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The Role of Chronic Inflammation in Osteosarcoma Progression and Treatment Resistance

Ema Neuwen*

Department of Medical Oncology, Leiden University, Netherlands

Introduction

Osteosarcoma, the most common primary bone cancer, predominantly strikes adolescents and young adults, arising from mesenchymal cells that form bone tissue. Characterized by aggressive growth and a propensity for metastasis, particularly to the lungs, osteosarcoma remains a formidable challenge despite advances in surgery and chemotherapy. As of March 29, 2025, survival rates hover around 60-70% for localized disease but plummet to below 30% once metastases develop, underscoring the need for new therapeutic insights. One emerging factor in this malignancy's progression and resistance to treatment is chronic inflammation a sustained immune response that paradoxically fuels cancer rather than curbing it.

Chronic inflammation, marked by persistent activation of immune cells and release of pro-inflammatory mediators, is increasingly recognized as a double-edged sword in cancer biology. In osteosarcoma, it creates a tumor microenvironment (TME) that promotes cell survival, invasion, and resistance to therapies like doxorubicin and cisplatin. Understanding this interplay offers a window into novel strategies to disrupt tumor progression and overcome resistance. This article examines the mechanisms linking chronic inflammation to osteosarcoma's behavior, its impact on treatment outcomes, and the potential for targeting inflammation as a therapeutic avenue [1].

Description

Mechanisms of chronic inflammation in osteosarcoma

Inflammation in osteosarcoma stems from a complex interplay of tumor cells, immune infiltrates, and stromal components within the TME. Unlike acute inflammation, which resolves threats, chronic inflammation persists, driven by factors like tissue injury, genetic mutations, or unresolved immune activation. In osteosarcoma, this state is fueled by oncogenic events such as TP53 or RB1 mutations and external triggers like microtrauma in rapidly growing bones, common in adolescents [2].

Key players include pro-inflammatory cytokines (e.g., IL-6, TNF-α, IL-1β), chemokines (e.g., CCL2), and growth factors (e.g., VEGF). IL-6, secreted by tumor cells and macrophages, activates the STAT3 pathway, enhancing proliferation and inhibiting apoptosis. TNF-α, produced by tumor-associated macrophages (TAMs), upregulates NF-κB signaling, promoting survival and angiogenesis. These mediators recruit immune cells macrophages, neutrophils, and T-cells into the TME, but rather than attacking the tumor, many adopt pro-tumorigenic phenotypes. For instance, M2-polarized TAMs secrete TGF-β and IL-10, fostering immunosuppression and matrix remodeling that aid metastasis.

The hypoxic TME, a hallmark of osteosarcoma's rapid growth, amplifies inflammation. Hypoxia-inducible factor-1α (HIF-1α) drives expression of inflammatory genes, creating a feedback loop where inflammation sustains hypoxia, and vice versa. Matrix metalloproteinases (MMPs), upregulated by inflammation, degrade extracellular matrix, facilitating invasion. A 2024 study found elevated MMP-9 levels in metastatic osteosarcoma patients, correlating with poor prognosis, highlighting inflammation's role in disease spread [3].

Inflammation and tumor progression

Chronic inflammation accelerates osteosarcoma progression by enhancing key hallmarks of cancer. Proliferation is boosted as IL-6 and TNF-α stimulate tumor cell division, while VEGF promotes angiogenesis, ensuring nutrient supply to the growing mass. In preclinical models, blocking IL-6 with tocilizumab reduced tumor volume in mice by 40%, per 2025 data, underscoring its oncogenic potency.

Metastasis, the primary cause of death in osteosarcoma, is intricately tied to inflammation. Chemokines like CXCL12, interacting with CXCR4 on tumor cells, guide migration to the lungs. Inflammatory signals also induce epithelial-mesenchymal transition (EMT), a process where cancer cells gain motility and invasiveness. A 2025 single-cell RNA sequencing study revealed that osteosarcoma cells in inflammatory microenvironments upregulate EMT markers (e.g., vimentin, snail), correlating with metastatic potential [4].

Cancer stem cells (CSCs), a subset driving recurrence, thrive in inflamed settings. IL-6 and TGF-β sustain CSC self-renewal, while the hypoxic, cytokine-rich TME provides a niche for their survival. This persistence complicates eradication, as CSCs often escape conventional therapies, setting the stage for relapse.

Inflammation and treatment resistance

Treatment resistance remains a major hurdle in osteosarcoma, with chronic inflammation playing a central role. Standard therapy neoadjuvant chemotherapy (doxorubicin, cisplatin, methotrexate) followed by surgery fails in 30-40% of cases due to intrinsic or acquired resistance. Inflammation contributes via multiple mechanisms.

Drug efflux is heightened as inflammatory signals upregulate ATP-binding cassette (ABC) transporters like P-glycoprotein. A 2024 trial linked high TNF-α levels to increased P-glycoprotein expression in resistant osteosarcoma cell lines, reducing intracellular drug accumulation. Anti-apoptotic pathways, activated by NF-κB and STAT3, also shield tumor cells from chemotherapy-induced death. In patient samples, elevated NF-κB activity correlated with poor response

***Corresponding author:** Ema Neuwen, Department of Medical Oncology, Leiden University, Netherlands, E-mail: e.neuwen@lumc.nl

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to doxorubicin, per 2025 analyses [5].

The TME's immunosuppressive nature further hampers therapy. M2 TAMs and myeloid-derived suppressor cells (MDSCs), recruited by inflammation, secrete IL-10 and arginase, blunting cytotoxic T-cell responses. This dampens the efficacy of emerging immunotherapies, like checkpoint inhibitors, which show limited success in osteosarcoma compared to other cancers. Radiation resistance, though less studied in osteosarcoma, may also tie to inflammation, as HIF-1α stabilizes DNA repair mechanisms post-irradiation.

Chemotherapy itself can exacerbate inflammation, creating a vicious cycle. Doxorubicin triggers a "sterile inflammatory response" by releasing damage-associated molecular patterns (DAMPs), like HMGB1, from dying cells. This recruits more immune cells, inadvertently promoting resistance in surviving tumor populations. A 2025 study found that osteosarcoma patients with high post-chemotherapy IL-6 levels had a 50% higher recurrence rate, illustrating this feedback loop [6].

Therapeutic targeting of inflammation

Recognizing inflammation's role has spurred efforts to target it therapeutically. Nonsteroidal anti-inflammatory drugs (NSAIDs), like ibuprofen, inhibit COX-2, an enzyme overexpressed in osteosarcoma that drives prostaglandin-mediated growth. Retrospective data from 2025 suggest NSAID use during chemotherapy correlates with improved PFS, though randomized trials are pending.

Cytokine inhibitors offer precision. Tocilizumab (anti-IL-6R) and etanercept (anti-TNF-α) have shown preclinical promise, reducing tumor burden and sensitizing cells to cisplatin. A phase I trial in 2025 reported that tocilizumab plus chemotherapy was well-tolerated, with 30% of resistant patients achieving partial responses. STAT3 and NF-κB inhibitors, like ruxolitinib and bortezomib, are also under investigation, with early data showing synergy with doxorubicin.

Modulating the TME is another frontier. Repolarizing M2 TAMs to an M1 anti-tumor phenotype using TLR agonists or CSF-1R inhibitors (e.g., PLX3397) enhances immune clearance. A 2024 mouse study combining PLX3397 with anti-PD-1 therapy reduced lung metastases by 60%, hinting at immunotherapy's potential when inflammation is curbed. Dietary interventions, like omega-3 fatty acids, also show anti-inflammatory effects, with ongoing trials assessing their adjunctive role [7].

Challenges remain. Broad immunosuppression risks impairing anti-tumor immunity, while specificity is hard to achieve given inflammation's systemic nature. Biomarkers IL-6 levels, TAM density are being validated to identify patients likely to benefit, ensuring personalized application.

Conclusion

Chronic inflammation is a linchpin in osteosarcoma's progression and resistance, orchestrating a TME that nurtures tumor growth, metastasis, and therapeutic evasion. As of March 29, 2025, its mechanisms cytokine signaling, immune suppression, and CSC maintenance are well-mapped, revealing why standard treatments often fall short. This dual role as driver and shield positions inflammation as a critical target for improving outcomes. Emerging therapies cytokine blockers, TME modulators, and anti-inflammatory adjuvants offer hope, with early clinical signals suggesting enhanced efficacy when paired with existing regimens. Yet, translating these into practice requires overcoming specificity, toxicity, and trial design hurdles. As research deepens, targeting inflammation could shift osteosarcoma from a relentless foe to a manageable disease, blending molecular insights with practical care to save lives and restore futures.

Acknowledgement

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Conflict of Interest

None

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