Osteosarcoma Metastasis and Immune Evasion: A Survey

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Abstract

Osteosarcoma, a prevalent primary malignant bone tumor, poses significant treatment challenges due to its high metastatic potential and resistance to existing therapies. This survey explores the intricate interplay between osteosarcoma cells and their immune microenvironment, emphasizing the tumor immune microenvironment's (TIME) role in cancer progression and immune evasion. The survey systematically analyzes osteosarcoma metastasis mechanisms, highlighting the critical stages of local invasion, intravasation, survival in circulation, and colonization at secondary sites. It underscores the influence of cancer stem cells (CSCs) and metabolic adaptations in facilitating metastatic plasticity. The immune microenvironment's composition, regulatory mechanisms, and its dualistic role in tumor suppression and facilitation are examined, with a focus on immune checkpoints, antigen presentation alterations, and CSCs' role in immune evasion. Emerging immunotherapeutic strategies targeting the TIME, including immune checkpoint inhibitors and personalized medicine approaches, are discussed for their potential to enhance treatment efficacy. The survey concludes by emphasizing the need for innovative therapeutic strategies that modulate the immune microenvironment and restore anti-tumor immunity, highlighting the significance of understanding these complex interactions for advancing osteosarcoma treatment and improving patient outcomes.

1 Introduction

1.1 Overview of Osteosarcoma

Osteosarcoma, the most common primary malignant bone tumor, predominantly affects children and adolescents [1]. This aggressive cancer is marked by rapid growth and a high tendency to metastasize, significantly impacting survival rates. Despite advancements in medical research, prognosis for osteosarcoma has remained largely unchanged since the 1970s, emphasizing the urgent need for innovative therapeutic strategies.

The tumor primarily comprises malignant mesenchymal cells and typically arises in the metaphyseal regions of long bones during rapid skeletal growth [2]. Its pathogenesis involves complex molecular mechanisms, including genetic mutations that drive abnormal somatic cell proliferation [3]. The tumor microenvironment, particularly the immune microenvironment, is crucial for tumor progression and metastasis, reflecting the intricate interactions between cancer cells and immune responses.

The propensity for metastasis presents substantial treatment challenges, particularly in pediatric osteosarcoma, which has high incidence and mortality rates, especially in metastatic cases. Early diagnosis and effective treatment strategies are critical for improving patient outcomes [4]. Current research focuses on targeting signaling pathways, utilizing immune checkpoint inhibitors, and developing novel drug delivery systems to enhance therapeutic efficacy [5]. Advancing the understanding of molecular pathogenesis and identifying new therapeutic targets remain essential for addressing the significant challenges posed by this aggressive cancer.

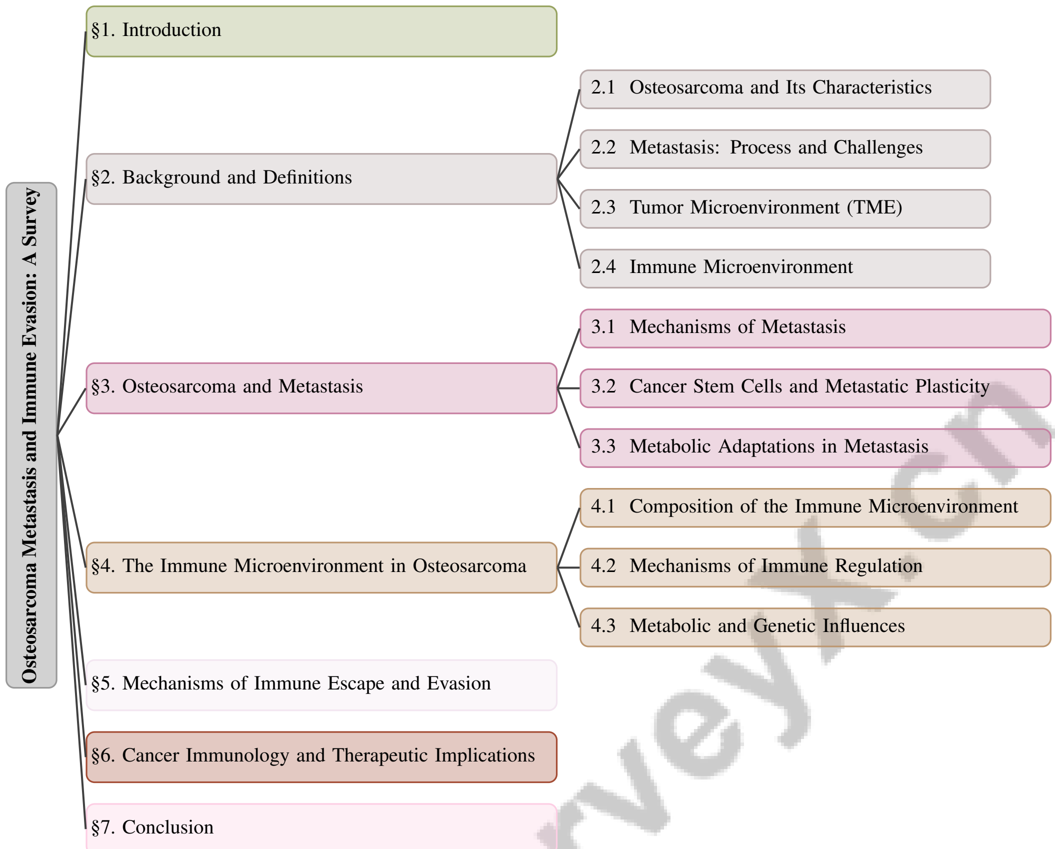

Figure 1: chapter structure

1.2 Significance of Metastasis

Metastasis in osteosarcoma is a critical factor influencing patient prognosis, primarily due to its role in disease progression and increased mortality rates. This multistep process involves the dissemination of malignant cells from the primary tumor to distant organs, representing a significant clinical challenge [6]. Secondary tumor formation is a major contributor to cancer-associated mortality, particularly in cases of secondary bone cancer stemming from osteosarcoma [7].

Despite advancements in therapeutic strategies over the past four decades, survival rates for osteosarcoma patients have plateaued, highlighting the need for a deeper understanding of metastasis mechanisms. The complexity of osteosarcoma metastasis is exacerbated by the tumor's high cellular heterogeneity and intricate microenvironment interactions [6]. The persistent treatment resistance in osteosarcoma further complicates the management of metastatic disease.

Current diagnostic methods, including histological-guided biopsies and MRI scans, often fail to accurately identify and prognose malignant bone tumors, underscoring the need for improved diagnostic tools and biomarkers. Late-stage diagnosis, coupled with radioresistance, necessitates the development of more effective treatment options, particularly for recurrent and metastatic cases [4]. Continued research is vital for developing innovative strategies to target metastatic osteosarcoma and enhance patient outcomes [8].

1.3 Role of the Immune Microenvironment

The immune microenvironment is a dynamic component of the tumor microenvironment (TME) in osteosarcoma, significantly influencing disease progression and metastasis through interactions among various cellular and molecular elements. Recent studies emphasize the complex interplay between immune cells, stromal components, and tumor cells, suggesting that understanding these interactions could lead to novel therapeutic strategies that improve outcomes for osteosarcoma patients

[9, 10, 11, 12]. This environment is characterized by interactions that promote both pro-tumorigenic and anti-tumorigenic pathways, impacting clinical outcomes.

In osteosarcoma, the interactions between tumor cells and the immune microenvironment are crucial for understanding the metastatic cascade. Myeloid-derived suppressor cells (MDSCs) play a key role in establishing an immunosuppressive milieu that facilitates tumor growth and metastasis. Additionally, the regulation of immune checkpoint molecules, such as PD-L1, and the PD-L1/PD-1 signaling axis complicate the immune landscape, contributing to immune escape and tumor progression [13]. The NKG2D receptor and its ligands also modulate immune responses, highlighting their significance in osteosarcoma's immune evasion strategies [14].

The spatial organization of the tumor immune microenvironment (TIME) is essential for determining immune cell distribution and interactions with tumor cells, thus influencing the efficacy of immune responses [15]. This heterogeneity necessitates a nuanced understanding for developing effective therapeutic interventions, as it significantly impacts treatment outcomes and the success of immunotherapeutic approaches [16]. Furthermore, the immune microenvironment is implicated in sustaining cancer stem cell (CSC) states, vital for ongoing tumor growth and metastatic potential, presenting additional challenges in osteosarcoma treatment [17].

Recent advancements in immunotherapy, which aim to modulate the TIME to restore anti-tumor immunity, highlight the therapeutic potential of targeting the immune microenvironment [18]. Dendritic cells (DCs) have emerged as key players in cancer immunology, with their diverse subsets offering promising avenues for therapeutic intervention [19]. Despite the challenges posed by osteosarcoma's complex biology and immune evasion tactics, ongoing research into the immune microenvironment continues to yield valuable insights that may enhance treatment efficacy and improve patient outcomes. This survey will address the complexities and variabilities within the TIME and its impact on the efficacy of immunotherapy, particularly immune-checkpoint blockade (ICB) [20].

1.4 Structure of the Survey

This survey is systematically organized to provide a comprehensive analysis of osteosarcoma metastasis and immune evasion. The initial sections introduce osteosarcoma, emphasizing its nature as a primary bone cancer with a marked propensity for metastasis and the critical role of the immune microenvironment in tumor progression. The background section defines and explains key concepts, establishing a foundation for understanding the complex interactions within the tumor microenvironment. Subsequent sections explore the mechanisms of osteosarcoma metastasis, including biological pathways, cancer stem cells, and metabolic adaptations. The immune microenvironment is examined in detail, focusing on its composition, regulatory mechanisms, and the influence of metabolic and genetic factors. The survey further analyzes immune escape and evasion processes, highlighting the roles of immune checkpoints, alterations in antigen presentation, and cancer stem cells. Finally, implications of cancer immunology in osteosarcoma treatment are discussed, categorizing existing research into distinct therapeutic approaches, including chemotherapy regimens, immunotherapies, and targeted therapies [21]. The survey concludes by summarizing key findings and emphasizing the importance of understanding the immune microenvironment and immune evasion for developing effective therapeutic strategies.The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Osteosarcoma and Its Characteristics

Osteosarcoma, the most prevalent primary malignant bone tumor, primarily affects adolescents and young adults during periods of rapid skeletal development. It is defined by malignant cells producing osteoid or immature bone [21]. Despite chemotherapy advancements, survival rates remain around 60

Osteosarcoma's derivation from human Mesenchymal Stromal Cells (MSCs) complicates early diagnosis, as distinguishing osteosarcoma cells from MSCs is challenging [22]. Advanced techniques, such as deep learning, are essential for accurate histological interpretation, as current clinical methods often fail to diagnose malignant bone tumors effectively. The biological behavior of osteosarcoma is influenced by regulatory networks and factors that impact its metastatic process [23]. Cancer stem cells significantly contribute to tumor heterogeneity and therapy resistance [24], while specific proteins like OS-9 enhance cell viability and apoptosis resistance, supporting tumor progression [25].

The inefficacy of current chemotherapy, which often harms healthy cells, underscores the need for targeted approaches [26]. Understanding how metastasis-initiating cells (MICs) sustain metastasis in distant organs is a key research focus [27], further complicated by the complexity of identifying specific targets for secondary bone cancer [28, 7].

2.2 Metastasis: Process and Challenges

Metastasis significantly impacts osteosarcoma prognosis, complicating treatment and reducing survival rates [29]. This multistep process involves local invasion, intravasation into the circulatory system, survival in the bloodstream, extravasation into distant tissues, and secondary tumor formation [30]. Each phase presents unique challenges, such as immune evasion and adaptation to new microenvironments, complicating therapeutic interventions [31]. Modeling these phases is challenging due to complex interactions between cancer cells and their microenvironment [32]. Advanced computational models are needed to simulate metastatic progression and identify therapeutic targets [30], yet conventional algorithms' slow processing speeds hinder timely data analysis [33].

Late detection of metastatic lesions significantly hampers treatment efficacy [23]. Current diagnostic methods, often invasive, inadequately classify individual cancer cells, delaying intervention [22]. Existing methods focusing on two-dimensional environments fail to replicate the tumor microenvironment, highlighting the need for understanding three-dimensional collective cancer invasion [34]. The high incidence of lung metastasis in osteosarcoma patients critically impacts prognosis and is associated with severe chemotherapy side effects, including toxicity and drug resistance [35]. Despite therapeutic advancements, survival rates for metastatic osteosarcoma have not significantly improved, reflecting the need for treatments addressing metastasis's complex biology [29]. The intricate nature of metastasis, involving multiple pathways and regulatory mechanisms, complicates identifying specific therapy-relevant genes or targets [7].

Additionally, the mechanisms by which tumor cells sense chemical gradients and migrate collectively during metastasis remain poorly understood [36]. This knowledge gap underscores the need for improved clinical trial designs and innovative therapeutic strategies targeting metastatic osteosarcoma cells' unique characteristics [3]. A nuanced understanding of cancer metastasis, often oversimplified as a one-way migration from primary to secondary sites, is essential to capture the bidirectional and dynamic interactions involved in progression [37].

2.3 Tumor Microenvironment (TME)

The tumor microenvironment (TME) is a dynamic ecosystem crucial to cancer progression, metastasis, and immune evasion in osteosarcoma [1]. It comprises stromal cells, immune cells, extracellular matrix (ECM), and signaling molecules, orchestrating interactions that influence tumor growth, survival, and therapy resistance [38]. ECM remodeling supports structural integrity and facilitates tumor growth and metastasis by influencing cellular behavior and immune evasion strategies [39].

Stromal cells within the TME modulate tumor dynamics, impacting proliferation and metastatic potential. These cells engage in bidirectional metabolic interactions with cancer cells, often mediated by exosomes, establishing feedback loops that enhance the tumor's ability to evade immune surveillance and resist therapies [39]. The interplay between stromal and cancer cells creates an immunosuppressive barrier, complicating conventional therapeutic efficacy. The TME also influences cancer cells' genetic and epigenetic landscape, contributing to tumor heterogeneity and affecting therapeutic responses and drug resistance, particularly in osteosarcoma [1]. Understanding these complex interactions requires advanced computational models capable of simulating the TME's dynamic nature, providing insights into potential therapeutic targets. Such insights are crucial for developing targeted interventions aimed at modulating the TME to improve treatment outcomes in osteosarcoma and other cancers.

2.4 Immune Microenvironment

The immune microenvironment in osteosarcoma, or tumor immune microenvironment (TIME), comprises a complex network of immune and stromal cells pivotal to tumor progression and immune evasion. This environment includes diverse immune populations, such as tumor-associated macrophages (TAMs), T lymphocytes, and natural killer (NK) cells, along with non-immune cells like mesenchymal stem cells (MSCs) and cancer-associated fibroblasts (CAFs), which collectively influence the dual role of the immune microenvironment in tumor metastasis [40]. Understanding the interactions between CAFs and immune cells is critical for grasping the dynamic and paradoxical nature of immune responses in cancer [20].

The spatial architecture of the TIME significantly impacts tumor immunity and therapeutic responses. The organization and distribution of immune cells within this environment are crucial for understanding immune response modulation, directly influencing the efficacy of immunotherapeutic strategies. The inherent complexity and variability of the TIME can drive cancer cell evolution and progression, posing challenges for effective cancer management [20]. Myeloid-derived suppressor cells (MDSCs) play a key role in establishing an immunosuppressive environment that supports tumor growth and immune evasion. These cells, along with other immune components, modulate immune responses through various molecular pathways, often facilitating tumor progression. Tumor cells can manipulate the expression of NKG2D ligands through post-transcriptional and post-translational mechanisms, allowing them to evade detection by NK cells [20].

The influence of the TIME extends beyond tumor progression to affect tissue regeneration, where interactions between immune cells and functional tissue cells are crucial. Stromal cells, including CAFs, adipocytes, endothelial cells, and MSCs, contribute to the complexity of the TIME [40]. These components, along with cytokines and extracellular vesicles, regulate PD-L1 expression and facilitate immune evasion [20]. Biomarkers within the immune microenvironment are categorized into diagnostic, prognostic, and therapeutic types, underscoring their clinical relevance in managing bone neoplasms, including osteosarcoma. Understanding these biomarkers and the mechanisms of immune interactions is essential for developing targeted therapies that modulate the immune microenvironment, ultimately improving treatment efficacy and patient outcomes [20]. The challenges of acquired resistance to immunotherapy, low response rates to immune checkpoint inhibitors, and the complex immunosuppressive nature of the TIME are critical considerations in advancing osteosarcoma treatment strategies.

3 Osteosarcoma and Metastasis

Understanding the complex relationship between osteosarcoma and its metastatic potential necessitates an exploration of the mechanisms underpinning this process. The progression from a localized tumor to widespread metastasis involves intricate biological events influenced by both inherent tumor characteristics and the surrounding microenvironment. This section examines the mechanisms of metastasis, emphasizing the critical stages and the tumor microenvironment's role in facilitating osteosarcoma cell dissemination.

To illustrate these concepts, Figure 2 presents a visual representation of the hierarchical structure of osteosarcoma metastasis mechanisms. This figure highlights the roles of various biological processes, the tumor microenvironment, cancer stem cells, and metabolic adaptations. The top-level categories represent the main aspects of metastasis, each with subcategories detailing specific processes and interactions that contribute to tumor progression and therapeutic challenges. By integrating this visual framework, we can better understand the multifaceted nature of osteosarcoma metastasis and the critical factors that influence its progression.

3.1 Mechanisms of Metastasis

The metastasis of osteosarcoma is a multifaceted process involving biological mechanisms that enable tumor cells to spread from the primary site to distant organs. This cascade includes local invasion, intravasation, survival in circulation, extravasation, and colonization at secondary sites. The tumor microenvironment (TME), comprising cellular and noncellular components like fibroblasts, immune cells, adipocytes, and the extracellular matrix (ECM), plays a pivotal role in tumorigenesis by providing structural and biochemical support that influences cancer cell behavior, immune responses, and therapeutic outcomes [41, 11, 12, 42].

During local invasion, osteosarcoma cells remodel the ECM and interact with stromal cells, processes enhanced by signaling molecules and exosomes [43]. Stromal cells, such as cancer-associated fibroblasts (CAFs), can either promote or inhibit tumor growth and metastasis, illustrating the complexity of these interactions.

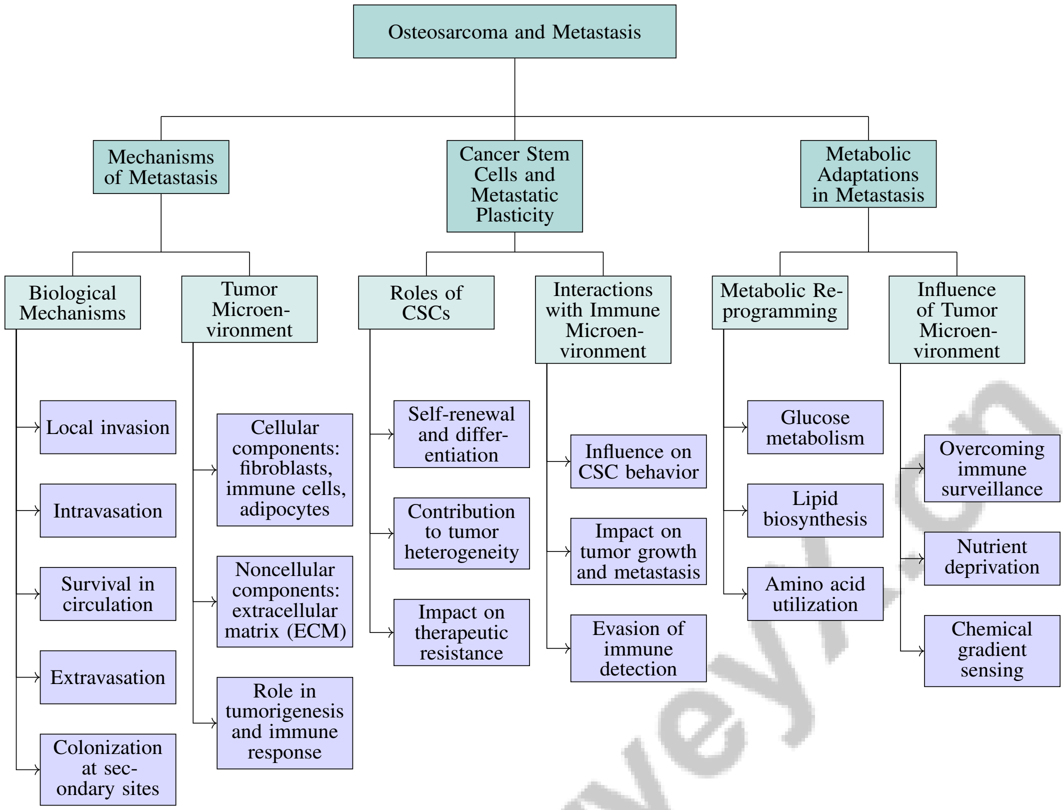

Figure 2: This figure illustrates the hierarchical structure of osteosarcoma metastasis mechanisms, highlighting the roles of biological processes, tumor microenvironment, cancer stem cells, and metabolic adaptations. The top-level categories represent the main aspects of metastasis, each with subcategories detailing specific processes and interactions that contribute to tumor progression and therapeutic challenges.

Intravasation involves tumor cells entering the vasculature, regulated by mechanical forces at the endothelial interface, creating transient gaps for tumor cell entry [44]. In circulation, tumor cells evade immune detection and survive hemodynamic forces, aided by anti-apoptotic factors and an immunosuppressive niche formed by myeloid-derived suppressor cells (MDSCs).

Colonization at secondary sites is driven by cancer stem cells (CSCs) and metastasis-initiating cells (MICs), which possess traits conferring metastatic capabilities [27]. The interactions between CSCs and immune cells, based on molecular mechanisms and immune evasion strategies, are crucial [17]. Despite pre-clinical advancements, translating these findings into clinical practice is challenging due to osteosarcoma's resistance to existing therapies [45]. The hypothesis that tumor growth follows a universal growth law offers insights into osteosarcoma's metastatic mechanisms, potentially guiding new therapeutic strategies [46].

Innovative computational methodologies, such as hierarchical classification algorithms, enhance data processing efficiency, aiding in identifying metastasis-related biomarkers and therapeutic targets [33]. Techniques like Diskoid In Geometrically Micropatterned ECM (DIGME) provide insights into mechanical and spatial factors influencing collective cancer invasion [34]. The Bone Cell Interaction Model (BCIM) simulates interactions between osteoclasts and osteoblasts, crucial for understanding osteosarcoma metastasis [28]. Advancing research in these areas is vital for improving patient outcomes and developing personalized treatment strategies.

As illustrated in Figure 3, this figure encapsulates the key mechanisms and innovative methodologies in osteosarcoma metastasis, emphasizing the role of the tumor microenvironment, metastatic processes, and advanced computational and experimental techniques. The examples provide a comprehensive exploration of the metastatic process in cancer cells, crucial for understanding cancer

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progression and treatment challenges. The first image illustrates the initial stages of metastasis, highlighting invasion and intravasation processes. The second image focuses on cancer cell preparation and colonization in a pre-metastatic niche, emphasizing extracellular vesicles and exosomes. The final image delves into metastatic dormancy and outbreak, presenting how dormant cells can reactivate and proliferate. These insights are pivotal for developing targeted therapies and improving osteosarcoma outcomes [47, 31, 27].

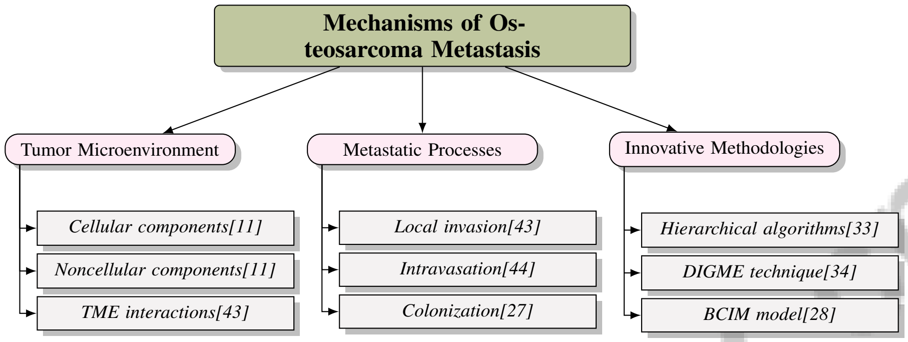


Figure 3: This figure illustrates the key mechanisms and innovative methodologies in osteosarcoma metastasis, emphasizing the role of the tumor microenvironment, metastatic processes, and advanced computational and experimental techniques.

3.2 Cancer Stem Cells and Metastatic Plasticity

Cancer stem cells (CSCs) are critical in osteosarcoma metastasis due to their self-renewal and differentiation capabilities, contributing to tumor heterogeneity and therapeutic resistance [24]. Their plasticity, enabling transitions between stem-like and differentiated states, is vital for metastatic progression and secondary tumor establishment, challenging the traditional hierarchical cancer cell model [48].

The interplay between CSCs and the immune microenvironment significantly influences metastatic plasticity. Immune cells within the TME affect CSC behavior, impacting tumor growth and metastatic potential [49]. CSCs' ability to evade immune detection and resist therapies is a major treatment barrier, necessitating novel strategies targeting these resilient populations [24].

Advancements in modeling approaches, like the Multiple Imputation for Cure Models (MICM), offer insights into metastatic behavior complexities, enhancing understanding of CSC roles and aiding in targeted intervention development [50]. Understanding CSC contributions to metastasis is crucial for developing effective therapies. The challenges of tumor heterogeneity and isolating pure CSC populations highlight the need for innovative research to unravel CSC-driven metastasis complexities [24]. Targeting CSC plasticity and signaling pathways may offer promising therapeutic avenues in osteosarcoma.

3.3 Metabolic Adaptations in Metastasis

Metabolic adaptations are crucial for osteosarcoma's metastatic progression, as cancer cells reprogram metabolic pathways to thrive in diverse microenvironments [51]. This plasticity supports tumor cells' energy demands during migration, invasion, and secondary tumor establishment. Recent research highlights these adaptations' complexity, involving energy-related metabolites and signaling pathways facilitating survival and proliferation [52].

Osteosarcoma cells exhibit metabolic reprogramming, including shifts in glucose metabolism, lipid biosynthesis, and amino acid utilization, enhancing growth and apoptosis resistance under stress [51]. Key metabolic regulators like AMP-activated protein kinase (AMPK) maintain energy homeostasis during metabolic stress [52].

The TME influences metabolic adaptations, necessitating continuous flexibility to overcome metastasis barriers like immune surveillance and nutrient deprivation [51]. Tumor cells' ability to sense and respond to chemical gradients is critical for metastatic success, though mechanisms remain under investigation [36].

Mathematical models simulate metastasizing tumor cells' metabolic behavior, offering insights into therapeutic targets disrupting adaptive processes [32]. However, current models often focus on limited metastatic aspects, highlighting the need for comprehensive approaches capturing tumor behavior complexity [30].

Integrating advanced imaging and computational modeling in three-dimensional (3D) culture systems, such as spheroids and bioprinted environments, provides accurate in vivo TME representation, facilitating metabolic adaptation studies in osteosarcoma [53]. These methodologies enhance understanding of metastasis's metabolic underpinnings, promising novel interventions targeting osteosarcoma cells' metabolic vulnerabilities.

4 The Immune Microenvironment in Osteosarcoma

Exploring the intricate relationship between osteosarcoma and its immune microenvironment necessitates understanding the composition and interaction of its cellular and molecular constituents. These elements collectively influence tumor behavior and response to therapies.

4.1 Composition of the Immune Microenvironment

The immune microenvironment in osteosarcoma is a complex system comprising diverse immune and stromal cells, alongside numerous signaling molecules that collectively impact tumor progression and immune responses [31]. Myeloid-derived suppressor cells (MDSCs) are particularly critical, orchestrating immune regulation and promoting tumor growth through immunosuppressive activities [54]. The interactions between osteosarcoma cells and their microenvironment, including bone, stromal, vascular, and immune components, are crucial for understanding tumor behavior and treatment response [55].

As illustrated in Figure 4, the composition of the immune microenvironment in osteosarcoma highlights key immune cells, their interactions with various components, and the signaling molecules involved. Key immune cells such as tumor-associated macrophages (TAMs), T lymphocytes, and natural killer (NK) cells contribute to the dualistic nature of the immune response, capable of either suppressing or facilitating tumor metastasis [31]. The spatial organization of these cells, influenced by the mechanical dynamics of endothelial cells, is essential for immune cell extravasation and interactions with tumor cells [44]. Techniques like DIGME allow precise manipulation of tumor organoid shape and ECM microstructure, aiding the study of immune microenvironment composition and function [34].

Cytokines and chemokines within the immune microenvironment modulate immune cell behavior and tumor progression, playing integral roles in communication networks that influence pro-tumorigenic and anti-tumorigenic pathways [56]. The concept of 'virtuous' and 'vicious' cells underscores the complexity of these interactions, highlighting distinct roles in microenvironmental interactions [57]. Genetic and epigenetic alterations in osteosarcoma cells further contribute to intra-tumor heterogeneity, influencing immune surveillance and therapeutic responses. Advanced computational models, like NaroNet, help characterize these interactions by learning local phenotypes and cellular interactions from multiplex images [43]. Understanding these components is essential for developing targeted therapies to modulate immune responses and improve osteosarcoma treatment outcomes. The immune microenvironment is also influenced by bone remodeling dynamics, particularly osteoblast proliferation and Wnt signaling [28].

4.2 Mechanisms of Immune Regulation

Immune regulation within the osteosarcoma microenvironment involves complex interactions among cellular components and signaling pathways that influence tumor progression, immune evasion, and therapeutic efficacy [9, 10, 12]. The tumor microenvironment (TME) features interactions between cancer cells, stromal cells, and immune components, where resource allocation, particularly glucose, plays a pivotal role in tumor escape mechanisms. This competition-driven model suggests metabolic constraints are crucial in facilitating immune evasion beyond genomic instability.

The spatial architecture of the tumor immune microenvironment (TIME) complicates immune regulation, with the distribution of immune cells and regulatory molecules determining immune

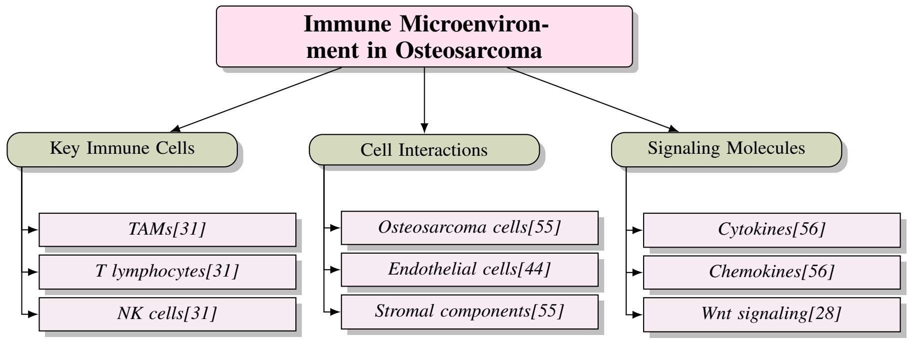


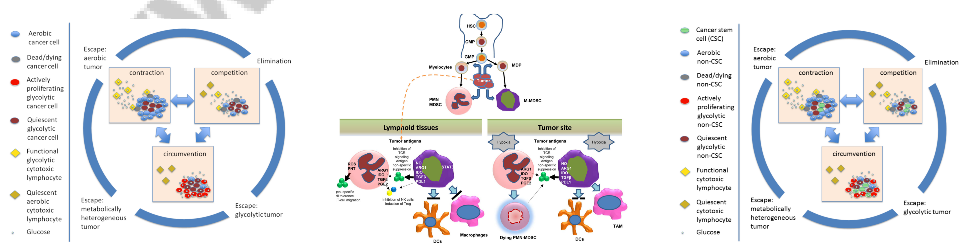
Figure 4: This figure illustrates the composition of the immune microenvironment in osteosarcoma, highlighting key immune cells, their interactions with various components, and the signaling molecules involved.

responses [15]. Cancer-associated fibroblasts (CAFs) are key players, employing immunosuppressive mechanisms to shape the tumor's immunosuppressive landscape [40]. CAFs modulate immune responses through their interactions with immune cells, fostering an environment conducive to tumor growth and metastasis.

Exosomes facilitate communication between cancer and stromal cells, enhancing understanding of tumor biology and identifying potential biomarkers and therapeutic targets [39]. These vesicles transfer molecular signals that modulate immune cell behavior, promoting an immunosuppressive environment. Dendritic cells, essential for antigen presentation, are often inhibited within the TME, leading to immune tolerance and reduced immune surveillance efficacy [19]. The interplay between CD4 and CD8 T cells is crucial, with CD4 T cells influencing CD8 T cell activation and function, modulating the overall immune response against tumor cells [58].

Cancer stem cells (CSCs) exhibit immunomodulatory properties contributing to immune evasion and tumor progression [17]. Interactions between CSCs and immune cells, influenced by microenvironmental cues, alter immune response efficacy [42]. Identifying potential therapeutic targets to disrupt CSC-established immunosuppressive networks is a focus of ongoing research.

Despite advancements in understanding immune regulation within the osteosarcoma microenvironment, studies are often limited by small sample sizes and retrospective analyses, affecting result reliability [35]. Nonetheless, ongoing research provides insights into the TME's role in cancer, leading to novel therapeutic strategies to enhance treatment efficacy by modulating immune responses [41]. Integrating these findings into clinical practice holds promise for improving osteosarcoma treatment outcomes.



(a) Escape and Elimination of Tumors: A Circular Process[59]

(b) Tumor-Induced Immunosuppression in Lymphoid Tissues and Tumor Sites[54]

(c) Escape and Elimination of Tumors: A Circular Model[60]

Figure 5: Examples of Mechanisms of Immune Regulation

Figure 5 provides a visual exploration of the dynamic interplay between tumors and the immune system, focusing on regulatory mechanisms influencing tumor progression and immune evasion. The figures illustrate tumor escape and elimination processes, highlighting strategies tumors use to manipulate immune responses. These visual representations offer insights into immune regulation mechanisms within the osteosarcoma microenvironment, underscoring challenges and potential strategies for targeting tumor-immune interactions for therapeutic interventions [59, 54, 60].

4.3 Metabolic and Genetic Influences

The immune microenvironment in osteosarcoma is significantly influenced by metabolic and genetic factors, crucial for tumor progression, metastasis, and therapy resistance. Metabolic adaptations within the tumor microenvironment (TME) enable cancer cell survival and proliferation under diverse and harsh conditions encountered during metastasis [51]. These adaptations involve shifts in energy metabolism, such as increased glycolysis and altered lipid biosynthesis, meeting the energetic and biosynthetic demands of proliferating tumor cells [52]. Techniques like pegylated nanographene oxide sheets inducing localized hyperthermia exemplify how metabolic profiling affects osteosarcoma cell behavior [52].

The TME modulates metabolic pathways, influencing cancer cell plasticity and facilitating phenotypic state transitions favorable for metastasis [48]. This plasticity is further complicated by interactions with stromal components, enhancing osteosarcoma cells' metastatic potential [24]. The stroma provides structural support and biochemical cues crucial for metastasis [24].

Genetic factors shape the immune microenvironment, affecting tumor cell behavior and therapeutic responses. The interplay between genetic mutations and the TME contributes to therapy resistance, as cancer cells adapt to immune surveillance and therapeutic pressures [1]. Despite advancements, significant gaps remain in understanding metastasis mechanisms, particularly regarding microenvironmental factors and genetic determinants.

Novel mathematical models capture the dynamic nature of metastatic growth, emphasizing the need for innovative approaches to study metabolic and genetic influences on the immune microenvironment [30]. These models provide insights into the spatial and temporal dynamics of tumor progression.

Future research should focus on elucidating the immune microenvironment's complex role in osteosarcoma metastasis, emphasizing developing immunotherapeutic strategies targeting osteosarcoma cells' unique metabolic and genetic vulnerabilities. This approach is crucial for improving survival rates and could leverage advancements in understanding tumor heterogeneity and interactions between cancer-associated fibroblasts and immune cells [9, 10, 40, 41]. By integrating insights from metabolic and genetic studies, researchers can better understand the TME's complex interactions and develop targeted therapies to enhance treatment efficacy and improve patient outcomes.

5 Mechanisms of Immune Escape and Evasion

5.1 Immune Checkpoints and Evasion Strategies

Osteosarcoma cells utilize sophisticated immune evasion strategies by modulating immune checkpoints like PD-1/PD-L1 and CTLA-4, crucial for immune regulation and tolerance maintenance. Dysregulation of these checkpoints facilitates immune escape, supporting tumor growth and metastasis [13]. The tumor microenvironment (TME) exhibits significant heterogeneity, complicating therapeutic target identification [11]. Myeloid-derived suppressor cells (MDSCs) are pivotal in establishing an immunosuppressive TME, impeding T cell activation and promoting tumor growth [29]. Moreover, the resilient cancer stem cells (CSCs) in the TME exploit metabolic resources, such as glucose, to survive immune challenges [59]. Targeting these metabolic pathways could bolster immune responses against osteosarcoma [51].

Structural dynamics in the TME, such as endothelial monolayer gaps, facilitate tumor cell extravasation while obstructing immune cell infiltration, enhancing immune evasion [50]. Tumor cells adjust NKG2D ligand expression, while NK cell NKG2D downregulation further impedes effective immune surveillance [14]. These mechanisms underscore the complexity of immune evasion and the need for innovative therapeutic approaches.

Current therapies often inadequately address metastasis, as many approved drugs overlook metastatic disease's unique challenges [29]. Innovative strategies, like multifunctional nanodevices delivering doxorubicin selectively to osteosarcoma cells, aim to overcome conventional chemotherapy's limitations while minimizing normal tissue toxicity [26]. Understanding immune evasion mechanisms is vital for developing therapies that modulate the immune microenvironment and restore anti-tumor

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immunity. Cancer cells thrive in diseased microenvironments, exhibiting higher fitness than normal cells, indicating immune evasion mechanisms [57]. Disrupting cell communication and collective sensing may provide therapeutic strategies against metastatic osteosarcoma [36]. Additionally, nGO-mediated hyperthermia selectively heating tumor cells may evade immune detection while preserving healthy tissues, enhancing therapeutic efficacy [52].

Research categorizes MHC I loss mechanisms, including genetic mutations, epigenetic regulation, and post-translational modifications, providing a framework for understanding tumor immune evasion [61]. Insights from cancer metastasis studies through diaspora and ecological principles can lead to innovative strategies that disrupt cancer cell migration and establishment, presenting new therapeutic avenues [37]. Integrating these findings into clinical practice is crucial for advancing osteosarcoma treatment and improving patient outcomes. Targeting ECM remodeling, critical in cancer progression and immune evasion, may enhance therapeutic efficacy [38]. Moreover, exosomes' multifaceted roles in cancer metabolism and progression complicate their specific impacts, necessitating further research [39]. Targeting cancer-associated fibroblasts (CAFs) could disrupt their immunosuppressive functions, enhancing cancer immunotherapy efficacy [40]. The failure of existing models to incorporate Wnt signaling in osteoblast proliferation may also represent a mechanism for immune evasion by osteosarcoma cells [28]. A significant challenge remains the lack of high-resolution data on the cellular composition and spatial distribution of immune cells within the tumor immune microenvironment (TIME), which hampers the prediction of treatment responses and the development of effective therapies [20].

5.2 Alterations in Antigen Presentation

Alterations in antigen presentation are central to osteosarcoma's immune evasion strategies, significantly impacting tumor escape from immune surveillance and contributing to poor prognosis. A key mechanism involves the downregulation or loss of Major Histocompatibility Complex (MHC) class I molecules on tumor cells, common in various cancers, including osteosarcoma [61]. MHC I loss impairs tumor antigen presentation to cytotoxic T lymphocytes (CTLs), reducing the immune system's capacity to recognize and eliminate cancer cells.

MHC I loss mechanisms include genetic mutations, epigenetic modifications, and post-translational alterations disrupting antigen processing and presentation pathways [61]. These disruptions lead to decreased MHC I expression on tumor cells, enabling immune escape and fostering a more immunosuppressive TME.

Restoring MHC I expression on tumor cells offers a promising therapeutic strategy to counteract immune evasion and improve immunotherapy efficacy. Potential approaches involve agents that modulate epigenetic regulators, enhance antigen processing machinery, or directly upregulate MHC I expression. Targeting pathways responsible for MHC I downregulation could enhance antigen presentation, increasing osteosarcoma cells' susceptibility to immune-mediated destruction [61].

Understanding the mechanisms behind altered antigen presentation, particularly MHC class I loss, is essential for devising effective strategies to counteract immune evasion in osteosarcoma. This loss impairs CD8 T cell recognition of tumor cells, complicating the effectiveness of immunotherapies, such as checkpoint blockade. Research focused on restoring MHC I expression could significantly enhance the immune system's ability to target and eliminate osteosarcoma cells, ultimately improving patient outcomes [9, 61]. These efforts hold the potential to enhance the effectiveness of current immunotherapeutic approaches and facilitate the development of novel treatment strategies.

5.3 Role of Cancer Stem Cells (CSCs) in Immune Evasion

Cancer stem cells (CSCs) are pivotal in osteosarcoma's immune evasion, contributing to tumor progression and treatment resistance. CSCs evade immune detection by surrounding themselves with non-stem cancer cells, creating a protective niche that shields them from immune surveillance [60]. This strategy facilitates immune evasion and supports the CSC population's maintenance within the TME.

CSCs' complexity is further underscored by their phenotypic plasticity, allowing them to switch between stem-like and non-stem-like states. This adaptability is critical for CSC survival under therapeutic pressures, posing significant challenges for treatment strategies aimed at eradicating these cells [48]. Targeting CSCs alone may be counterproductive, potentially increasing aggressive cancer cell populations due to this phenotypic flexibility.

Research has identified specific CSC markers instrumental in understanding their role in treatment resistance and immune evasion [24]. These markers provide valuable insights into CSCs' unique properties, offering potential targets for novel therapeutic strategies aimed at overcoming immune evasion. By focusing on the molecular pathways associated with CSCs, interventions can be devised that target these resilient cell populations while mitigating their immune evasion capabilities.

CSCs' involvement in immune evasion highlights the necessity for comprehensive therapeutic approaches addressing CSCs' multifaceted nature and their TME interactions. Synthesizing findings from recent studies on CSC markers and immune evasion mechanisms in osteosarcoma could lead to innovative therapeutic strategies that enhance the immune system's ability to target and eliminate osteosarcoma cells, potentially improving patient outcomes and survival rates in this challenging malignancy [9, 5].

6 Cancer Immunology and Therapeutic Implications

Category	Feature	Method
Personalized Medicine and Biomarker Discovery	Tumor Environment Insights	NN[43]
Therapeutic Challenges and Future Directions	Tumor Interaction Analysis	BCIM[28]

Table 1: This table provides a summary of methods relevant to personalized medicine and therapeutic challenges in osteosarcoma treatment. It highlights the use of computational models for tumor environment insights and interaction analysis, illustrating the integration of advanced technologies in biomarker discovery and therapeutic strategy development.

The field of cancer immunology has significantly advanced our understanding of the interactions between the immune system and tumor biology, particularly within the tumor immune microenvironment (TIME). Table 1 presents a concise overview of the methods employed in personalized medicine and therapeutic challenges, emphasizing their role in advancing osteosarcoma treatment strategies. Table 2 offers a comprehensive comparison of the current understanding of cancer immunology in osteosarcoma, emerging immunotherapeutic strategies, and the integration of personalized medicine and biomarker discovery, illustrating their collective impact on therapeutic advancements. This section delves into the current understanding of cancer immunology in osteosarcoma, with a focus on TIME's role and therapeutic implications. Investigating immune response mechanisms is crucial for developing more effective immunotherapeutic strategies.

6.1 Current Understanding of Cancer Immunology in Osteosarcoma

Recent studies emphasize the complex relationship between osteosarcoma and the immune microenvironment, highlighting TIME's critical role in cancer progression and treatment. Advances in cancer immunology suggest targeting TIME regulators could enhance immunotherapy efficacy, particularly in immune checkpoint blockade. The PD-L1/PD-1 pathway has become a pivotal target, driving significant treatment advancements [1].

MHC class I molecules are essential for antigen presentation, with immunotherapies like checkpoint inhibitors showing promise in reactivating immune responses against tumors presenting antigens via MHC I. Tumor cells often manipulate NKG2DL expression to evade NK cell detection, revealing potential therapeutic targets to enhance NK cell function and improve anti-tumor responses [14, 62, 63, 58].

Personalized medicine is increasingly recognized in osteosarcoma, where understanding interactions among immune, stromal, and vascular components is crucial for improving treatment efficacy, given current therapy limitations and tumor heterogeneity [55, 10]. Advanced computational models predict macrophage phenotypes and classify behaviors within the tumor microenvironment, offering valuable insights.

Metabolic interventions can influence osteosarcoma cells' metabolic state, impacting cancer immunology and treatment strategies. Comparative analyses show immune checkpoint inhibitors typically provide more potent and prolonged anti-tumor responses than conventional therapies, underscoring their potential in treating osteosarcoma, where survival rates have stagnated despite decades of research. Innovative therapeutic strategies, including nanomedicine, are being explored to enhance immunotherapeutic efficacy [10, 5, 21, 9, 62].

Understanding cancer immunology in osteosarcoma underscores the importance of TIME and advanced therapeutic strategies for improving patient outcomes. Continued research is essential for developing targeted interventions that modulate immune responses, as studies reveal TIME's role in influencing tumor heterogeneity, progression, and treatment resistance. By focusing on innovative strategies such as immune checkpoint inhibitors and advanced nanomedicine platforms, researchers aim to improve osteosarcoma treatments and survival rates, which have seen minimal progress over the past four decades despite chemotherapy and surgery advancements [21, 9, 10, 5].

6.2 Emerging Immunotherapeutic Strategies

Emerging immunotherapeutic strategies for osteosarcoma are gaining traction for their potential to improve treatment outcomes by effectively targeting the tumor immune microenvironment (TIME) compared to traditional methods [10]. A key focus is on myeloid-derived suppressor cells (MDSCs), which create an immunosuppressive environment supporting tumor growth and metastasis. Identifying specific MDSC markers is crucial for developing targeted therapies to enhance cancer immunotherapy efficacy [54].

The role of NKG2D ligands in cancer immunotherapy is emphasized, with membrane-bound NKG2D ligands linked to better patient survival and soluble ligands associated with reduced immune activity and poorer outcomes [63]. This highlights the potential of targeting NKG2D pathways to improve osteosarcoma immune responses.

Dendritic cells (DCs) are also targets of emerging immunotherapeutic strategies, including DC vaccination, chemotherapy, and immune checkpoint inhibitors. These strategies vary in effectiveness, and their integration into treatment regimens could enhance the overall therapeutic response in osteosarcoma patients [19].

The tumor microenvironment, particularly cancer-associated fibroblasts (CAFs), presents additional immunotherapy targets. Current strategies emphasize a multifaceted approach to address complex TIME interactions to modulate immune responses effectively [40]. Furthermore, integrating therapeutic strategies targeting cancer stem cells (CSCs) and their immunosuppressive microenvironment is crucial for enhancing existing cancer therapies [17].

These emerging immunotherapeutic strategies represent a promising frontier in osteosarcoma treatment, offering potential to overcome conventional therapy limitations and improve patient outcomes by effectively targeting the immune microenvironment [29]. Continued research and clinical trials are essential to refine these approaches and fully realize their clinical potential.

6.3 Personalized Medicine and Biomarker Discovery

Personalized medicine is a transformative approach in osteosarcoma treatment, emphasizing therapeutic strategy customization based on individual patient profiles and tumor characteristics. This approach relies on biomarker discovery and utilization, crucial for predicting treatment responses and tailoring interventions to enhance efficacy. Biomarkers elucidate the complex molecular and cellular composition of the tumor microenvironment (TME), influencing tumor initiation, progression, metastasis, and treatment response. Analyzing biomarkers allows researchers to identify specific interactions and alterations within the TME, paving the way for innovative therapeutic strategies that effectively target its unique characteristics and improve clinical outcomes [41, 64].

Recent advancements in computational models, such as NaroNet, demonstrate the potential to classify patients based on their tumor microenvironment, significantly contributing to biomarker discovery in osteosarcoma treatment [43]. By leveraging multiplex imaging data, NaroNet can identify local phenotypes and cellular neighborhoods, facilitating the characterization of the tumor immune microenvironment (TIME) and enabling novel biomarker identification.

Integrating biomarker discovery into personalized medicine strategies allows for stratifying patients into subgroups based on their unique tumor profiles. This stratification is crucial for enhancing treatment strategies, as it enables the identification of high and low-risk patient groups, improving prognostic accuracy and facilitating tailored therapeutic approaches that minimize adverse effects. Utilizing advanced methodologies such as deep learning for early cancer detection and gene expression profiling for predicting metastasis can optimize patient outcomes through personalized treatment regimens [22, 6, 56, 33, 29]. Biomarkers related to immune checkpoints, metabolic pathways, and genetic mutations are particularly relevant for selecting immunotherapeutic agents and other targeted therapies.

Ongoing research into biomarker discovery and personalized medicine promises to revolutionize osteosarcoma treatment by enhancing the precision and effectiveness of therapeutic interventions. As our understanding of the intricate tumor microenvironment in osteosarcoma evolves, the potential for developing personalized therapeutic strategies becomes increasingly viable. This advancement is crucial, particularly given that traditional treatments have yielded limited improvements in patient survival rates over the past several decades. By leveraging insights from recent research on the immune microenvironment and innovative approaches such as nanomedicine and immunotherapy, we can enhance treatment efficacy and ultimately improve patient outcomes in osteosarcoma management [55, 9, 10, 5].

6.4 Therapeutic Challenges and Future Directions

The therapeutic landscape of osteosarcoma presents significant challenges, primarily due to the tumor's complex microenvironment and inherent resistance to conventional therapies. A major obstacle is effectively targeting the tumor immune microenvironment (TIME), particularly myeloid-derived suppressor cells (MDSCs), which contribute to an immunosuppressive milieu supporting tumor growth and metastasis [54]. Understanding the spatial architecture of TIME and employing high-resolution techniques are crucial, as these factors significantly influence tumor behavior and immune responses, informing therapeutic strategies.

Future research should prioritize developing combination therapies that effectively remodel TIME to enhance anti-tumor immunity while addressing the risks of immune-related adverse events [18]. Integrating personalized medicine approaches, focusing on identifying specific mechanisms of MHC I loss in individual patients and creating targeted therapies to restore MHC I expression, is essential for enhancing treatment efficacy [61]. Large-scale clinical trials are necessary to evaluate promising therapies, explore molecular-targeted treatments, and develop strategies to overcome drug resistance [35].

A significant area of interest is elucidating the molecular mechanisms of extracellular matrix (ECM) remodeling and exploring novel therapeutic strategies targeting the ECM to enhance treatment outcomes [38]. Additionally, future research should focus on developing more efficient exosome isolation methods, exploring the role of exosomes in lipid and amino acid metabolism, and conducting large-scale clinical studies to validate exosome-based biomarkers [39].

Despite advancements, limitations persist due to the complexity of tumor microenvironment interactions and challenges in translating findings from models to clinical settings [41]. Future research should develop targeted therapies that can manipulate the TME effectively, utilizing advanced technologies like single-cell sequencing and AI [64]. Understanding osteoblast proliferation dynamics and their effects on bone remodeling may also present therapeutic challenges and future research directions in osteosarcoma treatment [28].

Refining cancer-associated fibroblasts (CAFs) targeting strategies is essential, as current approaches face significant challenges due to CAF heterogeneity and functional diversity [40]. Furthermore, future research should explore immunotherapies to enhance patient responses and develop targeted therapies that exploit specific genetic vulnerabilities [1].

Addressing the therapeutic challenges in osteosarcoma requires a multifaceted approach incorporating insights from genetic, epigenetic, and environmental studies. Future research should prioritize developing targeted therapies that effectively modulate the tumor microenvironment, enhance immune responses, and improve patient outcomes. Integrating mathematical modeling with experimental data and exploring personalized medicine approaches are crucial for enhancing our understanding of metastasis [30]. Future work could also focus on developing specific therapeutic interventions based on the diaspora model and further empirical studies to validate proposed ecological frameworks in cancer research [37].

Feature	Current Understanding of Cancer Immunology in Osteosarcoma	Emerging Immunotherapeutic Strategies	Personalized Medicine and Biomarker Discovery
Target Focus	Time Regulators	Mdscs And Nkg2d	Biomarkers
Therapeutic Strategy	Checkpoint Inhibitors	DC Vaccination	Stratified Therapies
Clinical Potential	Improved Efficacy	Enhanced Response	Tailored Interventions

Table 2: This table provides a comparative analysis of various aspects of cancer immunology and therapeutic strategies in osteosarcoma. It highlights the current understanding of cancer immunology, emerging immunotherapeutic strategies, and the role of personalized medicine and biomarker discovery. The table underscores the potential clinical implications of these approaches in advancing osteosarcoma treatment.

7 Conclusion

This survey highlights the pivotal role of the tumor immune microenvironment (TIME) in osteosarcoma progression and the inherent challenges it presents to effective treatment. Understanding the dynamics within the TIME is essential for developing therapeutic strategies that address both the tumor cells and their microenvironment. The complexity of immune interactions and their contribution to immune evasion are critical factors that impact the success of current osteosarcoma therapies.

The insights gathered underscore the importance of advancing our knowledge of the tumor microenvironment as a means to refine therapeutic approaches. Focusing on the mechanisms of immune escape, particularly through the modulation of immune checkpoints and alterations in antigen presentation, holds promise for innovative treatments that restore anti-tumor immunity. Translating these findings into clinical applications is crucial for improving the management of osteosarcoma and overcoming the significant hurdles posed by this aggressive cancer.

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