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REVIEW

Advances in Nano-Drug Delivery Systems for Osteosarcoma: From Targeting Strategies to Combating Lung Metastasis

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Abstract: Osteosarcoma (OS) is the most prevalent primary malignant bone tumor in children and adolescents, characterized by aggressive local invasion, early distant metastasis (predominantly lung metastasis), and poor prognosis. Conventional clinical regimens, mainly neoadjuvant chemotherapy combined with surgical resection, are limited by severe systemic toxicity, multidrug resistance, low tumor targeting, and unsatisfactory outcomes for metastatic OS, with the 5-year survival rate of metastatic patients remaining below 30%. Nanodrug delivery systems (NDDS) have emerged as a transformative strategy to address these bottlenecks by enabling targeted drug/gene delivery, controlled release, enhanced tumor accumulation, and reduced off-target effects. This review systematically summarizes the pathological characteristics and therapeutic dilemmas of OS, highlights recent advances in diverse NDDS including lipid nanoparticles, polymeric nanoparticles, carbon-based nanomaterials, extracellular vesicles, gold nanoparticles, and hydrogels for OS therapy, with a special focus on strategies to counteract lung metastasis. We further discuss the clinical translation challenges of NDDS in OS, especially pediatric-specific concerns, and propose future directions such as stimuli-responsive nanocarriers, biomimetic nanoparticles, combination therapy, and inhalable nanomedicines for pulmonary metastatic lesions. Overall, NDDS hold great promise to revolutionize OS treatment by improving therapeutic efficacy and safety, particularly in overcoming lung metastasis and chemoresistance.

Keywords: osteosarcoma, nanodrug delivery system, targeted therapy, lung metastasis, pediatric cancer

Introduction

Osteosarcoma (OS) is the most frequently diagnosed primary malignant bone tumor, predominantly affecting children and adolescents, with a second peak in older adults.[1] It most commonly arises in the long bones of the extremities, particularly around the knee joint, and is characterized by aggressive local invasion and early hematogenous dissemination. Approximately 15–20% of patients present with detectable metastases at initial diagnosis, with the lungs being the most common site (85%), followed by skeletal metastases[2]. The pathogenesis of OS is complex, involving genetic predisposition, bone growth and remodeling, and environmental factors. While ionizing radiation has been historically recognized as a contributing factor, recent studies suggest a multifactorial etiology involving germline mutations, somatic alterations, and epigenetic dysregulation.[3–5]

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Over the past three decades, the standard of care for localized OS has been neoadjuvant chemotherapy combined with wide surgical resection. Regimens including cisplatin, doxorubicin, and high-dose methotrexate have improved 5-year survival rates to approximately 68–78% for non-metastatic disease.[6–8] However, for patients with metastatic or recurrent OS, the 5-year survival rate remains below 30%, and clinical outcomes have stagnated since the 1980s.[9] Furthermore, conventional chemotherapy is associated with substantial toxicities, including cardiotoxicity, nephrotoxicity, ototoxicity, and bone marrow suppression, which are particularly concerning in pediatric populations.[10] Additionally, the development of chemoresistance frequently leads to treatment failure and disease progression.[11]

In this context, nanotechnology has emerged as a promising strategy to overcome these limitations. Nano-drug delivery systems offer several advantages, including improved drug solubility, prolonged circulation time, enhanced tumor accumulation via the enhanced permeability and retention (EPR) effect, and the ability to achieve active targeting through surface functionalization with ligands that recognize tumor-specific markers.[12] Moreover, nanocarriers can co-deliver multiple therapeutic agents or combine chemotherapeutics with nucleic acids, enabling synergistic effects and overcoming multidrug resistance.[13] Recent advances in intelligent nanomedicine systems have further expanded the potential for personalized treatment approaches.[14] This review aims to provide a comprehensive and updated overview of recent advances in the application of nano-drug delivery systems for osteosarcoma, with a particular focus on targeting strategies, the challenge of lung metastasis, and future directions for clinical translation.

Current Status of OS Treatment

Clinical Treatment of OS

The current standard of care for localized high-grade OS consists of neoadjuvant chemotherapy followed by limb-sparing surgery and adjuvant chemotherapy. Commonly used chemotherapeutic agents include cisplatin, doxorubicin, and high-dose methotrexate, which are classified as first-line regimens.[8] Despite the success in improving survival for localized disease, these agents are associated with significant dose-limiting toxicities.

Cisplatin is known to cause nephrotoxicity, ototoxicity, and neurotoxicity, with long-term hearing loss occurring in up to 70% of pediatric patients.[15] Doxorubicin-induced cardiotoxicity can manifest within weeks to months after treatment and may lead to irreversible heart failure.[16] High-dose methotrexate is associated with hepatotoxicity, nephrotoxicity, and neurotoxicity, requiring intensive hydration and leucovorin rescue.[10] In addition, the development of multidrug resistance —mediated by mechanisms such as P-glycoprotein overexpression, autophagy, and evasion of apoptosis—often leads to treatment failure and disease recurrence.[11]

For patients with metastatic OS, outcomes remain poor despite aggressive multimodal therapy. The 5-year survival rate for those with lung metastases at diagnosis is approximately 20–30%, and this figure has not significantly improved over the past three decades.[9] Surgical resection of metastatic lesions remains the only potentially curative intervention, but it is only feasible in patients with limited and resectable disease.[17]

Biological Heterogeneity and Therapeutic Challenges

Osteosarcoma is characterized by extensive intra-tumoral and inter-patient heterogeneity, which poses a major challenge to targeted therapy. The OS genome is highly aneuploid and exhibits complex structural rearrangements, with a higher mutation burden than most other pediatric cancers.[18] Common alterations include loss of TP53 (74%), RB1 (64%), and PTEN (56%), as well as amplifications of MYC (39%), CCNE1 (33%), and VEGFA (23%).[19] This genomic complexity limits the efficacy of single-agent targeted therapies and underscores the need for strategies that can address tumor heterogeneity, such as combination therapies delivered via nanocarriers.[20] Recent studies have highlighted the importance of the tumor immune microenvironment in OS progression, with tumor-associated macrophages playing a critical role in immunosuppression.[21,22]

Current Status of Treatment of OS Lung Metastases

Lung metastasis is the leading cause of death in OS patients. The process of metastasis involves the dissemination of tumor cells from the primary site, survival in the circulation, and colonization of the lung parenchyma.[23] Metastatic cells

exhibit distinct genetic and phenotypic characteristics compared to primary tumors, often acquiring properties that enhance survival in the pulmonary microenvironment.[24]

Current therapeutic options for lung metastases are limited. While surgical metastasectomy can be curative in select patients, it is not applicable to those with multifocal or unresectable disease.[17] Systemic chemotherapy has limited efficacy against established metastases, and the development of resistance is common.[25] Furthermore, the small size and high diversity of micrometastases make them difficult to target with conventional drug delivery systems.[26]

In light of these challenges, there is an urgent need for novel therapeutic strategies that can effectively target metastatic lesions, overcome chemoresistance, and minimize systemic toxicity. Nanotechnology offers a promising platform to address these unmet needs by enabling targeted delivery of therapeutic agents to metastatic sites, including the lungs.[27] Figure 1 schematically summarizes the major challenges of osteosarcoma lung metastasis—including hematogenous dissemination, formation of lung micrometastases, and resistance to conventional chemotherapy—along with corresponding nano-drug delivery strategies such as EPR effect-based passive targeting, active targeting, pulmonary inhalation, and combination therapy.

Application of Nanocarrier Systems in OS

Nanotechnology has enabled the development of diverse drug delivery systems that can enhance the pharmacokinetics, biodistribution, and targeting efficiency of therapeutic agents. Table 1 summarizes the key nanocarrier platforms applied in OS, along with their physicochemical properties and representative applications. The structural features of representative nanocarrier platforms used in osteosarcoma therapy, including lipid nanoparticles, polymeric nanoparticles, carbon-based nanomaterials, exosomes, gold nanoparticles, and hydrogels, are illustrated in Figure 2.

Lipid Nanoparticles (LNs)

Lipid-based nanocarriers, including liposomes and solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), are among the most extensively studied platforms for OS therapy. Their biocompatibility, ability to encapsulate both hydrophilic and hydrophobic drugs, and potential for surface functionalization make them highly versatile.[28]

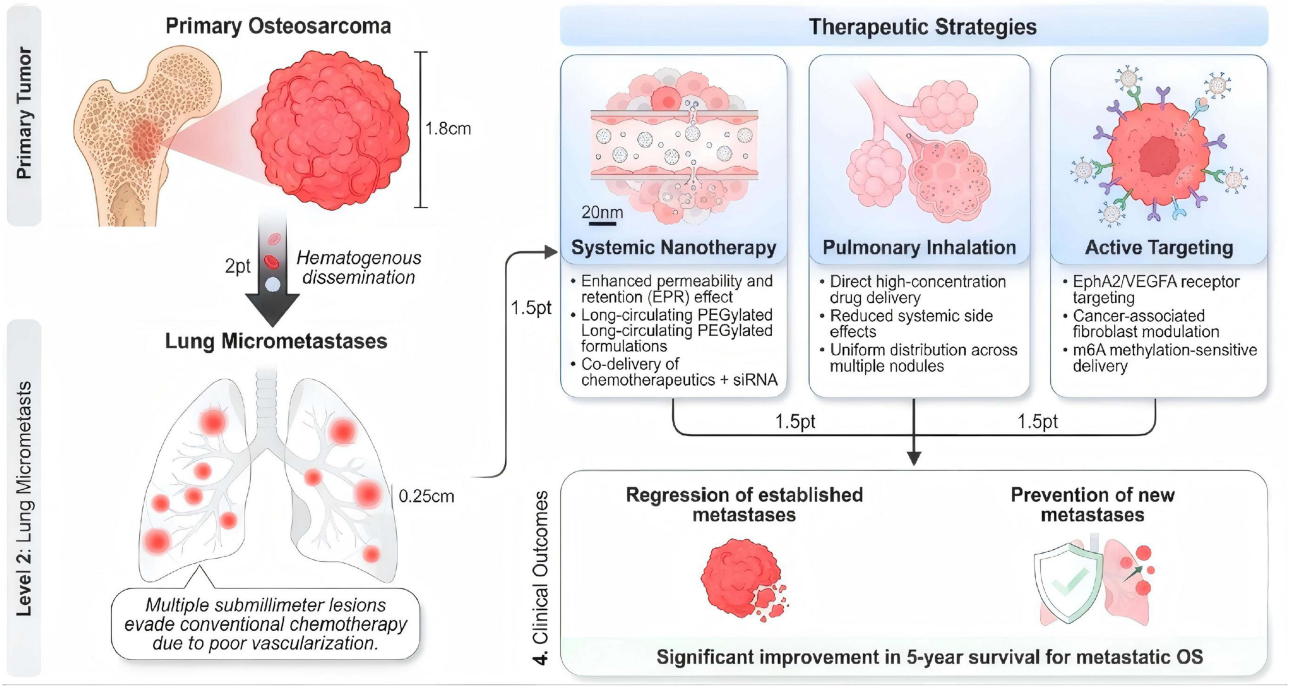

Figure 1 Schematic illustration of the major challenges in osteosarcoma lung metastasis and corresponding strategies enabled by nano-drug delivery systems.
Abbreviation: pt, patient(s).

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Table 1 Summary of Nanocarrier Platforms for Osteosarcoma Therapy, Including Their Physicochemical Properties, Advantages, and Representative Applications

Nanocarrier Type	Key Physicochemical Properties	Advantages	Representative Applications in OS
Lipid Nanoparticles (LNs)	Solid lipid matrix, biocompatible, biodegradable	High drug loading for lipophilic drugs, prolonged circulation, lymphatic uptake	EphA2-targeted liposomes co-delivering DOX and JIP1 siRNA;[28] mifamurtide (Mepact) for OS;[29] MTX-CuB-NLC for overcoming drug resistance[30]
Polymeric Nanoparticles	Natural/synthetic polymers, amphiphilic, modifiable surface	Controlled release, EPR-mediated passive targeting, co-delivery capability	PLGA nanoparticles co-loaded with paclitaxel and etoposide;[31] PLGA-LDH-MTX nanoparticles;[32] fungal-derived chitosan nanoparticles[33]
Carbon Nanomaterials	High surface area, π-π stacking, optical/thermal properties	High drug loading, stimuli-responsive release, theranostic potential	GO-PEI-miR-214 inhibitor for PTEN targeting;[34] self-oxygen-generating soft nanomotors for PDT[35]
Extracellular Vesicles (EVs)	Endogenous origin, biocompatible, low immunogenicity	Natural targeting, intercellular communication, tumor-homing properties	MSC-derived EVs delivering miR-101 to inhibit lung metastasis;[36] tumor-derived exosomes as therapeutic targets[37]
Gold Nanoparticles (AuNPs)	Inert, highly stable, tunable surface chemistry	Non-toxic, EPR-mediated accumulation, easy surface functionalization	Peptide-modified AuNPs for enhanced cellular uptake;[38] glutathione-stabilized AuNPs with anti-metastatic properties[39]
Hydrogels	3D crosslinked polymer networks, water-swollen	Localized delivery, bone regeneration, stimuli-responsive release	Thermosensitive hydrogel for sequential CA4 and DTX release;[40] ALN/oxaliplatin co-loaded thermogel;[41] hydrogel for sonodynamic therapy[42]
Biomimetic Nanoparticles	Cell membrane-coated, surfaceome-mimicking	Homotypic targeting, immune evasion, enhanced cellular uptake	OS cell membrane-coated PLGA nanoparticles for targeted gene therapy;[43] iRGD-modified biomimetic NPs targeting MCAM m6A[44]
Stimuli-Responsive Systems	pH/enzyme/redox-responsive moieties	Controlled release, reduced off-target effects	pH-responsive multi-component NPs for chemo-immunotherapy[45]

González-Fernández et al demonstrated that edelfosine-loaded lipid nanoparticles synergistically enhanced anti-tumor activity against multidrug-resistant OS cells and significantly reduced lung metastasis in preclinical models.[46] Haghiralsadat et al developed EphA2-targeted PEGylated cationic liposomes co-delivering doxorubicin and JIP1 siRNA, which restored chemosensitivity and reduced systemic toxicity.[28] Notably, the liposomal immunomodulator mifamurtide (Mepact) received marketing authorization for OS in 2009 and remains the only nanomedicine approved specifically for OS.[29]

Recent advances in lipid-based nanocarriers include the development of MTX-CuB-NLC (methotrexate-cucurbitacin B nanostructured lipid carriers), which demonstrated enhanced cytotoxicity against methotrexate-resistant U-2 OS cells and superior tumor targeting in vivo.[30] This formulation achieved particle sizes of approximately 44 nm with sustained release capabilities, representing a promising strategy to combat drug resistance in OS.

Polymers

Polymeric nanoparticles offer controlled release, high stability, and the ability to co-deliver multiple agents. Polylactic-co-glycolic acid (PLGA), polyethylene glycol (PEG), and Pluronic-based systems have been widely used.[31]

Wang et al developed PLGA nanoparticles co-encapsulating paclitaxel and etoposide, which exhibited controlled release and enhanced apoptosis in MG63 and Saos-2 OS cells.[31] Ray et al encapsulated methotrexate in PLGA-coated layered double hydroxide nanoparticles, achieving sustained release and reduced systemic toxicity.[32] Meshkini et al constructed a pH-responsive Pluronic F127-ZnHAP system loaded with methotrexate, which triggered lysosomal drug release and overcame chemoresistance.[47]

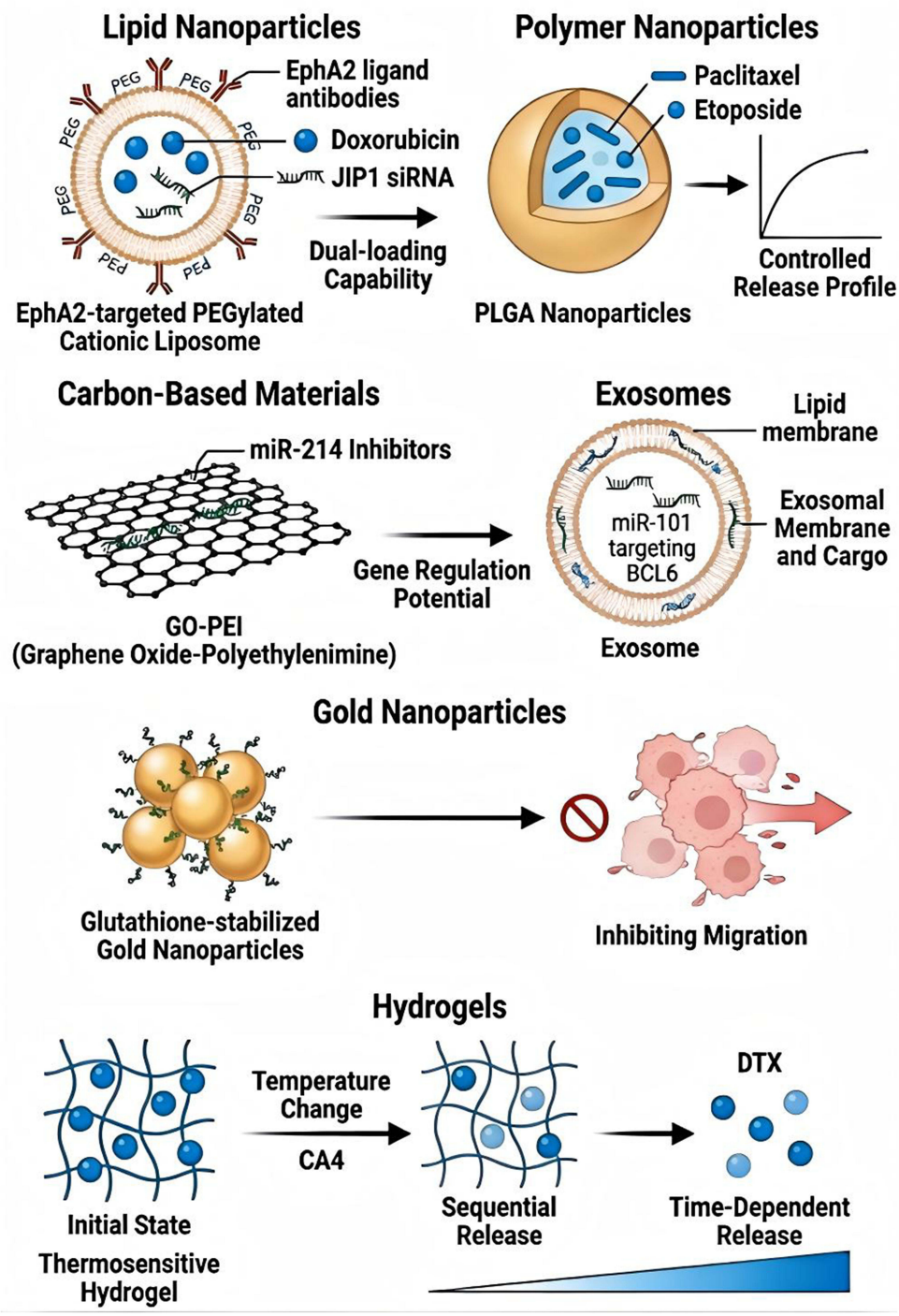

Figure 2 Schematic representation of the structural features of major nanocarrier platforms applied in osteosarcoma therapy, including lipid nanoparticles, polymeric nanoparticles, carbon nanomaterials, extracellular vesicles, gold nanoparticles, hydrogels, and biomimetic systems.

Polymeric nanocarriers have also been employed for nucleic acid delivery, including siRNA, miRNA, and CRISPR/Cas9 plasmids.[48] For example, Liang et al used aptamer-functionalized lipopolymers to deliver CRISPR/Cas9 targeting VEGFA, inhibiting OS growth and lung metastasis.[49]

Emerging sources of polymeric nanomaterials include fungal-derived chitosan nanoparticles fabricated from Aspergillus niger, which demonstrated multi-target molecular interactions with IL-6, BCL2, VEGF, and NF-κB in Saos-2 cells, inducing apoptosis through oxidative stress pathways.[33]

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Carbon Nanomaterials and Nanomotors

Graphene oxide (GO) and carbon nanotubes possess high surface areas and unique physicochemical properties suitable for drug loading and photothermal therapy. Ou et al developed GO-PEI nanosheets for delivery of miR-214 inhibitors, which suppressed OS progression via the PTEN/PI3K/Akt pathway.[34] Sun et al used nano-graphene oxide for co-delivery of doxorubicin and anti-VEGF siRNA, demonstrating enhanced anti-tumor efficacy.[50] Recent innovations in carbon-based nanocarriers include self-oxygen-generating soft nanomotors (SMONs-CAT-Ce6) that address the hypoxic tumor microenvironment. Tan et al demonstrated that catalase-powered soft nanomotors enhance photosensitizer penetration and accumulation in tumors while alleviating hypoxia, resulting in improved photodynamic therapy outcomes and reduced lung metastasis in 143B osteosarcoma-bearing mice.[35]

Extracellular Vesicles

Extracellular vesicles (EVs), including exosomes, are endogenous nanocarriers that mediate intercellular communication and exhibit natural tumor-homing properties. Zhang et al showed that EV-mediated delivery of miR-101 inhibited lung metastasis in OS by targeting BCL6.[36] Raimondi et al demonstrated that OS-derived EVs contain pro-osteoclastogenic miRNAs that modulate the tumor microenvironment.[51] Given their low immunogenicity and biocompatibility, EVs represent a promising platform for targeted OS therapy.[52]

Recent comprehensive reviews have highlighted the critical roles of tumor-derived exosomes in OS progression, immune evasion, and therapeutic resistance. Exosomes transport oncogenic proteins, immunosuppressive factors (TGF-β), miRNAs, and drug-resistance molecules, influencing key signaling cascades including Wnt/β-catenin and TGF-β pathways.[37] This has led to emerging strategies targeting exosome-mediated mechanisms for OS diagnostics and therapeutics.

Gold Nanoparticles (Gold NPs)

Gold nanoparticles (AuNPs) are inert, non-toxic, and can be functionalized with targeting ligands. Mandal et al demonstrated that AuNPs modified with cell-penetrating peptides exhibited enhanced uptake in OS cells compared to unmodified nanoparticles.[38] The unique optical properties of AuNPs also enable their use in photothermal therapy and imaging.[53]

Recent studies have revealed the anti-metastatic potential of glutathione-stabilized gold nanoparticles (Au-GSH NPs). Wilk et al demonstrated that Au-GSH NPs significantly inhibited migration and colony formation in canine osteosarcoma cells at concentrations of 200 μg/mL, while also suppressing angiogenesis in the chick embryo chorioallantoic membrane model.[39] Mechanistic studies revealed increased expression of alpha-2-macroglobulin (A2M) following Au-GSH NP treatment, suggesting a novel pathway for anti-metastatic activity.

Hydrogel

Hydrogel is a porous network polymer consisting of three-dimensional crosslinked polymers that swells in water, which not only serves as a drug carrier in tumor therapy but also mimics the cellular matrix and provides mesenchymal cells with a microenvironment for growth and differentiation, so in the case of OS, hydrogel not only treats tumors but also improves bone regeneration. Due to the complexity of tumorigenesis, it is often difficult to achieve the effect of single-drug treatment. Zheng et al[40] developed an injectable thermosensitive hydrogel system with co-encapsulation and sequential release of CA4 and DTX. CA4 is released first to rupture neovascularization while inhibiting the exchange of substances, and then DTX is released, which removes the cells on the surface of the tumor tissue and promotes apoptosis of cancer cells. Taking advantage of oxaliplatin (AXO), which is recognized as an anticancer drug that induces apoptosis, and alendronate (ALN), which has bone affinity as well as images of cancer cells destroying bone, Sun et al[41] co-loaded these two drugs onto mPEG45-PLV 19 thermosensitive hydrogel. It was found that this system not only inhibited the progression of OS but also prevented tumor lung metastasis.

Recent advances in hydrogel-based platforms include the development of localized delivery systems for sonodynamic therapy (SDT). Lin et al developed a hydrogel co-encapsulating the nano-sonosensitizer PCN-224@MnO2@HA (PMH) and the SMAD3 inhibitor SIS3. This system enhanced reactive oxygen species production through MnO2-mediated O2 generation and GSH depletion, while SIS3 reprogrammed cancer-associated fibroblasts to reduce collagen deposition by approximately 50%, achieving 76% tumor growth inhibition in OS mouse models.[42]

Biomimetic and Stimuli-Responsive Nanoparticles

Biomimetic approaches represent a frontier in nanomedicine development. Dash et al developed biomimetic nanoparticles by coating PLGA nanoparticles with membranes derived from osteosarcoma cells, creating cell membrane-coated nanoparticles (CMCNPs). These nanoparticles exhibited homotypic targeting to source cancer cells while evading macrophage detection and lysosomal degradation. Mechanistic studies identified Disabled Homolog-2 (Dab2) as a key mediator of CMCNP internalization, enabling efficient cytosolic delivery of survivin-targeting siRNA with significant tumor penetration and regression activity.[43]

Song et al developed iRGD-modified biomimetic nanoparticles for targeted delivery of METTL3-specific inhibitors to overcome doxorubicin resistance in OS. These nanoparticles targeted the METTL3-MCAM m6A modification axis, reducing MCAM m6A modification and decreasing proliferation and invasion of doxorubicin-resistant OS cells. In vivo studies demonstrated significant inhibition of tumor growth and lung metastasis.[44]

Stimuli-responsive systems offer controlled release at target sites. Li et al developed a pH-responsive multi-component nanoparticle system co-delivering doxorubicin, monophosphoryl lipid A (MPLA), and a PD-1/PD-L1-targeting peptide. The optimized nanoparticles (110 nm size, 97.15% encapsulation efficiency) exhibited pH-sensitive drug release and enhanced immunogenic cell death markers. In orthotopic LM8 osteosarcoma models, the nanoparticles significantly suppressed tumor growth, promoted cytotoxic T lymphocyte infiltration, and established long-term immune memory.[45]

Discussion

The application of nano-drug delivery systems in osteosarcoma has advanced significantly over the past decade, driven by the need to overcome the limitations of conventional chemotherapy. Nanocarriers offer multiple advantages, including enhanced tumor accumulation via the EPR effect, active targeting through ligand functionalization, co-delivery of synergistic agents, and the ability to modulate the tumor microenvironment.[12,27] As depicted in Figure 3, the therapeutic mechanisms of nano-drug delivery systems in osteosarcoma primarily involve passive targeting via the EPR effect, active targeting through ligand–receptor interactions (eg, EphA2, VEGFA, uPAR), stimuli-responsive release triggered by tumor microenvironment cues (pH, enzymes, redox), and modulation of the tumor immune microenvironment.

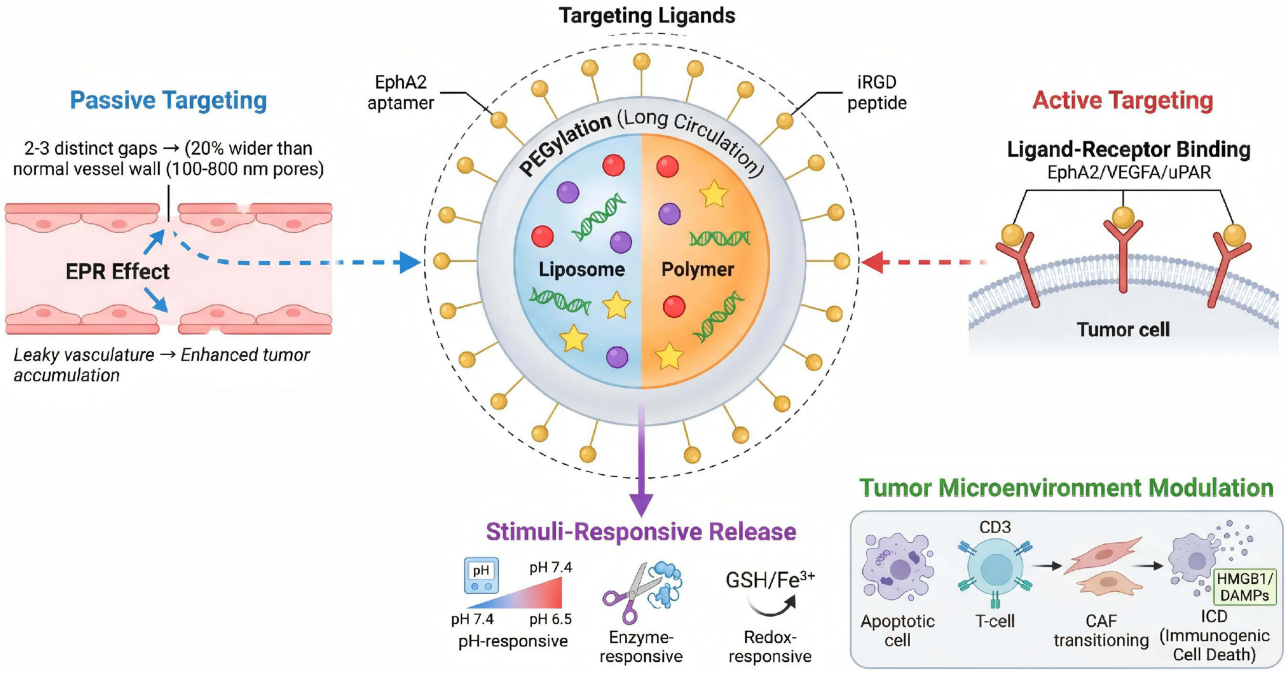

Figure 3 Key mechanisms of nano-drug delivery systems in osteosarcoma therapy, including passive targeting (EPR effect), active targeting (ligand–receptor interactions), stimuli-responsive release (eg, pH, enzyme, redox), and tumor microenvironment modulation.

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Despite these promising preclinical advances, clinical translation of nanomedicines for OS remains limited. Several key challenges must be addressed:

First, the EPR effect—which underpins passive targeting—is highly variable in human tumors and may be insufficient for achieving therapeutic concentrations in metastatic lesions.[54] Second, manufacturing complexities and batch-to-batch variability pose significant regulatory and economic hurdles.[10] Third, the pediatric population presents unique considerations, including differences in organ maturation, drug metabolism, and the potential for long-term toxicity affecting growth and development.[10] Currently, pediatric cancer patients are often treated with nanomedicines developed for adults without dedicated pediatric trials, highlighting a critical gap in drug development.[10] Additionally, biosafety, ethical, and regulatory challenges remain to be addressed before widespread clinical application.[14]

To address these challenges, several future directions warrant exploration:

Active targeting strategies using ligands such as peptides, aptamers, or antibodies against OS-specific markers (eg, EphA2, VEGFA, uPAR) can enhance selectivity and reduce off-target effects.[28,49] Stimuli-responsive nanocarriers that release payloads in response to pH, enzymes, or redox gradients within the tumor microenvironment offer the potential for controlled delivery.[55]

Biomimetic approaches, including cell membrane-coated nanoparticles and engineered extracellular vesicles, leverage natural homing mechanisms to improve targeting and reduce immunogenicity.[52,56] These systems can also be designed to evade clearance by the reticuloendothelial system and enhance accumulation at metastatic sites. The integration of artificial intelligence and big data platforms may further accelerate the development of intelligent nanomedicine systems tailored to individual patient needs.[14]

For lung metastasis, inhalation-based delivery of nanomedicines represents an attractive strategy. Inhaled nanoparticles can achieve high local concentrations in the lungs while minimizing systemic exposure, potentially improving efficacy and reducing toxicity.[57] Preclinical studies and early-phase clinical trials of inhaled lipid cisplatin have shown feasibility in OS patients with pulmonary metastases, supporting further investigation.[58]

Conclusions

In conclusion, nano-drug delivery systems hold substantial promise for improving the treatment of osteosarcoma, particularly in the context of lung metastasis and chemoresistance. The continued development of intelligent, biomimetic, and stimuli-responsive nanocarriers, combined with advances in understanding OS biology and the tumor microenvironment, offers hope for more effective and durable treatments. Ongoing efforts to refine targeting strategies, develop multifunctional platforms, and advance pediatric-focused clinical trials will be essential to translate these innovations into meaningful improvements in patient outcomes.

Disclosure

Siyu Jia, Boya Gong and Haidan Chen contributed equally to this work and should be considered co-first authors. The authors report no conflicts of interest in this work.

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