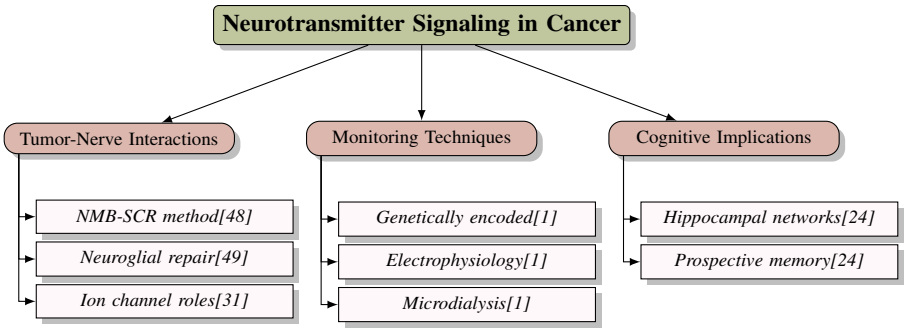

Figure 4: This figure illustrates the mechanisms of neurotransmitter signaling in cancer, focusing on tumor-nerve interactions, monitoring techniques, and cognitive implications. It highlights specific methods and findings from recent studies, emphasizing their role in understanding cancer progression and potential therapeutic targets.

as VEGF-A/VEGFR2/ARP2/3 are exploited by breast cancer cells to influence sensory neuronal growth [22]. In cervical cancer, PNI involves tumor cell interactions with Schwann cells, illustrating the complexity of tumor-nerve crosstalk [48]. The role of neuroligin 1 (NLGN1) in promoting cancer cell invasion along nerves, particularly with the neurotrophic factor GDNF, highlights the intricate mechanisms driving tumor-nerve interactions [5]. In colorectal cancer, PNI is crucial for tumor progression, necessitating targeted therapies to address this invasive behavior [9]. Recent studies indicate that tumors actively recruit and reprogram nerve fibers to support their progression, emphasizing the need for innovative therapeutic strategies to disrupt these pathways and improve cancer treatment outcomes [20, 14, 49, 12, 22].

4.3 Impact of Neurotransmitter Signaling on Tumor Progression and Metastasis

Neurotransmitter signaling is crucial in modulating tumor progression and metastasis by influencing tumor-nerve interactions. In PDAC, interactions between cancer cells and peripheral nerves reprogram Schwann cells and macrophages, promoting PNI [49]. This reprogramming greatly enhances PDAC's invasive potential, facilitating local tumor spread and increasing metastasis likelihood. PNI is a hallmark of aggressive tumor behavior and an important prognostic factor in PDAC, closely linked to local recurrence [50]. Neurotransmitter signaling within the tumor microenvironment enhances cancer cell invasiveness, exacerbating disease progression. It alters the expression of neurotrophic factors and signaling molecules, fostering metastasis, particularly through PNI, where tumors recruit neuronal components to promote progression. Recent research underscores the nervous system's role in tumor development, highlighting the significance of tumor-nerve relationships in cancer biology [12, 14]. This complex interplay necessitates targeted therapeutic strategies to disrupt these pathways and mitigate their impact on cancer progression and metastasis.

4.4 Neurotransmitter Detection and Challenges

Detecting neurotransmitters in cancer biology presents significant challenges due to their low concentrations and the complex biochemical milieu in the brain [23]. This complexity complicates the selective detection and quantification of neurotransmitters, which is essential for understanding their roles in tumor-nerve interactions and cancer progression. Accurately monitoring neurotransmitter dynamics is crucial for elucidating their impact on tumor behavior, as these molecules mediate cellular communication and influence cancer cell proliferation, invasion, and metastasis. Advanced analytical techniques are necessary to address these detection challenges, including sensitive and specific methods for in vivo sampling and imaging. Electrochemical methods and analytical chemistry approaches have improved neurotransmitter detection, providing insights into their spatial and temporal distribution within brain and tumor tissues. These methodologies enable researchers to investigate the complex signaling networks governed by neurotransmitters and neuromodulators, revealing crucial insights into their roles in health and disease, and paving the way for innovative therapeutic strategies for various neurological disorders [23, 3, 1, 14]. Despite technological advancements, significant gaps remain in understanding how neurotransmitter signaling contributes to cancer biology. Developing sophisticated detection techniques capable of distinguishing between

different neurotransmitter species and their metabolites is imperative for advancing our knowledge. Overcoming current challenges in monitoring neurotransmitter dynamics can improve therapeutic targeting of these pathways, potentially leading to enhanced treatment strategies and better clinical outcomes for cancer patients, particularly by addressing the metabolic adaptability crucial for cancer cell growth and survival [27, 1].

4.5 Potential Therapeutic Targets in Neurotransmitter Signaling

Exploring neurotransmitter signaling pathways unveils several promising therapeutic targets for cancer treatment. The transient receptor potential vanilloid 1 (TRPV1) channel is particularly significant due to its role in modulating cancer cell behavior and immune interactions. TRPV1 channels influence inflammation and apoptosis, making them attractive candidates for therapeutic intervention in oncology [41]. Targeting TRPV1 may disrupt signaling pathways that facilitate tumor progression and metastasis, thus improving patient outcomes. Advancements in neurotransmitter detection methods have significantly enhanced sensitivity and selectivity, enabling a deeper understanding of neurotransmitter dynamics in cancer biology [23]. These developments facilitate the identification of novel biomarkers and therapeutic targets within neurotransmitter pathways, leading to more effective cancer treatments. Integrating sensitive sensors for neurotransmitter monitoring is crucial, as these technologies provide real-time data on neurotransmitter fluctuations and their impact on tumor-nerve interactions [1]. Additionally, identifying specific biomarkers such as E-cadherin, Vimentin, CD80, and CD155 offers valuable insights into predicting responses to immunotherapies like anti-PD-1/PD-L1 treatments [28]. These biomarkers, associated with neurotransmitter signaling pathways, hold potential as therapeutic targets that could enhance the efficacy of existing cancer therapies by modulating the tumor microenvironment and immune responses. Targeting neurotransmitter signaling pathways presents a promising avenue for cancer therapy. By employing cutting-edge detection technologies and deepening our understanding of molecular interactions, researchers can formulate innovative strategies that address tumor heterogeneity and metabolic adaptability in cancer cells. This multifaceted approach not only disrupts critical signaling pathways but also enhances the precision of personalized therapies, ultimately leading to significantly improved therapeutic outcomes for cancer patients. Advances in computational methods, including machine learning and single-cell multi-omics, play a pivotal role in analyzing large-scale oncologic data, allowing for more tailored treatment plans that address the complexities of individual tumors and their microenvironments [27, 13, 51].

5 Cancer Cell Plasticity and Neuro-Cancer Interface

The intricate relationship between cancer cell plasticity and the neuro-cancer interface necessitates an understanding of the mechanisms governing cellular responses to mechanical and biochemical stimuli. This section explores mechanotransduction's role in shaping cancer cell dynamics, particularly the influence of mechanical forces on cellular signaling pathways and behavior. We will examine the specific processes of mechanotransduction and their implications for cancer cell adaptability, laying the groundwork for a deeper investigation into the mechanisms driving these phenomena.

5.1 Mechanotransduction and Cancer Cell Behavior

Mechanotransduction, the conversion of mechanical cues into biochemical signals, is pivotal in influencing cancer cell behavior and plasticity. Mechanosensitive ion channels, notably Piezo1 and TRPV1, mediate cellular responses to mechanical stimuli [31]. Piezo1 channels are critical in sensing mechanical forces and are implicated in various physiological and pathological processes, including cancer. Further exploration is needed to delineate Piezo1-mediated signaling pathways, such as apoptosis and ferroptosis, and to assess the long-term effects of targeting Piezo1 therapeutically [52].

The interplay between mechanotransduction and signaling pathways, including the OSM/IL-6/JAK axis, further influences cancer cell plasticity and metastasis, highlighting potential therapeutic targets [29]. Modulation of calcium, iron, and copper signaling in acinar cells contributes to cellular stress and injury, providing insights into the complex interactions of these ions in cancer pathophysiology [52].

Research on TRPV1's mechanotransductive properties has enhanced our understanding of its role in immune modulation, which is significant for cancer cell behavior and plasticity. TRPV1's ability to respond to mechanical stimuli and modulate immune responses positions it as a potential therapeutic target in oncology [53]. Innovative methodologies, such as culturing cancer cells in serum-free media to form tumorspheres, facilitate the assessment of changes in chemoresistance and stemness, shedding light on cancer cell plasticity.

Future research should emphasize developing targeted therapies that modulate mechanosensitive ion channels and elucidate the signaling pathways involved in mechanosensation in the gastrointestinal tract [31]. Advancing our understanding of these processes can help identify novel therapeutic targets and strategies to disrupt cancer progression and enhance treatment efficacy [50].

5.2 Mitochondrial Dysfunction and Energy Metabolism

Mitochondrial dysfunction and altered energy metabolism are pivotal in shaping cancer cell plasticity, influencing adaptability and treatment resistance. Mitochondria, as central energy production hubs, undergo significant alterations in cancer cells, contributing to metabolic reprogramming that supports rapid proliferation and survival in hostile tumor microenvironments. This often involves a shift from oxidative phosphorylation to glycolysis, even in the presence of oxygen, a phenomenon known as the Warburg effect [35].

Despite the reliance on glycolysis, mitochondrial function remains critical in cancer cells. Enhancing mitochondrial oxidative phosphorylation through alternative electron transfer pathways has been proposed as a therapeutic strategy, benefiting both neurodegenerative diseases and cancer [35]. This complexity underscores the potential of targeting mitochondrial pathways to disrupt the energy balance essential for cancer cell survival.

The genetic and metabolic heterogeneity of tumors presents challenges in understanding and targeting these metabolic pathways [27]. Each tumor's unique metabolic profile necessitates tailored therapeutic approaches, as the interplay between mitochondrial dysfunction and metabolic reprogramming is highly context-dependent. This heterogeneity complicates the development of universal metabolic interventions, emphasizing the need for personalized treatment strategies that consider the specific metabolic adaptations of individual tumors.

Investigating mitochondrial dysfunction and altered energy metabolism in cancer cell plasticity provides insights into the dynamic adaptations driving cancer progression and therapeutic resistance. These adaptations enable cancer cells to utilize various metabolic substrates and process them diversely, enhancing their ability to survive and proliferate in fluctuating microenvironments. Understanding these mechanisms is crucial for developing targeted therapies that effectively combat tumor heterogeneity and improve patient outcomes [27, 54, 53, 51, 30].

5.3 Neuro-Cancer Interface and Tumor Innervation

The neuro-cancer interface is vital for understanding tumor innervation mechanisms and cancer cell adaptability, emphasizing the complex interactions between neural elements and cancer cells. Tumor innervation significantly impacts growth, progression, and metastasis, highlighting the biological role of nerves within the tumor microenvironment [9].

Mitochondrial dysfunction and altered calcium signaling are integral to the neuro-cancer interface, affecting energy metabolism and contributing to cancer cell plasticity. This dysfunction is prevalent in neurodegenerative diseases and cancers, facilitating metabolic reprogramming that allows cancer cells to adapt to diverse microenvironmental conditions and resist therapeutic interventions. The involvement of calcium channels, including TRP channels and store-operated calcium channels (SOCs), in these processes underscores their potential as therapeutic targets [15].

The plasticity of Schwann cells significantly influences tumor behavior, as these cells can reprogram to create a supportive niche that promotes tumor growth and metastasis [21]. In pancreatic ductal adenocarcinoma (PDAC), significant neural injury and neuroglial cell reprogramming occur, characterized by unique transcriptomic signatures that highlight the neuro-cancer interface's role in cancer progression [49]. Moreover, strong perineural Tenascin C (TNC) expression in PDAC correlates with poor prognosis and locoregional recurrence, emphasizing the impact of neural components on cancer outcomes [50].

Interactions between breast cancer cells and sensory neurons exemplify the neuro-cancer interface, significantly influencing neuronal growth and activation [22]. Neuroligin 1 (NLGN1) is crucial in promoting tumor-nerve interactions, contributing to cancer cell adaptability [5]. These interactions suggest that cancer cells exploit neural components to create a supportive microenvironment conducive to tumor progression.

Future research should elucidate the signaling pathways associated with mechanosensitive ion channel (MICh) activation in cancer and explore therapeutic targeting of MIChs [18]. Investigating the neuro-cancer interface and its impact on tumor innervation and cancer cell adaptability reveals critical insights into mechanisms driving cancer progression. Targeting these interactions could lead to innovative therapeutic strategies to disrupt cancer progression and improve patient outcomes.

5.4 Cancer Stem Cells and Epithelial-Mesenchymal Transition

Cancer stem cells (CSCs) and epithelial-mesenchymal transition (EMT) are pivotal processes contributing to cancer cell plasticity, influencing tumor progression, heterogeneity, and therapeutic resistance. CSCs possess the ability to self-renew and differentiate into various cell types, playing a crucial role in tumor initiation and maintenance. Their dynamic plasticity, characterized by bidirectional transitions between CSCs and non-stem cancer cells (NSCCs), is fundamental to tumor adaptability and resistance to therapy [53]. This phenotypic plasticity is integral to the CSC model, where CSCs can generate diverse cancer cell populations, thereby contributing to tumor heterogeneity [29].

EMT enables epithelial cells to acquire mesenchymal characteristics, enhancing their migratory and invasive capabilities. This transition is a key mechanism by which cancer cells gain stem-like properties, further augmenting plasticity and contributing to metastasis and treatment resistance. The cooperative signaling between STAT3 and SMAD3, activated by Oncostatin M (OSM), enhances our understanding of mechanisms contributing to EMT and CSC properties [29]. The interplay between EMT and CSCs is evident in various cancers, including breast cancer, where molecular pathways governing cellular plasticity tightly regulate these processes [28].

Endoplasmic reticulum (ER) stress has emerged as a critical factor influencing cancer cell plasticity, promoting tumor progression and therapeutic resistance. Understanding the molecular mechanisms underlying ER stress-induced plasticity is essential for developing targeted therapies that effectively combat cancer heterogeneity and resistance. The role of JAG1 in maintaining cancer cell plasticity and tumor heterogeneity in pancreatic ductal adenocarcinoma (PDAC) underscores the complexity of these processes and their significance in cancer cell adaptability [50].

Future research should focus on elucidating the specific molecular pathways involved in CSC and EMT plasticity, aiming to identify novel therapeutic targets to improve treatment outcomes. Exploring niche interactions and the potential for therapeutic interventions that modulate CSC behavior offer promising avenues for advancing cancer treatment. Additionally, identifying differentially expressed genes, including ion channels, in esophageal squamous cell carcinoma (ESCC) highlights significant alterations in molecular pathways contributing to cancer cell plasticity, underscoring the need for comprehensive analyses to better understand these complex processes [50].

6 Mechanisms of Cancer Pain

6.1 Classification and Pathophysiology of Cancer Pain

Cancer pain comprises nociceptive, neuropathic, and mixed components, each with distinct mechanisms. Nociceptive pain, often linked to inflammation, arises from tissue damage, while neuropathic pain results from nerve injury, as seen in cancer-induced bone pain (CIBP) [55]. Mixed pain, combining these elements, complicates management [56]. Inflammatory mediators sensitize nociceptors, increasing pain perception, while neuropathic mechanisms involve changes in ion channel expression and neurotransmitter dynamics, with TRPV4 channels playing a significant role via oxidative stress pathways [57]. Current therapies often fall short, highlighting the need for innovative interventions like tissue engineering for novel analgesics [58]. Classifying pain into tumor- and treatment-related categories emphasizes understanding sensory abnormalities [59], crucial for targeted therapies addressing specific pain mechanisms.

CIBP's neuropathic mechanisms highlight the need for novel interventions [60]. Combining opioids with antidepressants or antiepileptic drugs has been explored to enhance relief [61], but many studies suffer from low quality and bias, necessitating rigorous research [61]. Cancer pain affects 66-70

6.2 Mechanisms of Cancer-Induced Bone Pain (CIBP)

CIBP, a blend of nociceptive and neuropathic pain, arises from cancer metastasis to bone and changes in the bone microenvironment [37]. It involves nociceptor activation by pro-inflammatory cytokines, sensory neuron sensitization, and bone remodeling, leading to persistent pain [55]. Pain intensity varies with metastatic burden and treatment response [55]. Conventional treatments often fail, prompting exploration of novel therapies [62]. Targeting molecular pathways, such as inhibiting S1PR1 signaling to address pain and neuroinflammation, shows promise [63]. TRPV4 antagonists offer potential neuropathic pain relief, indicating a novel pharmacological strategy [57]. Calcium signaling pathways, crucial in CIBP pathogenesis, necessitate targeted therapies minimizing side effects on normal cells [64]. Immune checkpoint inhibitors like nivolumab protect against bone destruction and alleviate pain, despite initial sensitivity increases, underscoring immune-based therapies' potential in CIBP management [60].

6.3 Neuropathic Cancer Pain and Sensory Abnormalities

Neuropathic cancer pain (NCP), resulting from nervous system dysfunction due to cancer or its treatments, presents significant management challenges [55]. It requires comprehensive evaluations due to its complex pathophysiology and symptom overlap. Advances in understanding NCP mechanisms have identified therapeutic targets. Perineural invasion (PNI) in cancer pain, especially in cervical cancer, highlights nervous system interactions in neuropathic pain [34]. Modulating neuropeptide signaling pathways offers innovative treatment options. The sphingosine-1-phosphate (S1P) signaling axis is a promising target for managing CIBP's neuropathic characteristics. Blocking S1P/S1PR1 signaling mitigates pain and reduces neuroinflammation, providing a therapeutic avenue [60]. The absence of a universally accepted classification system for cancer pain results in management inconsistencies.

Understanding cancer pain's sensory phenotype is critical. Studies reveal significant gaps in sensory abnormalities, particularly in thermal and mechanical detection thresholds [55]. Comprehensive models integrating cell type interactions in bone pain are needed. Peripheral sensory neurons (PSNs) influence tumor immunity and pain, suggesting therapeutic targets in neuropeptide signaling [34]. Resistance training alleviates pain and improves quality of life, showcasing its potential as an adjunctive therapy. Managing cancer pain is complicated by high adverse event risks with combination treatments and insufficient efficacy evidence. This lack of robust data complicates treatment decisions, underscoring the need for improved assessment methodologies for cancer-related pain, as nearly 40

7 Conclusion

7.1 Therapeutic Implications and Future Directions

Cancer neurobiology offers promising therapeutic avenues, particularly through the modulation of ion channels and neurotransmitter pathways. Mechanosensitive ion channels, such as Piezo1 and TRPV4, emerge as potential targets due to their roles in cancer cell dynamics and immune responses. The involvement of TRPV4 in neuropathic pain highlights the importance of exploring oxidative compounds for pain management. A deeper understanding of Piezo1's signaling within immune contexts could enhance its utility in cancer immunotherapy.

Future research should focus on the roles of non-peptidergic nociceptors in cancer, the interaction between peripheral sensory neurons and other neural pathways, and the influence of psychological stress on pain and tumor progression. Direct interactions between colorectal cancer cells and nerves, along with targeted therapies for nerve involvement, are critical areas of study. Establishing standardized guidelines for perineural invasion and exploring its molecular mechanisms are essential for developing innovative treatments targeting this aspect in colorectal cancer.

The potential of transient receptor potential channels in pain management and inflammatory disease presents promising research opportunities. Investigating immune evasion mechanisms related to cancer cell plasticity and developing therapies to overcome resistance are crucial. Integrating immunotherapy with conventional treatments, exploring metabolic adaptations of cancer stem cells, and preventing the reawakening of dormant cells are vital research directions.

In cancer pain management, developing advanced in vitro models that mimic the human skeletal environment is crucial for understanding cancer-induced bone pain. Refining pain classification and examining the link between treatment modalities and pain phenotypes in survivors are essential. Combining quantitative sensory testing with assessments of central pain mechanisms could enhance management strategies. Addressing the psychosocial aspects of cancer-induced pain is also vital for comprehensive care.

The integration of mechanobiology, ion channel modulation, and personalized medicine holds significant potential for advancing cancer therapies. Continued exploration of these interdisciplinary approaches may yield innovative treatments that improve patient outcomes and address the complexities of cancer biology. Additionally, the interplay between ubiquitination and other post-translational modifications presents another promising therapeutic avenue, particularly in targeting the ubiquitin-proteasome system across diseases.

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