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REVIEW

Nanotechnology-Driven Strategies in Osteosarcoma Advances in Treatment: Immunotherapy and Drug Delivery

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Abstract: Osteosarcoma (OS), the most prevalent primary malignant bone tumor, exhibits highly aggressive and metastatic potential, accounting approximately 56% of all primary malignant bone malignancies. While neoadjuvant chemotherapy with surgery remains standard, challenges persist: suboptimal margins, non-specific drug biodistribution, and systemic toxicity. Nanomaterial engineering offers transformative multifunctional platforms, integrating biomimetic targeting, stimuli-responsive release, and theranostics to enhance tumor penetration and reduce off-target effects. Immunotherapy combats OS by activating antitumor immunity, reprogramming the immunosuppressive tumor microenvironment (TME), and synergizing with checkpoint inhibitors/cell therapies. Ligand-functionalized nanocarriers significantly improve chemotherapeutic bioavailability and targeting. This review systematically explores the dual role of nanoplatforms in osteosarcoma therapeutics: (1) immunotherapy via TME reprogramming and (2) precision oncology through advanced drug delivery paradigms, providing critical insights into their translational potential for overcoming current therapeutic bottlenecks and ultimately improving clinical outcomes for OS patients.

Keywords: nanomaterials, osteosarcoma, tumor microenvironment, immune regulation, drug delivery

Introduction

Osteosarcoma (OS) is a malignant bone tumor, characterized by tumor cells that can directly produce bone-like tissue, more prone to lung metastasis, and poor prognosis.[1] OS, though rare in absolute terms (annual incidence: 3–4 cases per million), constitutes 56% of primary malignant bone tumors, with a striking predilection for adolescents and young adults (peak incidence: 10–30 years). The incidence of primary OS is high in adolescents, most often in 10 to 30 years old, and about 60% of OS patients are under 25 years old.[2] At present, the standard treatment of OS mainly includes surgical treatment, chemotherapy and postoperative chemotherapy. Although the treatment of OS has made some progress, the prognosis for patients with metastasis and recurrence remains poor.[3,4]

In recent years, the development and application of nanomedicine have overcome the side effects of traditional treatment methods and have become a key trend in clinical medical treatment.[5] The development of innovative dual-functional nano-platforms, integrating both targeted delivery to enhance drug accumulation specifically within tumor tissues while minimizing exposure to normal tissues and systemic toxicity, and immunomodulation to protect unstable nucleic acid or protein immune drugs from enzymatic degradation, thereby significantly improving bioavailability and ultimately augmenting immune efficacy, represents a key advancement in cancer treatment.[6–8]

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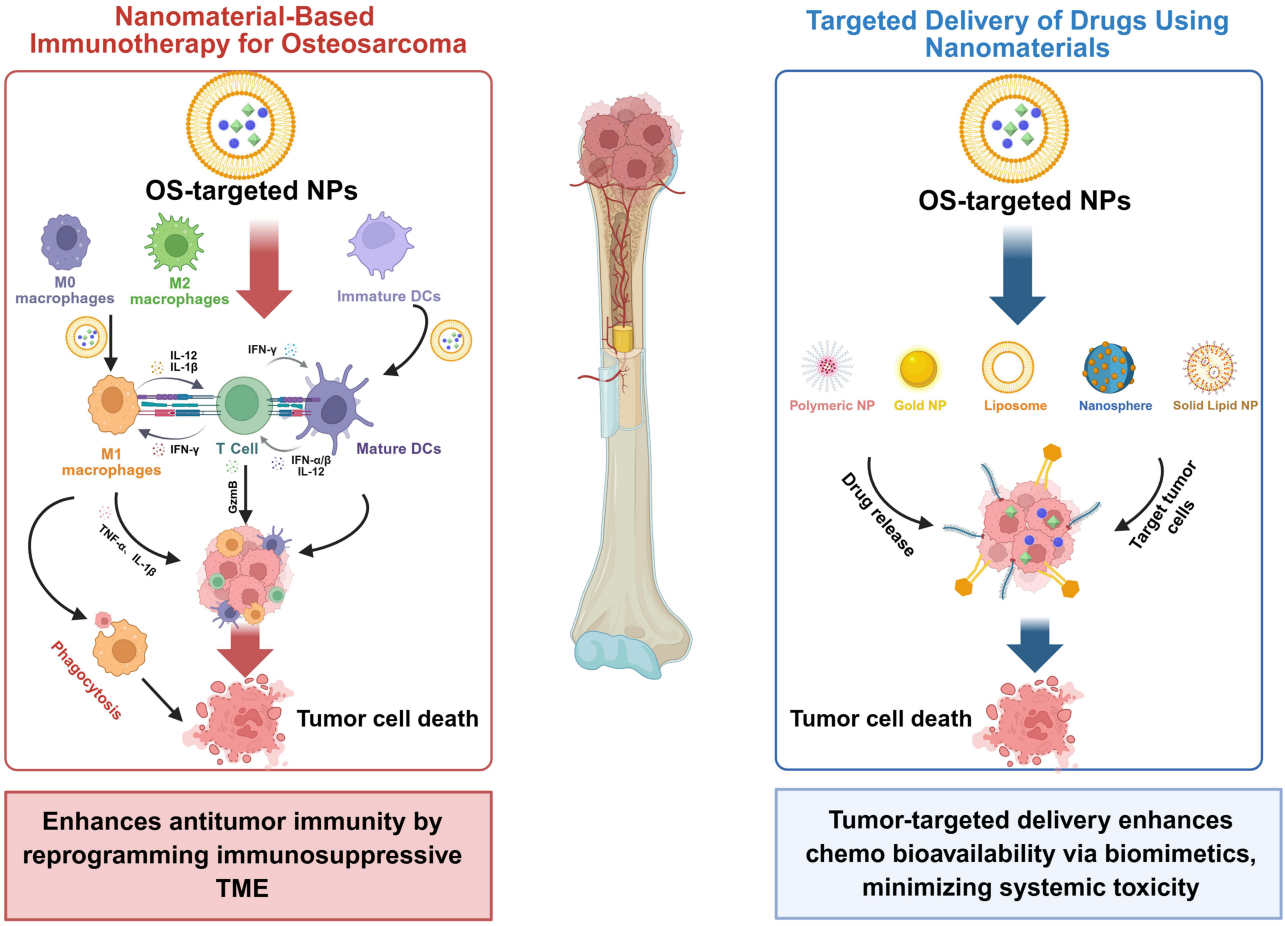
Graphical Abstract



This article reviews the role of nanomaterials in immune regulation and targeted drug delivery in the treatment of OS, and briefly introduces the immune microenvironment, immunotherapy, and current treatment strategies for OS. The advancements in nanotechnology hold the potential to enhance the effectiveness and safety of treatments, offering promising avenues for improving cancer therapy while minimizing side effects. This review systematically summarizes these cutting-edge advances in nanomaterials for OS treatment and critically discusses their translational challenges, thereby providing valuable insights and guidance for future research and clinical applications in nano-oncology.

Osteosarcoma

OS is a common malignant bone tumor in adolescents, characterized by tumor cells that can directly produce osteoid tissue.[9] OS mainly occurs at the metaphysis of long bones, especially the distal femur, proximal tibia, and proximal humerus. The symptoms of OS are diverse and develop progressively. In the early stage, pain is usually the first symptom. As the tumor grows and breaks through the cortex and invades the soft tissues, noticeable swelling will occur. In addition, patients may experience mobility impairment, and in severe cases, they may even be unable to walk. The tumor cells can destroy the cartilage tissue, making the bone fragile and prone to pathological fractures.[10,11] At the advanced stage of OS, patients often exhibit characteristic systemic manifestations such as persistent fever due to infection, significant weight loss, and profound fatigue, in addition to localized symptoms including severe bone pain, pathological fractures, and palpable masses.

Tumor Microenvironment

The tumor microenvironment of OS refers to the biological environment surrounding tumor cells, encompassing the combined effects of cells, matrix, blood vessels, immune cells, and other factors. The tumor microenvironment plays a crucial role in the pathogenesis of OS by controlling tumor growth, metastasis and drug resistance,[12] making it impossible to further improve the therapeutic effect by targeting OS cells only. Therefore, the focus of oncology research has shifted from a narrow emphasis on tumor cells to a broader understanding of the tumor microenvironment.

Cellular Components

The OS microenvironment is a complex and dynamic ecosystem orchestrated through continuous intercellular communication, which critically influences tumor progression, metastasis, and response to therapy. This cross-talk among various cellular components not only drives immune evasion and supports tumor survival but also harbors potential antitumor mechanisms, making it a central determinant of disease behavior and therapeutic outcome. As illustrated in Figure 1, key cellular interactions include: Pro-tumor effects: MSCs drive metastasis via IL-6/STAT3; CAFs promote invasion via SDF-1α/MMP-1; M2-TAMs/N2-TANs mediate immunosuppression and angiogenesis through Vascular endothelial growth factor (VEGF)/IL-8; MDSCs and Tregs suppress T-cell activity via TGF-β/IL-10; CTCs disseminate drug resistance via exosomal miRNAs (eg, miR-21). Anti-tumor potential: Activated DCs enhance $CD8^+$ T-cell cytotoxicity (IFN-γ/GZMB); N1-TANs induce apoptosis via TRAIL; NK cells target OSCs through NKG2D-dependent lysis, though inhibited by PD-L1/IL-10. Dual roles: B cells exert antibody-dependent tumor killing (IgG-mediated ADCC) but may also secrete IL-6/TGF-β to promote fibrosis. Targeting key nodes (eg, STAT3, PD-L1) or

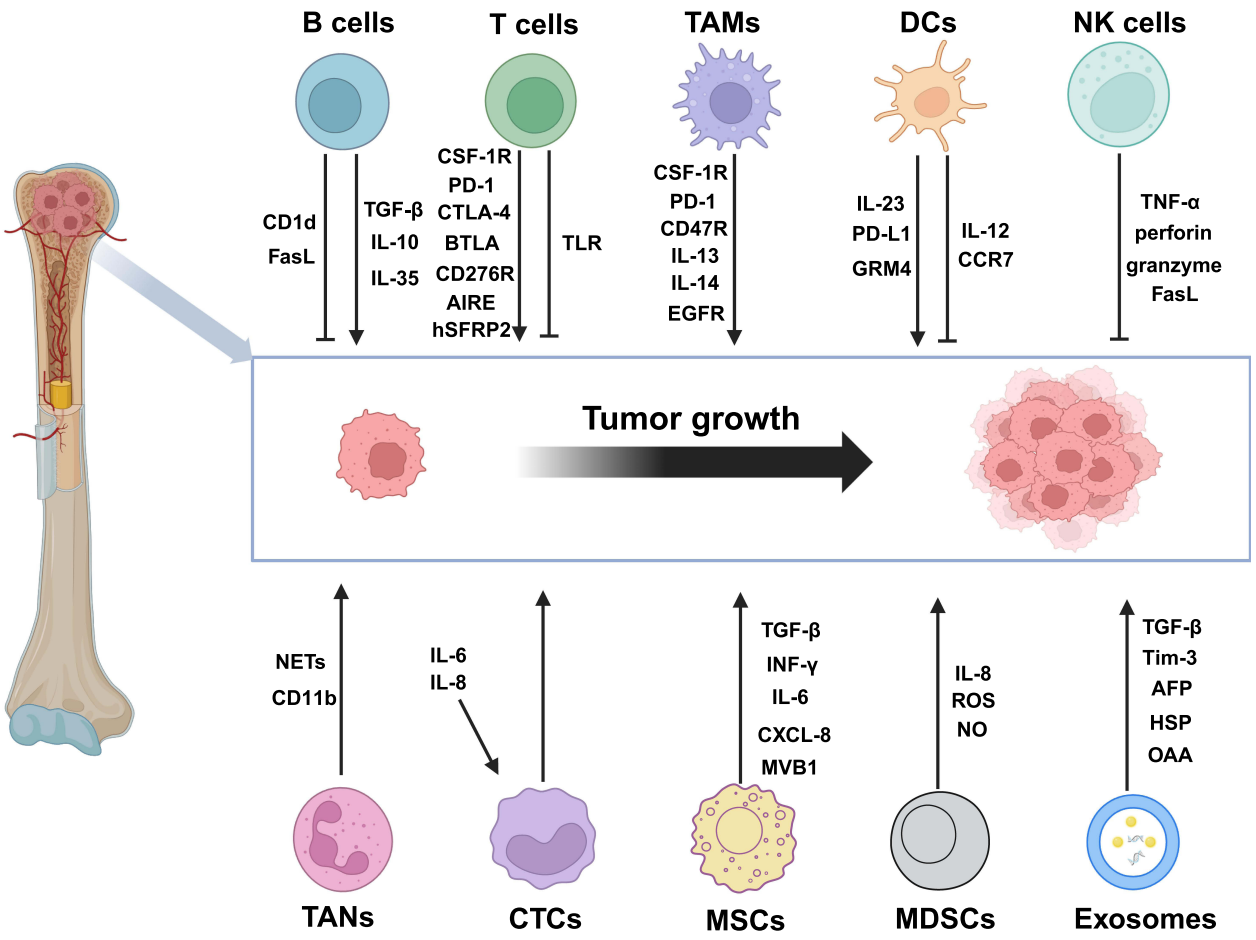


Figure 1 Regulatory network of key cellular components in the OS microenvironment: Schematic depicts dual roles of T cells, B cells, TAMs, TANs, DCs, NK cells, CTCs, MSCs, MDSCs, and exosomes via specific mediators (eg, IL-6, PD-L1).

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employing combinatorial immunotherapies (eg, DC vaccines, NK cell adoptive transfer) may help restore microenvironmental equilibrium.[8,13–17]

Myeloid Cells

Among myeloid-derived immune cells, Tumor-associated macrophages (TAMs) are one of the most significant members. TAMs dominate the OS immune landscape (>50% of infiltrating cells) and exhibit functional plasticity. Recent single-cell RNA sequencing studies have revealed that M2-polarized TAMs drive immunosuppression through the activation of the PD-L1/IL-10 axis, while promoting angiogenesis via the secretion of VEGF. According to different activation pathways, TAMs are divided into two phenotypes: classically activated macrophages (M1) and alternatively activated macrophages (M2). Among them, M1 can be activated by lipopolysaccharide (LPS), IFN-γ or granulocyte-macrophage colony stimulating factor (GM-CSF), and highly express interleukin IL-1, IL-6, IL-12, TNF-α and inducible nitric oxide synthase (iNOS), exhibiting pro-inflammatory, immunogenic and anti-tumor properties. The M2 type can be activated by IL-4, and IL-13 to produce TGF-β, IL-10, and angiogenesis factors, which have both anti-inflammatory and tumor-promoting effects. M1 macrophages recruit and activate NK cells by recruiting $CD8^+$ T cells and NK cells to secrete tumor-derived chemokines CXCL9, CXCL10 and CXCL11. Malignant tumor cells can secrete cytokines that promote M2 polarization, such as IL-10, to recruit monocytes into the tumor region and promote their differentiation into M2-type macrophages, which promotes the latency, growth, and metastasis of cancer cells by secreting cytokines, chemokines, and growth factors, and is associated with a poor prognosis for some malignant tumors.

In OS, DCs mainly consist of three clusters: conventional class 1 DCs (cDC1) ($XCR1^+CLEC9A^+$), conventional class 2 DCs (cDC2) ($CD1C^+CLEC10A^+$) and mature regulatory DCs (mreg DCs) ($CD83^+CCR7^+LAMP3^+$). Among them, mreg DCs, which specifically exist in OS, express CCR7, CCL17, CCL19, and CCL22 to recruit various types of infiltrating T cells. Moreover, studies have found that mreg DCs may promote tumor immune tolerance by recruiting regulatory T cells (Tregs) in the OS microenvironment.[18] DCs can trigger further immune responses by detecting tumor antigens and presenting them to helper T cells and cytotoxic T cells, during which they transform from immature DCs to mature DCs. Therefore, in the early stage, DCs actively proliferate and mature to activate helper T cells and cytotoxic T cells. During tumor growth, OS cells develop variants resistant to DCs and phagocytes, resulting in diminished DC activation and eventual immune escape.[14]

Tumor-associated neutrophils (TANs) are broadly categorized into anti-tumor (N1) and pro-tumor (N2) subtypes. N1 TANs contribute to tumor cell killing through ROS-mediated cytotoxicity and may participate in antigen presentation. In contrast, N2 TANs promote tumor progression via the secretion of factors such as MMP-9 and VEGF.[19] Neutrophils can participate in the development of OS through interactions with other immune cells. They recruit monocytes by secreting IL-37, CCL2, and CCL3.[20] Research has indicated that the recruited monocytes and macrophages may further attract neutrophils by releasing CXCL8. Additionally, TANs can release substances such as ROS, Reactive nitrogen species (RNI), and Prostaglandin E_2 (PGE2), which directly inhibit the anti-tumor effects of T cells and NK cells.[9,21] Neutrophil extracellular traps (NETs) are reticular chromatin structures formed by granular proteins and chromatin secreted by neutrophils.[22] These can activate dormant cancer cells, enhance the migration and invasion capabilities of cancer cells, induce the epithelial-mesenchymal transition (EMT) of tumor cells, and capture circulating cancer cells to promote their metastasis.[23]

Myeloid-derived suppressor cells (MDSCs), originating from bone marrow hematopoietic stem cells, are precursors of DCs, macrophages and granulocytes and exhibit strong immunosuppressive activity. In the tumor microenvironment, MDSCs express immune checkpoint molecules, such as PD-L1, suppressing the anti-tumor activity of T cells and NK cells,[24,25] and also secrete immunosuppressive factors like IL-10 and TGF-β to promote the differentiation of other immunosuppressive cells including Tregs, M2 macrophages, and MDSC, thereby forming an extensive immunosuppressive network.[26–28] In addition, MDSCs also promote angiogenesis by producing VEGF and FGF2, which provide nutrients for tumor growth.[29] Studies have shown that MDSCs also produce IL-6 and TGF-β, cytokines that stimulate EMT in cancer cells, and secrete matrix metalloproteinases (MMPs),[30] which promote cancer cell invasion and metastasis.

Lymphoid Cells

Tumor-infiltrating lymphocytes (TILs) are mainly distributed in the area expressing human leukocyte antigen class I, while $CD4^+$ and $CD8^+$ T cells are mainly concentrated at the junction of lung metastases and normal tissues.[31] The number of T cells in metastatic lesions was significantly higher than that in primary and recurrent lesions. At the same time, some T cells may play an anti-tumor role in the OS microenvironment, especially $CD8^+$ T cells, which can recognize and kill tumor cells, thereby inhibiting tumor growth and proliferation.[32,33] The study by Casanova et al revealed that the presence of tumor-infiltrating $CD4^+$ cells provided protection for OS patients, and $CD8^+$ cells had a significant impact on the overall survival and progression-free survival (PFS) of patients.[34] Some Tregs may inhibit the attack of immune cells on tumors, thereby promoting tumor growth and evading immune surveillance.[35]

NK cells have the innate ability to recognize and kill tumor cells, which play an important role in the microenvironment of OS.[36] As a heterogeneous group of innate effector cells, NK cells exhibit a range of anti-tumor effects, including cytolysis and cytokine production.[37] However, the tumor microenvironment usually exerts a certain degree of inhibition on immune cells, which may include weakening the activity of NK cells or escaping their recognition. Some studies have shown that the activity of NK cells may be inhibited in patients with OS, which may be related to the immune escape mechanism in the tumor microenvironment. The cytotoxicity of NK cells is precisely controlled by the complex interaction of its receptor-mediated activation and inhibition signals. NK cells participate in anti-tumor immunity by directly interacting with tumor cells or secreting cytokines and chemokines to regulate adaptive immunity, thereby controlling tumor growth.

While NK cells and $CD8^+$ T lymphocytes both possess cytotoxic capabilities to eliminate malignant cells, their functional synergy is constrained by reciprocal immunoregulatory mechanisms that balance tumor surveillance and immune homeostasis. In addition, IFN-γ secreted by NK cells stimulates the activation of $CD4^+$ T cells, which is necessary for the proliferation of $CD8^+$ T cell precursors.[38]

Non-Immune Cells

MSCs in the tumor microenvironment are classified into naive mesenchymal stem cells (MSCs) and tumor-derived mesenchymal stem cells (T-MSCs). Naive MSCs can either promote or inhibit tumor progression, whereas T-MSCs, influenced by the tumor microenvironment, tend to promote tumor progression.[39] There is a complex and close relationship between OS and MSCs. Due to the multi-lineage differentiation potential of MSCs, they are prone to gene mutations and abnormal differentiation in response to tumor-causing factors, thereby triggering OS development.

MSCs critically influence OS proliferation and metastasis. OS-derived factors (eg, SDF-1, IL-6, PDGF) recruit MSCs to the tumor site.[39] A bidirectional IL-8 signaling loop between OS cells and MSCs enhances their mutual IL-8 expression, promoting OS invasion and metastasis.[40] Furthermore, interaction with bone marrow-derived MSCs (BM-MSCs) upregulates aquaporin-1 (AQP1) in OS cells, facilitating BM-MSC-induced migration/invasion.[41] Tumor-resident BM-MSCs can differentiate into cancer-associated fibroblasts (CAFs) upon OS cell interaction, significantly augmenting OS proliferation, migration, and invasion.[42,43]

Exosomes

Extracellular vesicles (EVs), including exosomes, present in the OS microenvironment carry bioactive molecules (eg, miRNAs, proteins, cytokines) that modulate cellular signaling and functions within the tumor microenvironment.[44] Among them, exosomes are the key medium for intercellular communication. Cells control the substances in exosomes and have the effect of changing their own or other cell fates.[45] As satellites of host cells, exosomes contain a large amount of biological information, including proteins, lipids, and genetic materials. Their functions exceed initial expectations and are involved in regulating various cell functions and disease states. Cancer cells generally produce more exosomes than normal cells. These exosomes serve as crucial mediators of mutual communication between tumor cells and microenvironment. They possess a strong ability to remodel both local and distal microenvironments, thereby significantly influencing tumor development and metastasis.[46] Studies have shown that cancer cell-derived miR-21, carried by exosomes in the TME, can influence both cancer cells and surrounding stromal components, including immune cells, endothelial cells and fibroblasts. Multiple target genes of miR-21 are involved in tumor progression, metastasis, angiogenesis and immune escape in OS by enhancing cancer cell plasticity.[47]

Angiogenesis

Angiogenesis in the OS microenvironment refers to the formation of vascular networks around the tumor. Angiogenesis in OS is a complex process involving the interaction of tumor cells, vascular endothelial cells, stromal cells and a variety of growth factors. OS tumor cells secrete a series of pro- angiogenic factors, such as VEGF, basic fibroblast growth factor (bFGF) and TGF-β, which stimulate the proliferation and migration of vascular endothelial cells, leading to new angiogenesis.[48] Additionally, cytokines and chemical mediators released by inflammatory cells can induce the activation of vascular endothelial cells and angiogenesis in TME. In general, angiogenesis in the OS microenvironment is a crucial factor in tumor growth and metastasis. Understanding this process is of great significance for the development of therapeutic strategies for OS.

Current Therapeutic Frontiers in Osteosarcoma

Current OS treatment combines surgery and chemotherapy, but chemoresistance and systemic toxicity limit its efficacy (Figure 2). Immune-based therapies offer superior outcomes by targeting tumor-specific immune evasion mechanisms, achieving enhanced tumor control with reduced off-target effects compared to conventional therapies.

Surgery and Chemotherapy

Surgery (limb salvage or amputation) remains integral to OS comprehensive care.[49] For high-grade non-metastatic OS, limb salvage and amputation yield comparable survival and local recurrence rates when adequate margins are achieved,

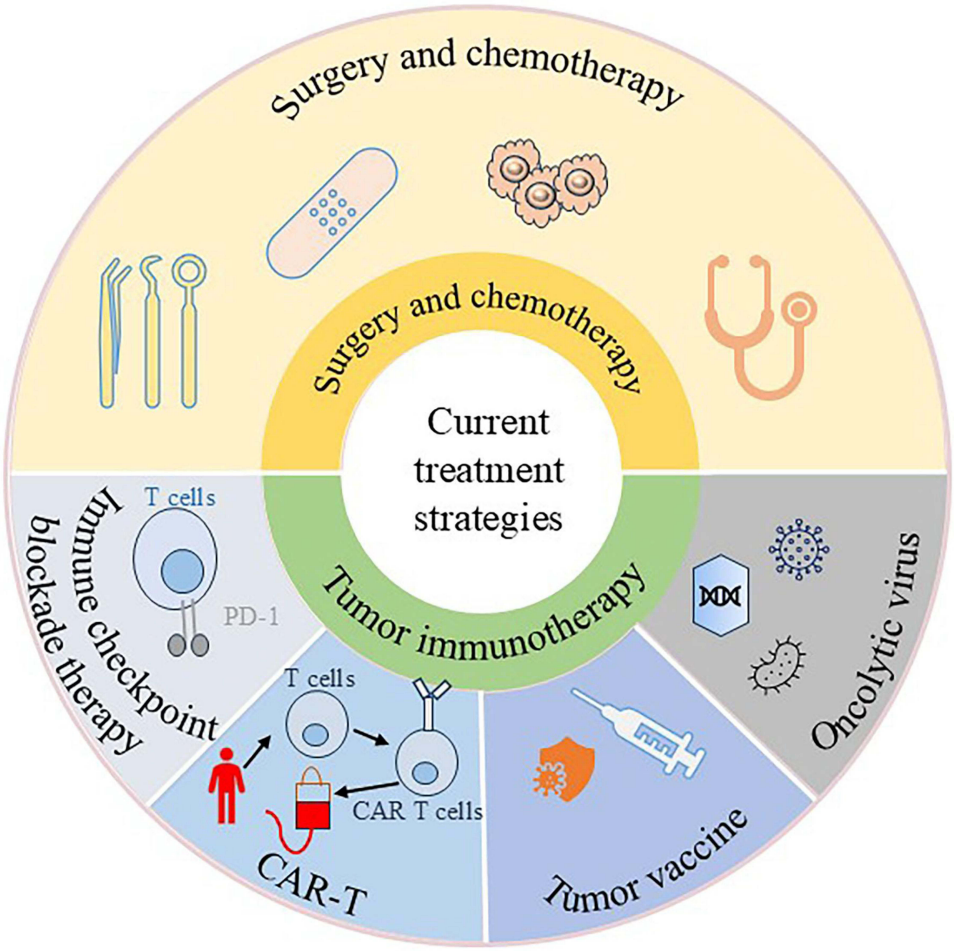

Figure 2 Overview of the treatment strategies for OS. Current clinical management primarily relies on surgery combined with chemotherapy, while emerging tumor immunotherapy paradigms encompass four major approaches: (1) Immune checkpoint blockade therapy (targeting PD-1/PD-L1 and related pathways), (2) Chimeric antigen receptor T-cell immunotherapy (CAR-T), (3) Tumor vaccines (including peptide vaccines and dendritic cell vaccines), and (4) Oncolytic virus therapy (selectively targeting tumor-specific antigens).

though limb salvage offers superior functional outcomes. Neoadjuvant chemotherapy responders are optimal candidates for limb-sparing surgery if wide resection margins are attainable.[50] Amputation is reserved for tumors in anatomically unfavorable locations precluding adequate resection. Chemotherapy (adjuvant/neoadjuvant) significantly improves prognosis in localized OS.[51] Early regimens combined agents like doxorubicin, cisplatin, bleomycin, cyclophosphamide, ifosfamide, daclizumab, and high-dose methotrexate. For metastatic OS, initial management mirrors non-metastatic disease: neoadjuvant chemotherapy followed by resection of both primary tumor and all metastatic sites.

Tumor Immunotherapy

In the past 40 years since the introduction of chemotherapy, the survival rate of OS patients has not been significantly improved, and the current second-line treatment effect is limited. This treatment dilemma may arise from treating highly heterogeneous OS as a single disease and applying the same treatment plan. Therefore, new treatment methods are urgently needed. Immunotherapy, as a new beneficial treatment for the disease, is receiving increasing attention.[52,53]

Immune Checkpoint Blockade Therapy

Immune checkpoint therapy for OS is a treatment that exploits the inhibitory mechanisms that suppress the immune system's attack on cancer cells, typically by using antibodies to block immunosuppressive signals on tumor cells, thereby activating the patient's own immune system to attack and eliminate tumor cells.[54] In OS, the main goal of immune checkpoint therapy is to activate patients' T cells and other immune cells by inhibiting immunosuppressive signals and enhancing their ability to attack tumor cells.[55] Commonly used immune checkpoints include: (1) PD-1/PD-L1 inhibitors: PD-1 (programmed death-1) is an immune checkpoint molecule expressed on activated T cells, and binds to it ligand PD-L1. PD-L1 is usually overexpressed by tumor cells and binds to PD-1, thereby suppressing T cells mediated immune response.[56] Beyond T cells, PD-1 is also expressed on various immune cells—NK cells and B cells[57]—where its interaction with tumor-derived PD-L1 delivers inhibitory signals that dampen immune activity. PD-1/PD-L1 inhibitors act by blocking this interaction, thus restoring anti-tumor T cell activity. Dhupkar et al demonstrated that PD-1 inhibitors impede OS metastasis in murine models. This effect is associated with a phenotypic shift of macrophages from the M2 to the M1 subtype, which is likely mediated by IFN-γ released from reactivated T cells.[58] Building on this finding, Ge et al combined biodegradable magnesium rods (acting as thermo-magnetic agents under alternating magnetic fields) with PD-L1 inhibitors, achieving complete OS remission.[59] (2) CTLA-4 inhibitor: CTLA-4 (cytotoxic T lymphocyte-associated protein-4) is another important immune checkpoint molecule that inhibits the primary activation of T cells by competitive binding with ligands.[60] It exerts inhibitory effects primarily by competing with CD28 for the ligands CD80 and CD86 on antigen-presenting cells (APCs). In addition, CTLA-4 also enhances the immunosuppressive function of Tregs while inhibiting helper T cell (Th) activity. CTLA-4 inhibitors block the CTLA-4 mediated signaling, promote T cell activation and proliferation, and enhance the anti-tumor immune response.[61]

However, in OS, the immunosuppressive microenvironment limits the efficacy of single-agent immune checkpoint inhibitors (ICIs), prompting exploration of combination strategies, primarily anti-PD-1/PD-L1 with anti-CTLA-4 antibodies. Preclinical studies show that anti-PD-L1 monotherapy can induce compensatory CTLA-4 upregulation, driving resistance, which is overcome by combination therapy.[62] Clinical evidence includes a case report where nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA-4) controlled metastatic OS, with biomarker analysis suggesting patient selection importance,[63] and trials indicating superior response rates for combination therapy versus nivolumab monotherapy.[64] Thus, dual checkpoint blockade represents a promising approach for advanced, treatment-refractory OS, though requiring careful toxicity management.

Immune checkpoint therapy has yielded significant clinical results in various cancer types and has become a primary treatment option. However, the application of immune checkpoint therapy in the treatment of OS is still in the stage of research and clinical trials. Nevertheless, immune checkpoint therapy may provide a new treatment option for patients with advanced or recurrent OS, and clinical studies are being actively conducted to evaluate its safety and efficacy.[65]

Chimeric Antigen Receptor T-Cell Immunotherapy

Tumor cells may down-regulate the expression of their own HLA and tumor antigens, so that they cannot be recognized by T cells. Engineered T cells have high affinity for tumor-specific antigens and can recognize tumor cells without the background of HLA presentation. This T cell is called chimeric antigen receptor T cells (CAR-T).[66] T cells can recognize antigens through

TCR composed of α and β chains, but αβ-TCR can recognize response antigens only when the antigens exist in the form of 8–11 amino acid long peptides, indicating that the conditions for T cells to recognize tumor antigens in humans are harsh.[67] Unlike TCR, CAR molecules do not require MHC to directly recognize and bind to target molecules expressed on the cell surface. CAR molecule is a synthetic fusion protein composed of the extracellular domain, hinge region, transmembrane domain and intracellular signal domain that recognizes target antigen. First, it is necessary to collect, separate, and purify T cells from the peripheral blood of tumor patients, and then use a viral vector to insert the gene construct of the CAR molecule into the T cell genome, allowing the T cells to express CAR molecules on their surface. The resulting CAR-T cells are amplified in vitro (typically requiring a magnitude of billions to billions of times) and reinfused into patients.[68]

CAR-T therapy is more challenging than hematological tumors in identifying suitable CAR targets in solid tumors and overcoming the immunosuppressive tumor microenvironment in these tumors. As a potential target, researchers have analyzed the expression of immune checkpoint B7-H3 in OS cell lines and evaluated the ability of anti-B7-H3 monoclonal antibody (anti-B7-H3-FITC mAb) coupled with FITC to control the anti-tumor activity of anti-FITC CAR-T cells;[69] the B7-H3-targeted CAR-T cells showed strong B7-H3-specific tumor cell killing ability in vitro, and showed significant tumor inhibition in the PDX model in vivo, showing its great potential for OS treatment in future clinical trials.[70] Further demonstrating functional potential in OS, CD70-specific CAR T cells successfully migrated through confined 3D microchannel networks and exhibited anti-tumor activity against OS via chemotaxis, with efficacy dependent on effector-to-target ratios.[71] In OS, CAR-T cell therapy may be an effective strategy because primary bone tumors often exhibit a low mutation burden and are accompanied by rare natural anti-tumor T cells.[72]

Tumor Vaccine

Tumor vaccine is an immunotherapy method that aims to induce an anti-tumor response of the human immune system by exposing tumor antigens. These vaccines can include in vitro-cultured cancer cells, tumor-associated antigens, or immune cells, which are then injected into patients.[73] The therapeutic objective is to reinvigorate immune surveillance by reactivating cytotoxic T lymphocytes (CTLs) against tumor-associated antigens, thereby overcoming immune evasion mechanisms and inducing tumor-specific cytotoxicity to control or eradicate neoplastic growth. At present, the most mature tumor vaccine technology is the cervical cancer vaccine. The incidence of cervical cancer is mainly induced by human papillomavirus (HPV), so cervical cancer vaccines are divided into preventive vaccines (against HPV infection) and therapeutic vaccines (exposing tumor antigens).[74] DCs, as professional antigen-presenting cells, can activate CTLs and enhance their proliferation. As the cornerstone of tumor vaccination strategies, DC vaccines have been employed across diverse malignancies to eradicate malignant cells in chemotherapy-resistant neoplasms; notably, their preeminence is most pronounced in OS applications.[75] Tumor vaccines have also shown potential as an individualized immunotherapy strategy for OS. They can stimulate tumor-specific immune responses by guiding the human immune system to recognize and attack tumor cells. Tumor vaccines are mainly divided into immune cell vaccines and non-cell vaccines. Among these types, immune cell-based vaccines utilize innate immune cells to activate effector T lymphocytes. However, a significant challenge lies in regulating migration and activation, as these processes are influenced by immunosuppressive substances in the tumor microenvironment and by the quantity and quality of the patient's immune effector cells.[76,77]

Oncolytic Virus

Oncolytic virus has become a vital immunotherapy involved in the treatment of tumors. After years of research, oncolytic virus therapy has developed rapidly. More than ten viruses including herpes virus, enterovirus, and vaccinia virus have been developed into oncolytic virus drugs and entered clinical trials. Oncolytic viruses can selectively replicate in tumor cells and trigger virus-specific or tumor-specific inflammatory responses within TME.[78]

Nanomaterial-Based Immunotherapy in Osteosarcoma

Innate Immune Cell Mediated Strategies

Innate immune cells, including macrophages and DCs orchestrate OS progression by remodeling the tumor microenvironment. Both repolarizing TAMs and enhancing DCs' antigen presentation synergizes with PD-1/PD-L1 blockade; however, the metabolic heterogeneity of these cells and the immune-tolerant niche demand further mechanistic studies to facilitate clinical translation.

Tumor-Associated Macrophages

Current research on TAMs within the OS microenvironment remains primarily focused on phenotypic reprogramming, with strategic repolarization from immunosuppressive M2 to pro-inflammatory M1 phenotypes demonstrating potent activation of M1-mediated antitumor immunity.

The high heterogeneity and mutational burden of tumor cells pose significant challenges for drug development. Coating nanomaterials with tumor cell membranes offers a promising strategy for precise therapy. In some studies, nanodrugs loaded with the sonosensitizer IR780 and the CD47 inhibitor RRx-001 were successfully constructed and coated with OS cell membranes. These nanomedicines exhibited enhanced uptake in OS cells and augmented the efficacy of both sonodynamic therapy (SDT) and CD47 blockade. As shown in Figure 3, IR780-induced SDT promotes macrophage migration to tumor sites, polarizes M2-type TAMs toward the pro-inflammatory M1 phenotype, and enhances phagocytic activity against cancer cells.[79] Furthermore, anti-CD47 monoclonal antibodies (mAbs) activate TAMs to engulf and eliminate tumor cells, thereby synergizing with nanomedicine-driven immune remodeling to suppress tumor progression.

Recent studies have revealed that manganese ions (Mn^{2+}) promote macrophage polarization toward the M1 phenotype. Previous work has shown that bovine serum albumin (BSA)-templated manganese dioxide nanosheets (BMSNs) can be functionalized with hydrophilic drug derivatives to induce reactive oxygen species (ROS) generation and immune activation

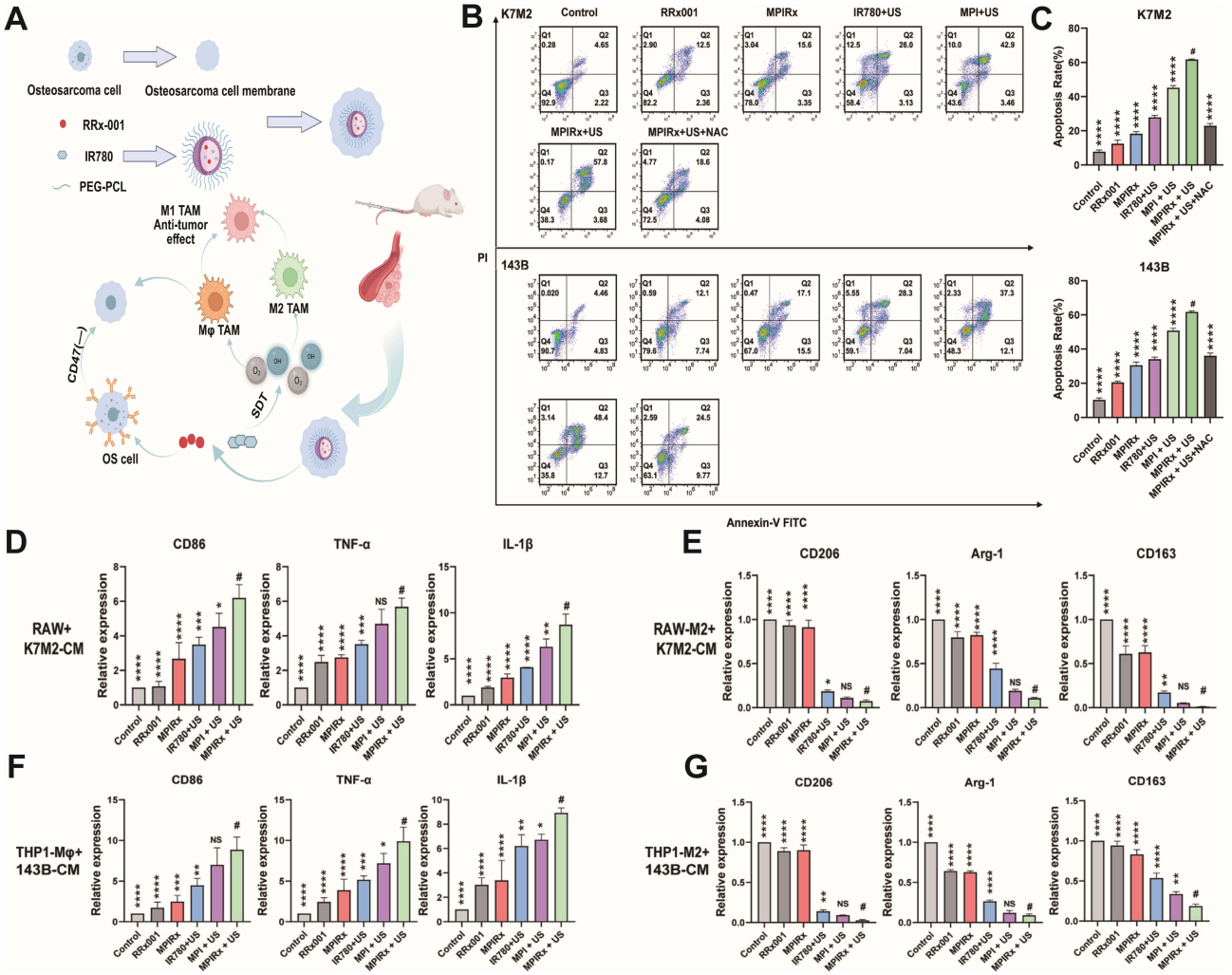

Figure 3 IR780-mediated SDT recruits and repolarizes macrophages to the M1 phenotype while enhancing phagocytosis, synergized with anti-CD47 mAb-activated TAM clearance for tumor suppression. (**A**) Schematic of biomimetic nanomedicine for OS therapy. (**B** and **C**) Synergistic anti-OS effect of MPIRx nanodrugs. (**D**–**G**) SDT treatment with IR780, MPI, or MPIRx promoted M1-type macrophage polarization (upregulation of CD86, TNF-α, IL-1β, CD68, iNOS, and IL-6) and suppressed M2-type polarization (downregulation of CD206, Arg1, CD163, and IL-10) in OS-conditioned medium-treated macrophages. All values are the mean ± SD, *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001, NS stands for not statistically significant (P≥ 0.05). # indicates a group which was compared with other groups (Adapted from Ref.[79]).

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upon internalization by macrophages, thereby stimulating M1 polarization within the tumor microenvironment.[80] This dual-modal immunostimulatory mechanism demonstrates significant potential for reprogramming TAMs in OS microenvironments.

Furthermore, advanced OS exhibits a high propensity for lung metastasis, underscoring the critical need to suppress metastatic spread for effective treatment. Mechanistically, PD-1 expression on TAMs has been shown to inhibit phagocytosis and facilitate OS metastatic progression. Yu et al investigated the synergistic effect of photodynamic therapy (PDT) and the autophagy inhibitor 3-methyladenine (3-MA) in OS treatment, demonstrating that 3-MA-mediated downregulation of PD-L1 enhances the efficacy of PDT and suppresses distant metastasis via modulation of the immune microenvironment. Concurrently, they confirmed that reduced PD-L1 expression under combined PDT and 3-MA treatment significantly inhibits tumor growth in metastatic models.[81]

The dual role of TAMs in tumor development has established them as a key therapeutic target. Evidence indicates that TAMs promote tumor progression both by providing structural support and by shaping an immunosuppressive microenvironment through secreted signaling molecules and EVs.[12] Therefore, modifying the OS tumor microenvironment and specifically targeting TAMs with nanomaterials can promote macrophage-mediated phagocytosis of OS cells.

In OS, TAMs drive immunosuppression via M2 polarization, PD-1/PD-L1 signaling, and impaired phagocytic function. Therapeutic approaches aimed at modulating TAM plasticity—through metabolic reprogramming or immune checkpoint intervention—enhance antitumor immunity. However, TAM heterogeneity, stromal crosstalk, and adaptive resistance mechanisms continue to challenge sustained therapeutic efficacy, highlighting the need for precisely targeted strategies that disrupt microenvironmental communication.

Dendritic Cells

Insufficient immune activation contributes to the failure of tumor immunotherapy. In response, promoting crosstalk between innate and adaptive immunity has emerged as a promising strategy to enhance antitumor efficacy. As illustrated in Figure 4, Liu et al designed a titanium carbide MXene-based nanoplatform conjugated with Mn^{2+}-loaded ovalbumin (OVA) for photothermal-immunotherapy. Under near-infrared (NIR) irradiation, this system triggered the release of mitochondrial DNA (mt-DNA), OVA, and Mn^{2+}. The synergistic effect of mt-DNA and Mn^{2+} activated the cGAS–STING pathway to bolster innate immunity, while OVA and tumor-derived antigens promoted DC maturation and cytotoxic T lymphocyte (CTL) infiltration. In OS models, this nanoplatform effectively suppressed both primary and metastatic tumors by facilitating innate and adaptive immune crosstalk.[82]

Wang's team developed a bioinspired BSA-scaffolded calcium phosphate nanoagent co-loaded with methotrexate and the immunomodulator CpG. This system enables synergistic chemo-immunotherapy through pH-responsive drug release: CpG activates DCs via TLR9 signaling to initiate CD8+ T cell responses, while the acidic tumor microenvironment controls drug release to inhibit OS progression and lung metastasis.[83] Li et al constructed a nanoscale metal–organic framework (MOF), designated TZM, which enhances radiodynamic therapy (RDT) sensitivity. TZM-mediated RDT promotes DC maturation through immunogenic cell death and upregulates PD-L1 expression via the cGAS–STING pathway, eliciting robust antitumor immunity.[84]

In OS, DC activity significantly influences tumor progression. As essential components of the immune system, DCs identify and present tumor-associated antigens, direct immune responses against tumors, and serve as the foundation for DC-based vaccines and nanomaterial-enhanced immunotherapies.

Myeloid-Derived Suppressor Cells

The immunosuppressive TME can be therapeutically targeted by inhibiting MDSCs, which dualistically promote tumorigenesis through structural scaffolding and immunosuppressive cytokine secretion. The hyaluronic acid (HA)-coated zeolitic imidazolate framework-8 (HA/ZIF-8) nanocomposite co-encapsulates gemcitabine (Gem, a DNA synthesis inhibitor) and D-1-methyltryptophan (D-1-MT, an indoleamine 2,3-dioxygenase (IDO) antagonist). This dual-action system depletes MDSCs through Gem-induced apoptosis while blocking the IDO-mediated tryptophan/kynurenine immunosuppressive pathway.[85] Concurrently, D-1-MT inhibits IDO enzymatic activity, blocking the tryptophan/kynurenine (Trp/Kyn) metabolic axis to reverse MDSC immunosuppressive polarization. Notably, D-1-MT exerts dual-

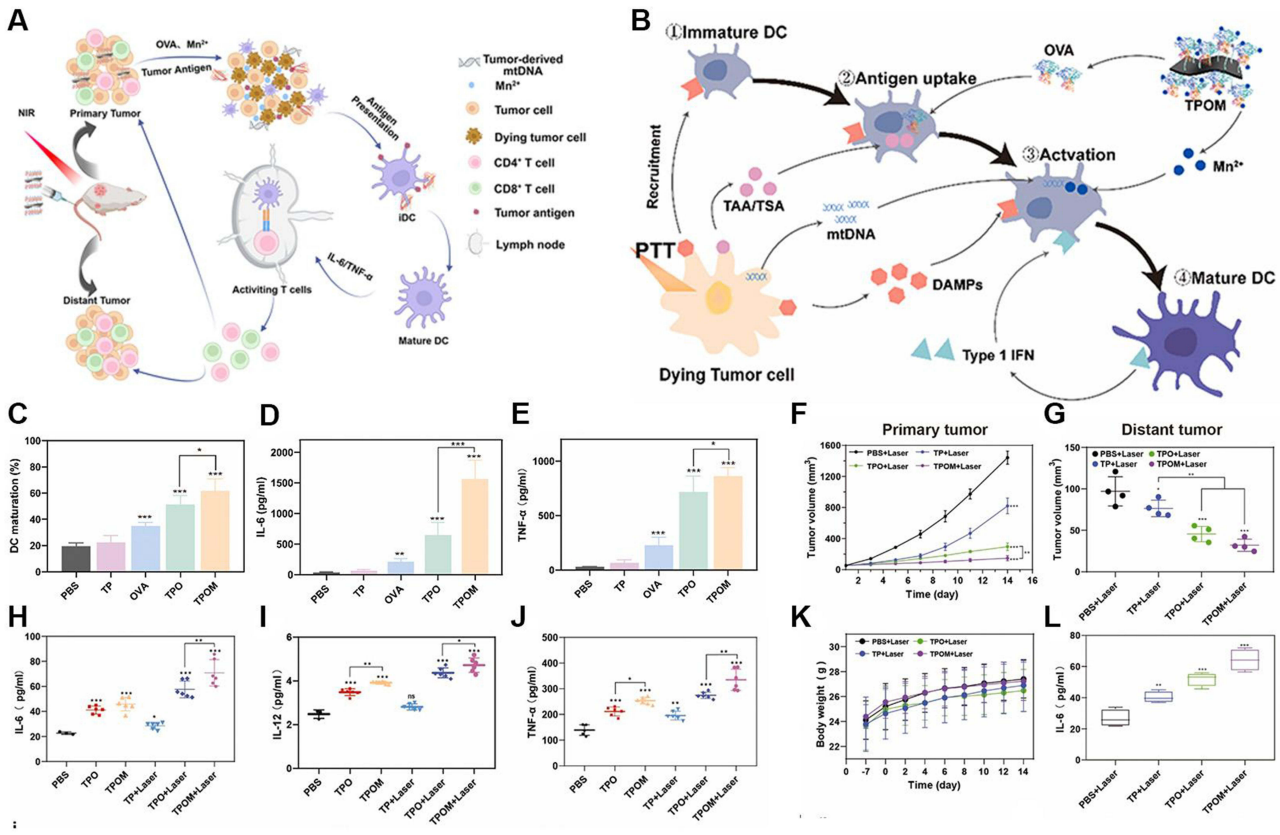

Figure 4 An NIR-triggered Ti_3C_2 MXene-OVA-Mn^{2+} nanoplatform releases mtDNA and OVA/Mn^{2+} to activate cGAS-STING innate immunity and promote DC/CTL-mediated adaptive immunity, suppressing primary and metastatic osteosarcoma. (**A**) Mechanism of Ti_3C_2 MXene-Mn^{2+}/OVA nanoplatform for photothermal-immunotherapy against OS. (**B**) Schematic illustration of TPOM-mediated immunotherapy based on PTT throughout the whole process of DCs mature. (**C**–**E**) Mature DCs secrete pro-inflammatory cytokines to activate T cells and induce systemic immunity. (**F, G, K** and **L**) This PTT-triggered immunotherapy elicits persistent systemic immune responses extending beyond the treatment period. (**H**–**J**) PTT-triggered release of OVA and Mn^{2+} can enhance the maturation of DCs. All values are the mean ± SD, *P < 0.05, **P < 0.01, ***P < 0.001 (Adapted from Ref.[82]).

functional effects: (1) systemic IDO inhibition attenuates Treg differentiation and enhances $CD8^+$ T cell activation; (2) direct cytotoxicity against OS cells induces caspase-mediated apoptosis through ROS overproduction. This synergistic immunotherapeutic strategy demonstrates enhanced tumor penetration and sustained drug release, achieving 78.3% tumor growth inhibition in orthotopic OS models while preserving normal tissue viability.

Adaptive Immune Cells Mediated Strategies

Adaptive immune cells, such as cytotoxic T cells, mediate OS immunosurveillance through tumor antigen recognition but are often limited by T-cell exhaustion and immune checkpoint signals. Although combining checkpoint blockade with strategies to enhance T-cell infiltration can alleviate immunosuppression, deficits in antigen presentation and stromal barriers continue to hinder clinical translation.

T cell infiltration constitutes a critical determinant of anti-tumor immunity in OS. Given the pivotal role of T cells within the OS tumor microenvironment, T cell-based immunotherapeutic strategies have emerged as a vigorous research focus with substantial translational potential.[86]

T cell exhaustion, characterized by functional impairment and PD-1 overexpression, critically limits anti-tumor efficacy. To reverse T cell exhaustion in OS, a biomimetic cell membrane-coated, glucose/oxygen-consuming nanoreactor (PGT@cRGD-M) has been developed, which downregulates HIF-1α to modulate key immune checkpoints by suppressing PD-L1 expression while enhancing granzyme B production.[87] This nanoreactor system demonstrates dual-functional effects: (1) inducing macrophage polarization and reducing TME angiogenesis; (2) depleting intratumorally glucose/oxygen to amplify hypoxia, thereby synergizing starvation therapy with hypoxia-activated chemotherapy for

enhanced OS suppression. Complementarily, gold nanodendrites (AuNDs) coated with programmed death receptor 1 antibodies (anti-PD-1) have been engineered as AuNDs@aPD-1 complexes. Following intravenous administration and localized infrared irradiation, these nanoparticles convert "cold" tumors to "hot" phenotypes by activating CTLs through sustained anti-PD-1 release from dendritic structures, achieving simultaneous primary and metastatic OS destruction.[88]

Tregs promote tumor progression, invasion, and metastasis by suppressing anti-tumor immunity, underscoring their significance as therapeutic targets. Recent studies emphasize the need to elucidate Treg heterogeneity within the OS TME to identify novel therapeutic strategies.[89] Cheng et al integrated single-cell and bulk RNA-seq data to construct a prognostic model of Treg-specific genes in OS, enabling the prediction of targeted drugs for OS patients.[35] Leveraging tumor cell membrane camouflage technology, Fu et al developed alendronate/K7M2 cell membrane-coated hollow manganese dioxide ($HMnO_2$) nanoparticles (Rh2@$HMnO_2$-AM) for co-delivering ginsenoside Rh2. This system enhances serum IL-6, IFN-γ, and TNF-α secretion while reducing intratumoral $FOXP3^+$ Treg populations, demonstrating dual immunotherapeutic and chemotherapeutic efficacy.[90]

T cell infiltration underpins anti-tumor immunity in OS yet limited by exhaustion and immunosuppressive Tregs. Reversing T-cell dysfunction and targeting Tregs reshape immune landscapes, but microenvironment heterogeneity, Treg plasticity, and antigen-specific inefficacy hinder clinical translation.

Non-Immune Cells Mediated Strategies

Non-immune cells (eg, fibroblasts, MSCs) promote OS immunosuppression via stromal remodeling and immunoregulatory signaling.[14] Targeting their fibrogenic or immunosuppressive traits disrupts microenvironment tolerance, yet functional heterogeneity, mechanometabolic crosstalk, and dynamic plasticity impede therapeutic refinement.

Cancer-Associated Fibroblasts

In OS, therapeutic efficacy is significantly constrained by cancer-associated fibroblasts (CAFs), which remodel the tumor stroma through the deposition of a dense extracellular matrix (ECM) and the secretion of pro-tumorigenic cytokines.[91] Targeted ablation of CAFs not merely fails to mitigate immunosuppression but may also accelerate metastatic dissemination due to compensatory activation of alternative stromal pathways.[92]

Reversing the activation state of CAFs in the OS microenvironment represents a promising therapeutic strategy to potentiate antitumor immunity. Remodeling CAFs toward a less immunosuppressive phenotype can facilitate the infiltration of effector T cells into tumor tissues. Based on this rationale, an injectable hydrogel system with sequential responsiveness was developed, composed of carboxymethyl chitosan (CMCS) and four-arm polyethylene glycol succinimidyl glutarate (4S-PEG), encapsulating both a NOX4 inhibitor and liposomal doxorubicin (L-DOX). The NOX4 inhibitor is released first and acts on CAFs, reducing tumor fibrosis, enhancing the delivery of L-DOX, and promoting T-cell infiltration. Subsequently, doxorubicin (DOX) is released to directly kill OS cells.[91]

CAFs exacerbate OS immunosuppression via stromal remodeling and protumorigenic signaling. Targeting CAF activation enhances T-cell infiltration, yet compensatory stromal adaptations and fibrotic resistance demand balanced stromal-immune modulation.

Mesenchymal Stem Cells

MSCs exhibit immunomodulatory properties, positioning them as promising therapeutic agents in OS treatment.[93] They secrete immunosuppressive factors such as TGF-β, indoleamine 2,3-dioxygenase (IDO), and prostaglandin E2 (PGE2), which suppress effector T-cell proliferation and promote Treg differentiation, thereby dampening anti-tumor immunity.[94]

However, this intrinsic immunosuppression can be harnessed to mitigate excessive inflammation in CAR-T cell therapy, reducing cytokine release syndrome while preserving tumor-targeting efficacy. Preclinical studies demonstrate that MSCs engineered to overexpress interferon-beta (IFN-β) or tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) migrate to OS sites via CXCR4/CXCL12 chemotaxis, enhancing local immune activation and inducing caspase-mediated tumor apoptosis.[95] Notably, MSC-derived EVs carrying PD-L1 siRNA reverse immunosuppressive

tumor microenvironments by upregulating $CD8^+$ T-cell infiltration and granzyme B expression in murine OS models. Despite concerns that MSC-mediated immunosuppression may potentially favor tumor progression, recent Phase I trials (eg, NCT04385746) have confirmed their safety and immune reprogramming capacity when combined with immune checkpoint inhibitors.[96]

These findings underscore dual role of MSCs as both immunosuppressors and immunotherapeutic engineers, with their tropism and secretion profiles offering transformative potential for precision immunotherapy in OS. This dual-function paradigm highlights unique capacity of MSCs to reprogram tumor-immune microenvironment, bridging innate immunosuppression and adaptive antitumor responses for synergistic therapeutic outcomes.

Targeted Delivery Strategies of Nanosystems for Osteosarcoma Therapy

Nanomedicine can be designed, characterized, produced, and applied by controlling the size (1–100 nm) and shape of nanomaterials,[97] especially as drug delivery systems[98] (Figure 5). Nanosystems can promote drug retention in tissues, prevent enzyme degradation, enhance cellular uptake, and trigger drug release by stimulation through enhanced permeability and retention effect (EPR), which is highly targeted.[99] With the development of nanomedicine, various inorganic nanomedicine delivery systems, lipid nanodelivery systems, polymer nanodelivery systems, nanogels, and EVs have come into public view. These nanomaterials are widely used for targeted drug delivery to tumor tissues due to their adjustability, high carrying capacity, high bioconversion efficiency, and some of them have photothermal effects, providing a new scheme for the treatment of OS.

Inorganic Nanomedicine Delivery System

Inorganic nanomaterials such as gold, iron, and silica have gained extensive applications in drug delivery and bioimaging due to their exceptional physicochemical properties.[100] Through precise synthesis techniques, researchers can tailor the size, structure, and geometric morphology of these nanomaterials,[101] enabling them to achieve customized functionalities for specific biomedical applications.

Hydroxyapatite

Hydroxyapatite (HAp), the primary inorganic constituent of vertebrate bones and teeth, has emerged as a star material in bone tissue engineering (BTE). Its outstanding biocompatibility, osteoinductive capacity, and mechanical strength make it ideal for constructing bioactive scaffolds and implant coatings.[102,103]

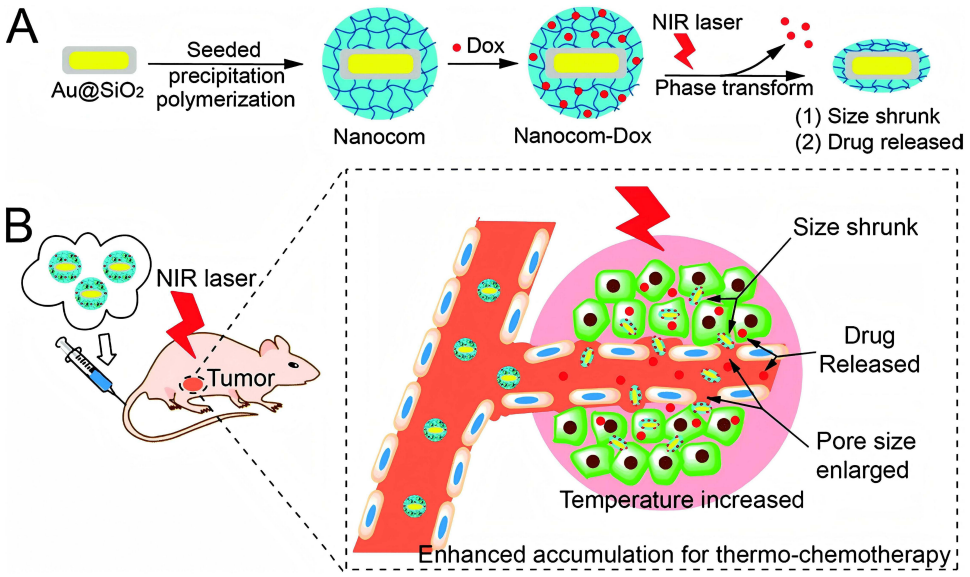

Figure 5 (**A**) Design and synthesis of hybrid nanogels through controlled nanomaterial properties (1–100 nm); (**B**) Near-infrared (NIR) laser-activated targeted drug delivery for tumor therapy. Reprinted with permission from.[98] Copyright 2014 American Chemical Society.

With breakthroughs in nanotechnology, HAp-based nanomaterials have demonstrated promising potential in tumor-targeted therapy owing to their unique surface chemistry and inherent bone-targeting capabilities. Studies reveal that HAp nanoparticles co-loaded with bisphosphonate (BP, a bone-targeting agent) and the small-molecule bromodomain inhibitor JQ1 significantly suppress the migratory activity and viability of K7M2 OS cells in 2D/3D in vitro models.[104] Building on this foundation, Liu et al[105] innovatively developed a ternary nanocomposite system comprising HAp, BSA, and paclitaxel (PTX). This system not only inhibits postoperative recurrence and metastasis of orthotopic OS through sustained PTX release but also promotes osteogenic differentiation via its HAp component, achieving dual repair effects for bone defects. This advancement provides novel insights into comprehensive bone tumor therapy. Notably, targeted modification strategies for nanocarriers further enhance drug delivery efficiency. For instance, self-assembled alendronate-modified human serum albumin (HSA-AD) nanoparticles loaded with DOX exhibit the strongest pro-apoptotic effects in cellular experiments. This efficacy is attributed to ligand-receptor-mediated bone-targeting mechanisms and the positive regulation of cell death pathways.[106] These developments collectively mark significant progress in inorganic-organic hybrid nanosystems for precision therapy of bone tumors.

Graphene and Its Derivatives

Graphene (Gt), a two-dimensional honeycomb crystal composed of carbon atoms bonded via sp^2 hybridization, has emerged as a research hotspot in nanobiomedicine due to its exceptional mechanical strength, superior electrical conductivity, and ultrahigh specific surface area.[107] Notably, its ability to efficiently absorb near-infrared light and convert it into localized hyperthermia has been successfully harnessed for precise tumor ablation through photothermal therapy (PTT) in animal models.[108] Building on these properties, Zeng et al[109] developed a multifunctional nanocomposite system, TPP-PPG@ICG. By conjugating the mitochondrial-targeting ligand 4-carboxybutyl triphenylphosphonium bromide (TPP) to polyethylene glycol-modified nano-graphene oxide (PPG) loaded with indocyanine green (ICG), this system achieves specific mitochondrial targeting in tumor cells, demonstrating synergistic photothermal-photodynamic effects that significantly enhance therapeutic efficacy against drug-resistant OS.

As a derivative of graphene, graphite oxide (GtO) exhibits a graphite-like layered structure. When exfoliated into monolayers of atomic thickness, it is termed graphene oxide (GO).[110] Functionalized graphene oxide (GO) nanoparticles induce oxidative stress-mediated apoptosis in OS cells by elevating intracellular ROS levels by 3.2-fold compared to controls ($p<0.01$). Concurrently, GO disrupts mitochondrial membrane potential ($\Delta\Psi m$ reduction: 68±5%) and activates caspase-3/7 pathways, as demonstrated in Saos-2 cell models.[111] For instance, exposure to nano-graphene oxide (nGO) markedly disrupts the metabolomic homeostasis of human Saos-2 OS cells, while nGO-mediated hyperthermia amplifies this metabolic perturbation.[112] To overcome the limitations of monotherapy, Huang's team[113] engineered a functionalized GO-based synergistic platform. By covalently modifying GO with polyethylene glycol (PEG), folic acid (FA), and the photosensitizer ICG, they constructed a nanodelivery system (PEG-GO-FA/ICG) capable of co-loading the MTH1 inhibitor TH287 and DOX. MTH1, a critical protease for repairing DNA oxidative damage, becomes a therapeutic target—its inhibition sensitizes tumor cells to ROS, thereby potentiating PDT. Experimental validation confirmed that this nanosystem effectively suppresses OS cell proliferation and migration via a chemotherapy-PDT combined strategy, demonstrating unique advantages of multimodal synergistic therapy.

Graphene-based nanomaterials serve as multifunctional platforms for OS therapy, enabling targeted drug delivery, synergistic photothermal/photodynamic effects, and oxidative stress-induced apoptosis. Their osteogenic potential further integrates tumor suppression with bone regeneration, offering multidimensional therapeutic strategies.

Metals and Their Derivatives

Metal nanoparticles (such as gold (Au), silver (Ag), zinc (Zn), calcium (Ca), etc.)[114] have become important research materials in biomedical, pharmaceutical and clinical medicine fields due to their unique biological characteristics, excellent stability and easy preparation.[115]

Gold nanoparticles (AuNPs) exhibit biocompatibility, controllable surface chemistry, direct synthesis, and tunable optical scattering/absorption properties.[116] Yan et al[117] engineered AuNR@SiO_2-GelMA core-shell nanoparticles loaded with DOX/ALN for targeted delivery and photothermal responsiveness. Single low-dose peritumoral injection suppressed OS growth. Silver nanoparticles (AgNPs) are renowned for their applications in antimicrobial and anticancer therapies, as well as in promoting bone

healing, wound repair, enhancing vaccine immunogenicity, and exerting antidiabetic effects.[118] AgNPs regulate ROS, promote inflammasomes, and release Ag+, inducing lipid peroxidation, proteotoxicity, and apoptosis.[119,120] In addition, Hu et al[121] demonstrated fructose-coated AgÅPs suppressed tumor growth/metastasis, outperforming cisplatin with minimal toxicity. Calcium, as the most abundant element in bone and an essential element for diverse physiological processes, plays a pivotal role in maintaining bone homeostasis, regulating OS progression, and modulating immune responses. Due to its profound impact on bone homeostasis, calcium-based materials hold unique advantages in OS therapy.[122] Zhou et al[123] engineered CPPA-DOX hybrids with pH-responsive release, suppressing OS and enhancing hBMSC osteogenesis via AMPK activation. Wang et al[124] engineered a mineral-based nanomedicine comprising europium-doped calcium fluoride nanoparticles (CaF_2: Eu NPs) to enhance the efficacy of adjuvant radiotherapy (ie, postoperative radiotherapy) against tumor cell proliferation and OS metastasis.

Metals and their derivatives have shown multifunctional advantages as nanodrug delivery systems in the treatment of OS.[125] With their excellent biocompatibility and controllable properties, gold, silver, calcium and other metal nanoparticles can not only achieve the targeted delivery and controlled release of drugs, but also enhance the therapeutic effect through photothermal, photodynamic and other effects, while having imaging and anti-infection functions.[126–128] Calcium-based materials enhance OS therapy and osteogenesis via TME modulation, apoptosis induction, and metastasis inhibition, enabling high-efficacy, low-toxicity strategies.

In addition to the inorganic nanodrug delivery systems described above, inorganic nanomaterials such as HAp and silica also show excellent drug delivery performance. Table 1 systematically summarizes the properties of these inorganic nanomaterials and their application effectiveness in anti-tumor drug delivery, providing an important reference for the design and optimization of nanomedical drug delivery systems.

Table 1 Inorganic Nanomaterials for Optimized Tumor Drug Delivery

Type of Nanomaterials	Loaded Drug	Feature	Anti-Cancer Effect	References
HA	PTX	Nanobiomaterials/ antitumor drug complexes	Effectively inhibit OS tumor metastasis and promote osteogenic differentiation	[105]
HAS-AD	DOX	Self-assembled human serum albumin nanoparticles	Effective targeted therapy for OS	[106]
PPG	TPP	Mitochondrial targeting	Therapy for Drug-Resistant Osteosarcoma	[109]
GO	DOX	Chemo-Photodynamic Therapy	Suppression of Proliferation and Migration of Osteosarcoma Cells	[113]
SiO2@MgAl-LDH	MTX	SiO_2 dot coated double hydroxide nanocomposites	Deliver chemotherapy drugs to the OS cells to kill the tumor cells	[129]
MSNs	DOX	pH responsive and highly selective	The antitumor effect of the drug delivery system was increased eight-fold	[130]
Bi2S3@MSN NPs	DOX	Synergistic photothermal therapy - chemotherapy	Significantly ablate highly malignant OS and prevent its recurrence	[131]
CPPA	DOX	pH-Responsive	Promotion of Osteogenic Differentiation in Mesenchymal Stem Cells	[123]
AuNR@SiO2	DOX	Photothermal Response	Receptor-Mediated Endocytosis in Cancer Cells	[117]
mPEG-b-PGA	DOX	Selective Drug Release	Enhanced Tumor Accumulation and Reduced Systemic Toxicity	[132]
Sim-3DTi	Cisplatin	Osteosarcoma Ferroptosis	Enhanced Tumor Cell Apoptosis and Reduced Systemic Toxicity	[133]
DOX-BRE-IONPs	DOX	pH-Responsive	Chemo-Photothermal Therapy for Osteosarcoma	[134]
H-mMnO_2	TPP	pH/NIR Dual-Responsive Release Performance	Mitochondria-Mediated Apoptosis	[135]
DFHHP	DOX	Sonically activated	Overcoming hypoxia-induced chemotherapy resistance, inducing tumor cell apoptosis and synergistic iron death to effectively inhibit tumor growth	[136]

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Liposome Nanomedicine Delivery System

Lipid nanoparticles (LNP) are lipid vesicles with a homogeneous lipid core. These vesicles are widely used for small molecule drug and nucleic acid delivery and have recently received a lot of attention for their remarkable success as a COVID-19 mRNA vaccine delivery platform.[137] At present, various lipid carriers have been developed, such as solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), liposomes and lipid polymer hybrid nanoparticles. Many studies involving lipid-based nanocarriers have been reported for the delivery of anticancer drugs.[138]

Liposome

Liposome, an early version of LNP, is a multifunctional nanomedical drug delivery platform, and it is also the first nanomedical drug delivery platform to successfully move from concept to clinical application, with a number of approved drug preparations.[139] Liposome plays a vital role in the treatment of OS as a drug carrier. As early as 2017, researchers prepared a novel polyethylene glycol cationic liposome that binds cholesterol via a disulfide bond (Chol-SS-mPEG), coated with HA and added DOX. HA can bind to CD44 overexpressed by cancer cells to increase the specific recognition and uptake of OS cells, thus achieving inhibition and targeted therapy of OS.[140] Subsequently, Gazzano et al[141] evaluated the efficacy of synthetic dox (Sdox) with HA-binding liposomes encapsulated with H_2S releasing fragments on preclinical OS models expressing P-glycoprotein (Pgp) and HA receptor CD44, and experimental data showed that no secondary resistance was developed during treatment. Liposomes, as drug delivery carriers, have demonstrated significant advantages in enhancing the bioavailability and therapeutic efficacy of insoluble components of Chinese medicine. Studies have shown that liposomes can significantly improve the efficacy of targeted therapy for OS through reasonable structural modification and functional design. For instance, Jing et al[142] demonstrated that quercetin inhibits JAK2 non-covalently through its JH2 domain, thereby suppressing OS proliferation and immune evasion via the JAK2-STAT3-PD-L1 signaling axis. To address the limitations of quercetin's low water solubility and poor oral bioavailability, they encapsulated quercetin in folate-modified liposomes, offering a novel therapeutic strategy for OS. Similarly, Zhang et al[143] developed honokiol (HNK)-loaded liposomes modified with a hyaluronic acid-phospholipid conjugate (HA-DOPE) for OS treatment (Figure 6). Zhu et al[144] synthesized and characterized folate-conjugated resveratrol liposomes (FA-Res/Lps), which exhibited robust tumor-targeting capability, effectively inhibiting in vivo tumor growth and lung metastasis. To advance ferroptosis therapy in OS, He et al[145] engineered GA-Fe@CMRALi liposomes by co-loading hydrophobic all-trans retinoic acid (ATRA) and hydrophilic ferroptosis initiator GA-Fe. These liposomes amplified ROS-triggered ferroptosis and apoptosis, demonstrating potent efficacy against OS with homing targeting capacity to tumor sites.

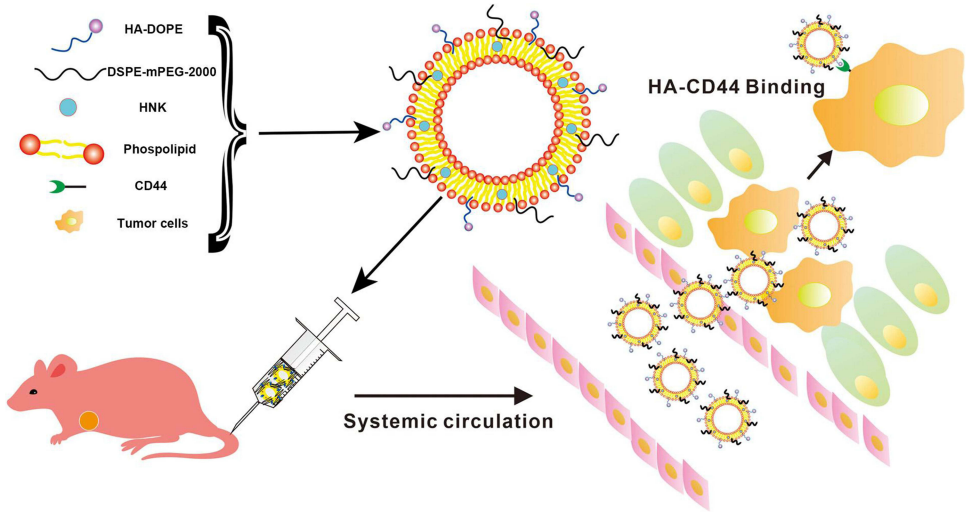

Figure 6 CD44 receptor-targeted delivery of honokiol (HNK) for osteosarcoma therapy: Schematic illustration of HA-DOPE-modified liposomes (HA-DOPE@Lips/HNK) developed by Zhang et al. Reprinted with permission from.[143] Copyright DovePress.

Other Lipid-Based Systems

LNPS composed of lipid cores, namely lipid core nanoparticles (LCNPs), such as microemulsions (MEs) and nanoemulsions (NEs) are also widely used. LCNP is divided into liquid lipid nanoparticles (LLN) according to the physical state of its lipid core components, including lipid nanoemulsions (LNEs) and lipid nanocapsules (LNCs), solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC).[146] Wang et al[147] engineered Fe_3O_4/PB-loaded PLGA microcapsules enabling multimodal imaging and chemo-photothermal synergy, achieving tumor-specific ablation and NIR-triggered DOX release for OS theranostics.

Extracellular vehicles (EVs), including exosomes, mediate intercellular communication by transferring bioactive payloads, modulating recipient cell physiology.[148] The Rab22a-NeoF1 fusion protein in OS is sorted into exosomes via HSP90 recognition of its KFERQ-like motif, where it cooperates with exosomal PYK2 to drive lung metastasis by polarizing macrophages toward M2 phenotype through STAT3 activation and inducing RhoA-mediated pre-metastatic niche formation in recipient cells—a process targetable by PYK2-disrupting RGD peptides.[149]

Liposomal drug delivery system significantly improves the efficacy of insoluble drugs in the treatment of OS by improving drug solubility, stability and targeting. Its functional modification can enhance tumor site accumulation, achieve controlled release, and cooperate with chemical, photothermal and other therapies to inhibit tumor proliferation and metastasis and induce cell apoptosis or iron death, providing an efficient and low-toxicity delivery strategy for OS treatment.

Polymer Nanomedicine Delivery System

Natural Polymer Drug Carrier

Natural polymers such as chitosan, alginate, gelatin, cyclodextrin, dextran and HA are widely used in drug delivery.[138] Chitosan, a linear polysaccharide and primary derivative of chitin, is characterized by its positively charged nature, which enables it to bind to nucleic acids through electrostatic interactions. It exhibits biological adhesiveness, low toxicity, and anticancer properties, making it a promising candidate for biomedical applications. Chitosan's unique physicochemical and biological properties position it as a promising drug delivery platform for OS treatment, with demonstrated potential to enhance therapeutic efficacy while reducing adverse effects.[150,151] Yang et al[152] developed a pH-responsive drug delivery system based on mesoporous ZSM-5 zeolite/chitosan core-shell nanosheets (ZSM-5/CS/DOX), which could efficiently load DOX and significantly improve the therapeutic effect of chemotherapy drugs on OS. In the field of thermotherapy-chemotherapy combination therapy, Amini et al[153] innovatively co-loaded cisplatin and magnetic bioactive glass (MBGs) in chitosan grafted poly (ε-caprolactone) (PCL) nanofibers. This system enables controlled drug release at different pH values and temperatures (37°C and 43°C), offering precise regulation of drug delivery under different physiological and thermal conditions. Additionally, it enhances the cytotoxicity against MG-63 OS cells through the synergistic effects of magnetothermal therapy and chemotherapy. For siRNA delivery, Saravanabhavan et al[154] designed a graphene oxide functionalized chitosan nanoparticle, which can effectively protect siRNA from degradation and achieve its targeted delivery to Saos-2 and MG-63 OS cells. The effects of different concentrations and pH conditions on the release behavior of siRNA were also studied. In addition, alginate has shown broad application prospects in the field of drug delivery systems due to its excellent biocompatibility and degradability.[155]

Hydrogel Drug Carrier

Nanogels are nanoscale hydrogel particles that integrate the properties of hydrogels and nanomaterials. They exhibit high water content, large surface area, tunable chemical and physical structures, excellent mechanical properties, biocompatibility, and the ability to actively or passively target specific sites of action.[98] Additionally, nanogels exhibit rapid responsiveness to environmental stimuli such as light, pH, or temperature.[156] These advantageous features make nanogels ideal candidates for applications in nanomedicine. Dipankar et al[157] developed a dextrin (Dxt) and acrylic acid (AA, as monomer)-based nanogel [n-Dxt-p(MBA)-pAA] via radical polymerization in the presence of N,N'-methylene bisacrylamide (MBA) crosslinker, enabling targeted delivery of DOX hydrochloride to human OS cancer cell lines. Similarly, Zhang et al[158] fabricated cisplatin (CDDP)-crosslinked HA nanogels for DOX delivery in OS therapy. Fiona et al[159] formulated a miR-29b nanoparticle system using HA hydrogel for localized and sustained release. Their study revealed that miR-29b, a member of the microRNA family,

is silenced or downregulated in OS. miR-29b promotes osteoblast differentiation by suppressing TGF-β3 signaling and plays a critical role in bone remodeling. In vitro experiments demonstrated that miR-29b delivery inhibits OS cell proliferation and migration, induces apoptosis, and enhances chemosensitivity. Liu et al[160] constructed a methacrylated gelatin/oxidized dextran/montmorillonite-strontium/polypyrrole (GOMP) hydrogel. The GOMP hydrogel features a dual-network structure enabling sustained DOX release, while polypyrrole imparts conductivity and superior photothermal conversion efficiency (31.61% under 808 nm laser irradiation). This multifunctional DOX-loaded GOMP hydrogel, integrating bone regeneration, photothermal therapy, and chemotherapy, holds significant potential for OS treatment.

Synthetic Polymer Drug Carrier

In the treatment of OS, synthetic polymers mostly act as inert scaffolders or carriers for the delivery of individual bioactive agents. These polymers improve pharmacokinetic parameters, such as solubility and circulation time, while greatly reducing off-target effects.[161] It has been reported that the borated dendrites are assembled with the toxin protein Saporin to form nanoparticles, which are then coated with anionic polymer (aspartic acid) to shield their positive charge and provide bone targeting function. This nanoparticle can effectively inhibit the OS growth and inhibit tumor-related osteolysis.[162] Targeting OS stem-like/progenitor cells that overexpress VEGFR2-JMJD3, Wang et al[163] developed glutathione scavenging nanoplatform using cysteine-polydisulfide polymer (Cys-8E) to effectively co-deliver Apa (VEGFR2 inhibitor) and J4 (JMJD3 inhibitor) to OS stem-like/progenitor cell population, thereby increasing drug uptake by tumor cells. Optimize the intracellular release time of drugs to improve the synergistic effect on drug-resistant OS cells. For OS-associated antigen IL-11Rα, some researchers have installed IL-11Rα-specific peptides on REDOX responsive encapsulated adriamycin (DOX) polymers (IL11-PDOX), thus achieving lower toxicity, chemotherapy specificity and better OS inhibition than free DOX.[164]

The polymer nanodrug delivery system also includes polymer micelles, metal-organic frameworks (MOFs), etc. The polymer micelles form core-shell structures through self-assembly, allowing for the efficient encapsulation hydrophobic drugs and improving their solubility and bioavailability. MOFs exhibit unique advantages in targeted drug delivery due to their high porosity and adjustable pore sizes, enabling efficient loading and controlled release of drugs. Its specific functions are shown in Table 2.

Table 2 Structural-Functional Polymeric/MOF Nanocarriers for OS Therapy

Modification	Payload	Therapies Involved	Outcome	References
PM	OPDEA, DCA	Immunotherapy, targeted therapy	Targeting mitochondria, inhibiting oxidative stress induced by PDHK1, leading to immunogenic pyrosis of OS cell line and inducing the secretion of PD-L1 molecules	[165]
PM	NC-6300, anti-PD-L1	Immunotherapy	Enhance the efficacy of anti-PD-L1 antibodies and increase T cell migration and proliferation	[166]
PEG-PCL	IR780, RRx-001	Immunotherapy, targeted therapy	Induced OS cell apoptosis and immunogenic cell death	[79]
SCK	PTX	Targeted therapy	Aerosol-based delivery for the treatment of OS lung metastasis	[167]
Cu-TCPP	TCP	Immunotherapy, PTT	Inhibit and kill a large number of OS cells, significantly stimulate osteogenic differentiation	[168]
UiO-66 MOF	PDA, PFA, TPZ	Immunotherapy, PTT	It significantly enhanced hypoxia and effectively inhibited tumor growth	[169]
ZIF-8, HA	Gem, D-1-MT	Chemotherapy, immunotherapy	For OS combined chemotherapy and immunotherapy	[85]
CBZP	CUR	Immunotherapy	Activation of immunogenic cell death (ICD) by autophagy death to enhance the immunotherapy response to PD-1/PD-L1 blocking	[56]
MOF	D-Arg	Immunotherapy	Enhance tumor ablation and prevent lung metastasis	[170]
TZM	Ta-Zr	Immunotherapy, RT, RDT	Triggers a powerful anti-tumor immune response	[84]

Additionally, polymer nanodrug delivery system enables controlled drug release through pH response and temperature changes, thereby enhancing targeting precision and therapeutic efficacy in OS treatment. They can carry functional molecules, such as chemotherapy drugs and siRNA, in combination with the synergistic effect of hyperthermia and gene therapy, effectively promoting tumor cell apoptosis. It also exhibits good biocompatibility and stability, providing a multifunctional delivery platform for OS treatment.

Conclusions and Perspectives

The integration of nanomaterials into OS therapeutics represents a paradigm shift in oncology, offering unprecedented opportunities to overcome the limitations of conventional therapies. By leveraging the unique physicochemical properties of nanomaterials—such as tunable surface chemistry, controlled drug release, and tumor-targeting capabilities—researchers have developed multifunctional platforms capable of modulating the immunosuppressive TME and enhancing therapeutic precision. Notably, nanomaterial-based strategies targeting innate immune cells (eg, macrophages, DCs) and adaptive immune cells (eg, T cells) have demonstrated remarkable potential to rebalance immune dysregulation in OS. For instance, engineered nanoparticles loaded with immune checkpoint inhibitors or cytokines have shown enhanced tumor penetration and reduced systemic toxicity compared to free drugs, thereby improving the efficacy of immunotherapies like PD-1/PD-L1 blockade and CAR-T cell therapy. Similarly, biomimetic nanocarriers that mimic cellular membranes or EVs exhibit improved biocompatibility and active targeting, enabling the precise delivery of chemotherapeutics or gene-editing tools to tumor sites.

Despite these advances, critical challenges still remain. The heterogeneity of OS and its dynamic TME necessitate the development of personalized nanomedicine approaches. For example, nanomaterials designed to simultaneously target CAFs and MSCs—key contributors to drug resistance and metastasis—could synergize with immune-modulatory therapies to achieve durable remission. Translational barriers, including scalable synthesis, reproducibility, and regulatory hurdles, must also be addressed to facilitate clinical adoption.

Looking ahead, the convergence of nanotechnology with emerging fields such as artificial intelligence (AI)-driven drug design, single-cell omics, and CRISPR-based gene editing holds immense promise. AI-powered models could optimize nanocarrier designs for patient-specific TME profiles, while advanced imaging-guided nanosystems may enable real-time monitoring of therapeutic responses. Additionally, the integration of oncolytic viruses or tumor vaccines into stimuli-responsive nanoplatforms (eg, pH- or enzyme-activated hydrogels) could amplify antitumor immunity through spatiotemporally controlled antigen release. These considerations crystallize into three pivotal translational challenges: (1) Standardizing nanoparticle batch-to-batch reproducibility under GMP guidelines; (2) Mitigating long-term toxicity of non-degradable nanomaterials—exemplified by HAp where surface engineering strategies (eg, ternary HAp-BSA-PTX composites or HSA-AD biomimetic coatings) modulate degradation kinetics and inflammatory potential; and (3) Overcoming stromal barriers in hypoxic OS niches through combinatorial ECM-remodeling strategies. These advancements collectively underscore nanotechnology's transformative role in reshaping OS therapeutics. By enabling precision modulation of the TME, enhancing immunotherapy delivery, and providing bone-specific targeting capabilities, engineered nanomaterials offer unprecedented opportunities to overcome conventional therapeutic limitations. Future success hinges on interdisciplinary collaboration to navigate translational barriers—optimizing material safety profiles, advancing personalized nanocarrier design through AI integration, and validating combinatorial approaches in clinically relevant models. The convergence of these efforts holds immense promise for transforming refractory OS from a lethal diagnosis to a manageable condition, ultimately redefining oncology care paradigms.

Abbreviations

CSF-1R, colony-stimulating factor 1 receptor; PD-1, programmed cell death protein-1; EGFR, epidermal growth factor receptor; IL, interleukin; NETs, neutrophil extracellular traps; ROS, reactive oxygen species; NO, nitric oxide; TGF-β, transforming growth factor-beta; IFN-γ, interferon-gamma; CXCL-8, C-X-C motif chemokine ligand 8; AFP, α-fetoprotein; HSP, heat shock protein; Tim-3, T cell immunoglobulin and mucin domain-containing protein-3; OAA, osteosarcoma-associated antigens; PD-L1, programmed cell death protein ligand-1; GRM4, glutamate metabotropic receptor 4; CCR7, chemokine receptor 7; TNF-α, tumor necrosis factor-alpha; CTLA-4,

cytotoxic T-lymphocyte-associated protein-4; BTLA, B And T-lymphocyte attenuator; AIRE, autoimmune regulator expression; hSFRP2, humanized secreted frizzled-related protein 2; TLR, toll-like receptor; TAMs, tumor-associated macrophages; TANs, tumor-associated neutrophils; MDSCs, myeloid-derived suppressor cells; MSCs, mesenchymal stem cells; CTCs, circulating tumor cells; DCs, dendritic cells; NK cells, natural killer cells; OS, Osteosarcoma.

Data Sharing Statement

All raw data and code are available upon request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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