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Beyond osteogenesis and angiogenesis: The immunomodulatory role of macrophages in hAMSC-sEV-mediated repair of osteoradionecrosis of the jaw

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Abstract

Osteoradionecrosis of the jaw (ORNJ) is a severe late complication of radiotherapy driven by vascular injury, hypoxia, fibrosis, persistent inflammation, and impaired bone remodeling. A recent study demonstrated that human amniotic mesenchymal stem cell-derived small extracellular vesicles (hAMSC-sEVs) improve ORNJ repair by restoring osteogenic differentiation of irradiated bone marrow mesenchymal stem cells through PI3K/AKT signaling and enhancing endothelial angiogenic activity through Wnt/β-catenin signaling. These findings establish an important regenerative framework but leave the immune compartment largely unexplored. We propose that macrophages represent a critical mechanistic link between hAMSC-sEV therapy and coordinated tissue repair. By reprogramming radiation-dysregulated macrophages toward pro-resolving, reparative phenotypes, hAMSC-sEVs may suppress chronic inflammation while simultaneously supporting osteogenesis and neovascularization. Defining the extracellular-vesicle cargo and macrophage signaling networks responsible for this effect could advance osteoimmunology-informed strategies and improve the translational development of cell-free therapies for ORNJ. This perspective highlights priorities for experimental validation and future clinical translation.

Highlights

What is current knowledge?

hAMSC-derived small extracellular vesicles promote osteogenesis and angiogenesis through PI3K/AKT and Wnt/β-catenin signaling, respectively.

What is new here?

- Macrophages are proposed as a key mechanistic link between inflammation resolution, osteogenesis, and angiogenesis in osteoradionecrosis repair.
- hAMSC-sEVs may reprogram radiation-dysregulated macrophages toward pro-resolving and tissue-reparative functional states.
- This macrophage-centered model expands the current osteogenic and angiogenic framework and identifies priorities for experimental validation and clinical translation.

Introduction

Osteoradionecrosis of the jaw (ORNJ) remains one of the most challenging late complications of radiotherapy for head and neck malignancies. Head and neck cancers impose a substantial global burden, with approximately 0.91 million new cases and 0.50 million deaths estimated worldwide in 2021 (1). Establishing a single global incidence of ORNJ is difficult because of variations in diagnostic criteria, radiotherapy techniques, follow-up, and dental risk factors; however, a recent meta-analysis reported an incidence of 8% (95% confidence interval, 6%-11%) among patients with oral cavity cancer treated with intensity-modulated radiotherapy (2).

Despite advances in radiation delivery and supportive care, ORNJ continues to cause substantial morbidity, including chronic pain, exposed necrotic bone, recurrent infection, soft-tissue breakdown, fistula formation, and, in advanced cases, pathological fracture (3-5). Its pathogenesis cannot be attributed to a single cellular defect. Instead, radiation creates a persistently hostile tissue microenvironment characterized by vascular rarefaction, hypoxia, oxidative stress, fibrosis, dysregulated immune responses, impaired cellular regeneration, and defective bone remodeling (6).

In this context, the recent study by Zhou et al. (7) provides important mechanistic evidence supporting the therapeutic potential of human amniotic mesenchymal stem cell-derived small extracellular vesicles (hAMSC-sEVs). Using an experimental rat model of ORNJ, together with irradiated bone marrow mesenchymal stem cells (BMSCs) and human umbilical vein endothelial cells (HUVECs), the authors demonstrated that the local administration of hAMSC-sEVs improved post-extraction socket healing and promoted new bone formation and vascularization. Mechanistically, hAMSC-sEVs partially restored radiation-impaired osteogenic differentiation by activating PI3K/AKT signaling in BMSCs and enhanced angiogenesis by activating Wnt/β-catenin signaling in endothelial cells (7).

These findings considerably advance our understanding of the regenerative effects of hAMSC-sEVs. However, they also raise an important question: can successful repair of the irradiated jaw be fully explained by direct effects on the osteogenic and endothelial compartments? We propose that the answer is likely no. The immune microenvironment-and macrophages in particular-may represent a third, interconnected component of hAMSC-sEV-mediated tissue repair. From an osteoimmunological perspective, effective regeneration requires not only the restoration of osteoblast differentiation and vascular function but also the resolution of persistent inflammation and the reconstruction of a microenvironment conducive to tissue repair.

Macrophages as a missing mechanistic link in ORNJ repair

Macrophages occupy a central position at the intersection of inflammation, vascular remodeling, fibrosis, and bone homeostasis. Their functional phenotypes are highly plastic and are shaped by local cytokines, metabolic signals, oxygen availability, extracellular matrix composition, and tissue-derived danger signals (8,9). Although macrophage activation is frequently described using the simplified M1/M2 paradigm, macrophages in vivo exist along a dynamic spectrum of activation states rather than as two discrete populations (8). Nevertheless, the conceptual distinction between predominantly pro-inflammatory and predominantly pro-resolving or reparative phenotypes remains useful for understanding tissue regeneration.

In healthy bone repair, an early inflammatory phase is required to remove damaged tissue and initiate regenerative signaling. This inflammatory response must subsequently transition toward a resolution phase that permits angiogenesis, extracellular matrix remodeling, progenitor-cell differentiation, and new bone formation (9). Failure of this transition can result in persistent inflammation and defective regeneration.

ORNJ is particularly relevant to this concept. Radiation-induced cellular damage generates oxidative stress and tissue injury while simultaneously compromising the vascular supply and regenerative cell populations (6,10-12). Under such conditions, macrophages may remain exposed to persistent damage-associated signals, hypoxia, necrotic tissue, microbial products, and an abnormal extracellular matrix. This environment could sustain maladaptive inflammatory activation and prevent the orderly transition from tissue injury to tissue restoration. Consequently, macrophages should not be considered merely secondary participants in ORNJ. They may act as critical regulators that determine whether the irradiated microenvironment remains chronically inflammatory or progresses toward regeneration.

hAMSC-sEVs: Beyond direct osteogenic and angiogenic effects

The therapeutic effects of mesenchymal stromal cells are increasingly attributed to their paracrine activity rather than to durable engraftment and differentiation. Small extracellular vesicles represent an important component of this paracrine communication system because they can transfer proteins, lipids, mRNAs, microRNAs, and other biologically active molecules between cells (13,14).

Extracellular vesicles are lipid-bilayer particles released by cells that cannot replicate independently. Compared with the administration of living MSCs, sEV therapy is cell-free and may reduce the risks associated with ectopic differentiation, microvascular entrapment, and immune rejection while facilitating storage and dose formulation. These benefits are balanced by important limitations: sEVs cannot dynamically respond to the recipient microenvironment, may exhibit rapid clearance or limited tissue retention, and display donor-, culture-, and isolation-dependent heterogeneity. Scalable production, potency testing, biodistribution, and batch-to-batch consistency also remain unresolved (15).

Human amniotic mesenchymal stem cells are particularly attractive for regenerative applications because of their proliferative capacity and immunomodulatory properties. Previous studies have demonstrated that hAMSCs can enhance bone regeneration, osteogenic differentiation, and angiogenesis under various pathological conditions (16-21). Importantly, hAMSC-mediated bone regeneration has also been associated with modulation of the local immune response and the promotion of macrophage phenotypes favorable to tissue repair (16).

The study by Zhou et al. (7) elegantly demonstrated the uptake of hAMSC-sEVs by irradiated BMSCs and endothelial cells. However, macrophage uptake and functional responses were not directly investigated. This represents an important opportunity for further study. Macrophages are highly phagocytic and are therefore biologically well positioned to internalize extracellular vesicles. EV-derived cargo can subsequently modify transcriptional, metabolic, and signaling programs within recipient macrophages. Studies using MSC-derived extracellular vesicles from other sources have demonstrated that the EV-mediated transfer of regulatory molecules can alter macrophage inflammatory responses and promote the resolution of inflammation (22). It is therefore plausible that hAMSC-sEVs administered to irradiated jaw tissue interact simultaneously with stromal, endothelial, and immune cell populations. Under this proposed model, the effects observed by Zhou et al. would represent two components of a broader multicellular regenerative network rather than two isolated signaling events (7).

Connecting macrophage reprogramming with osteogenesis

The PI3K/AKT pathway, identified by Zhou et al. (7) as an important mediator of hAMSC-sEV-induced osteogenic recovery, provides a potential point of convergence between immune regulation and bone regeneration.

Here, macrophage reprogramming denotes a stimulus-driven, potentially reversible change in macrophage transcriptional, metabolic, and secretory programs that shifts cells away from radiation-sustained inflammatory activity and toward functions that resolve inflammation and support repair. It does not imply conversion to a fixed M2 subtype; rather, it reflects movement along a context-dependent activation spectrum. In ORNJ, such reprogramming could reduce the inflammatory inhibition of osteoblast differentiation and help restore coupling among bone formation, resorption, and vascular repair (8,9).

Radiation substantially impairs the viability and differentiation potential of BMSCs (10) and can damage the bone marrow microenvironment required to maintain functional progenitor cells (11). Zhou et al. demonstrated that hAMSC-sEV treatment increased phosphorylated AKT levels in irradiated BMSCs and restored the expression of osteogenesis-associated proteins, including collagen-1, alkaline phosphatase, RUNX2, and osteopontin (7). Inhibition of PI3K/AKT signaling attenuated these effects, supporting a mechanistic role for this pathway.

However, osteogenic cells do not function independently of immune-derived signals. The persistent production of inflammatory mediators can inhibit osteoblast differentiation, alter osteoclast activity, and disrupt coupling between bone formation and resorption. Conversely, pro-resolving macrophage populations can create a local environment more favorable to progenitor-cell survival, matrix formation, and tissue remodeling (9). Therefore, hAMSC-sEV-induced osteogenesis may occur through at least two complementary mechanisms. The first involves the direct activation of regenerative signaling within radiation-damaged BMSCs, as experimentally demonstrated by Zhou et al. (7). The second, which remains to be experimentally established in ORNJ, may involve the indirect improvement of the osteogenic niche through macrophage reprogramming and the resolution of inflammation.

This distinction is important. Restoring PI3K/AKT signaling within BMSCs may be insufficient if the surrounding tissue remains dominated by persistent inflammatory and oxidative signals. Re-establishing an immunologically permissive microenvironment could therefore amplify or sustain the direct osteogenic effects of hAMSC-sEVs.

Linking macrophage function with angiogenesis

Vascular injury is another defining feature of ORNJ. Histopathological analyses of irradiated mandibular bone have demonstrated substantial alterations in bone vascularity (12). Radiation can simultaneously damage mature endothelial cells and compromise the microenvironment required for vascular regeneration.

Zhou et al. (7) showed that hAMSC-sEVs restored several radiation-impaired endothelial functions. Treatment enhanced HUVEC proliferation, migration, and tube formation and increased the expression of angiogenesis-associated molecules, including VEGF. Their experiments further implicated Wnt/β-catenin signaling in this response, as pharmacological inhibition attenuated the pro-angiogenic effects of hAMSC-sEVs. The involvement of Wnt/β-catenin signaling is consistent with previous evidence that MSC-derived extracellular vesicles can stimulate endothelial angiogenesis through Wnt-related pathways (23).

Yet angiogenesis is also strongly influenced by immune cells. Reparative macrophages can support vascular regeneration by secreting angiogenic and tissue-remodeling mediators, whereas sustained inflammatory activation can exacerbate endothelial dysfunction and perpetuate tissue injury. A macrophage-centered interpretation therefore adds another dimension to the findings of Zhou et al. (7) Rather than functioning solely as independent targets of hAMSC-sEVs, endothelial cells and macrophages may engage in reciprocal signaling. hAMSC-sEV-mediated macrophage reprogramming could improve the angiogenic microenvironment, while restored vascularization could reduce hypoxia and thereby further influence macrophage activation.

Such reciprocal communication could establish a positive regenerative loop in which hAMSC-sEV delivery promotes the resolution of inflammation, thereby improving endothelial function and neovascularization. Enhanced vascularization may subsequently alleviate tissue hypoxia, support stromal-cell function, and ultimately facilitate osteogenesis and tissue repair. This integrated model may more accurately reflect the complex biology of ORNJ than approaches that consider individual cellular pathways in isolation.

From macrophage polarization to macrophage re-education

Macrophage re-education refers to the therapeutic redirection of maladaptive macrophage states toward context-appropriate functions that resolve inflammation and support tissue repair. Unlike a binary M1/M2 switch, the term emphasizes macrophage plasticity, functional recovery, and the potential existence of multiple intermediate states (8).

Future investigations should move beyond the simple measurement of conventional M1 and M2 markers. Although this classification remains experimentally convenient, macrophage states within irradiated tissues are likely to be heterogeneous and temporally dynamic (8). The more relevant question is whether hAMSC-sEVs can re-educate dysfunctional macrophages toward phenotypes that actively promote the resolution of inflammation and regeneration.

This possibility could be investigated by examining inflammatory and reparative macrophage programs at multiple time points following irradiation and hAMSC-sEV treatment. Candidate readouts could include inflammatory mediators such as TNF-α, IL-1β, IL-6, inducible nitric oxide synthase, and reactive oxygen species, alongside pro-resolving or reparative mediators such as IL-10, TGF-β, arginase-1, VEGF, and other tissue-remodeling factors.

More importantly, these phenotypic measurements should be integrated with functional assays. Macrophages exposed to hAMSC-sEVs could be co-cultured with irradiated BMSCs or endothelial cells to determine whether macrophage-derived signals enhance osteogenic differentiation or angiogenesis. Conditioned-medium experiments and transwell systems could distinguish effects mediated by soluble factors from those mediated by direct cell-cell interactions. Such approaches would provide direct evidence for or against the macrophage–osteoblast–endothelial crosstalk proposed in Figure 1.

Identifying the active cargo of hAMSC-sEVs

A second major research priority is the identification of the molecular cargo responsible for macrophage regulation. Extracellular vesicles contain diverse bioactive molecules, and their biological effects depend strongly on the state and origin of the parent cells (13,14). Regulatory microRNAs are particularly compelling candidates because individual miRNAs can simultaneously influence multiple inflammatory and metabolic pathways. In other experimental settings, MSC-derived extracellular vesicles have already been shown to transfer regulatory miRNAs capable of modifying macrophage responses (22).

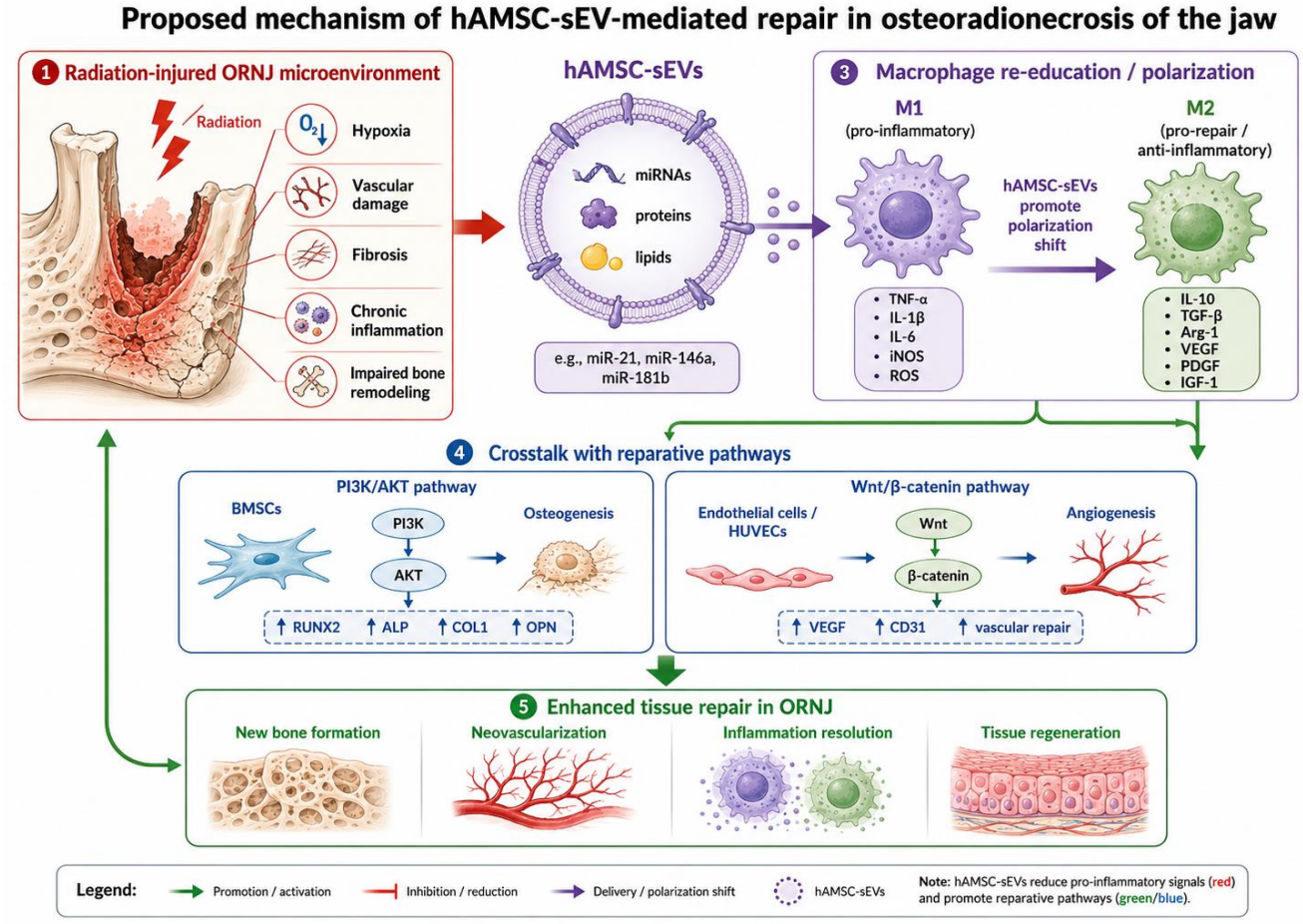

Figure 1. Proposed immunoregenerative mechanism of human amniotic mesenchymal stem cell-derived small extracellular vesicles (hAMSC-sEVs) in osteoradionecrosis of the jaw (ORNJ). Radiation injury establishes a hostile ORNJ microenvironment characterized by hypoxia, vascular damage, fibrosis, chronic inflammation, and impaired bone remodeling. hAMSC-sEVs carry biologically active cargo, including regulatory RNAs, proteins, and lipids, that may act on multiple cellular compartments. In addition to the experimentally demonstrated activation of PI3K/AKT signaling in irradiated bone marrow mesenchymal stem cells (BMSCs), promoting osteogenic recovery, and Wnt/β-catenin signaling in endothelial cells, promoting angiogenesis, we propose that hAMSC-sEVs may reprogram radiation-dysregulated macrophages from predominantly pro-inflammatory states toward pro-resolving and tissue-reparative phenotypes. Reduced inflammatory signaling and increased production of regenerative mediators may subsequently enhance osteogenesis, neovascularization, inflammation resolution, and tissue regeneration. The macrophage-mediated component represents a proposed mechanism that requires direct experimental validation in ORNJ models. Abbreviations: AKT, protein kinase B; ALP, alkaline phosphatase; Arg-1, arginase-1; BMSCs, bone marrow mesenchymal stem cells; CD31, cluster of differentiation 31; COL1, collagen type I; hAMSC-sEVs, human amniotic mesenchymal stem cell-derived small extracellular vesicles; HUVECs, human umbilical vein endothelial cells; IGF-1, insulin-like growth factor 1; IL, interleukin; iNOS, inducible nitric oxide synthase; M1, classically activated macrophage state; M2, alternatively activated macrophage state; miR/miRNA, microRNA; OPN, osteopontin; ORNJ, osteoradionecrosis of the jaw; PDGF, platelet-derived growth factor; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; RUNX2, runt-related transcription factor 2; TGF-beta, transforming growth factor beta; TNF-alpha, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor; Wnt, Wingless/Int-1 signaling protein.

Accordingly, comprehensive profiling of hAMSC-sEV cargo using small-RNA sequencing and proteomics could identify molecules preferentially associated with macrophage reprogramming. Candidate molecules should then be validated through gain- and loss-of-function experiments rather than through association alone. Similarly, the signaling pathways activated within macrophages require systematic investigation. NF-κB, STAT-family pathways, PI3K/AKT, MAPK signaling, and regulators of cellular metabolism represent plausible targets. Because macrophage phenotype is closely linked to metabolic state, the integration of transcriptomic data with metabolomic analyses may be particularly informative.

The ultimate objective should be to establish a clear mechanistic framework that identifies the specific hAMSC-sEV cargo responsible for modulating macrophage signaling, determines how these signals induce functional macrophage reprogramming, and clarifies how such immune changes subsequently influence osteogenic and angiogenic responses to improve ORNJ repair.

Translational considerations and future directions

The findings of Zhou et al. (7) provide a strong experimental rationale for the further development of hAMSC-sEV-based approaches, but several issues should be addressed before clinical translation.

First, the immune effects of hAMSC-sEVs should be demonstrated directly in validated ORNJ models. The spatial characterization of macrophage subsets within irradiated bone and the surrounding soft tissue would be particularly valuable. Multiparametric flow cytometry, immunofluorescence, spatial transcriptomics, or single-cell RNA sequencing could reveal whether hAMSC-sEV treatment alters macrophage abundance, localization, and functional state.

Second, temporal analysis is essential. Macrophage-driven inflammation is not intrinsically detrimental; an appropriately controlled early inflammatory response is required for tissue repair. Therapeutic strategies should therefore aim to restore normal inflammatory dynamics rather than indiscriminately suppress macrophage activity.

Third, EV manufacturing and characterization require standardization. Vesicle isolation, particle concentration, purity, cargo composition, storage conditions, administration route, and treatment frequency can all influence biological activity. Determining the optimal therapeutic dose is especially important because EV-mediated signaling may not exhibit a simple linear dose-response relationship. Because parent-cell culture conditions can alter vesicle yield and cargo, standardized culture methods and transparent reporting are essential for reliable and reproducible exosome isolation (24). Production and characterization should also follow the MISEV2023 recommendations for EV nomenclature, separation, characterization, and functional studies (25).

Finally, preclinical experiments should evaluate hAMSC-sEV therapy in combination with existing ORNJ management strategies. The greatest clinical utility may ultimately arise from integrating cell-free regenerative approaches with surgical debridement, vascularized tissue reconstruction, or other treatments according to the disease stage.

Conclusion

The work of Zhou et al. establishes a compelling mechanistic framework in which hAMSC-sEVs restore two fundamental components of ORNJ repair: osteogenesis through PI3K/AKT activation in BMSCs and angiogenesis through Wnt/β-catenin signaling in endothelial cells (7). However, the regeneration of irradiated tissue is unlikely to depend solely on these two cellular compartments.

Macrophages may constitute a crucial third component linking the resolution of inflammation with vascular and skeletal regeneration. We therefore propose an expanded model in which hAMSC-sEVs act as multicellular regulators of the ORNJ microenvironment by directly restoring osteogenic and endothelial function while potentially reprogramming radiation-dysregulated macrophages toward pro-resolving and tissue-reparative states.

Importantly, this macrophage-mediated mechanism remains a hypothesis that requires direct experimental validation in ORNJ. Establishing whether such immunomodulatory crosstalk occurs-and identifying the responsible EV cargo and signaling pathways-could move the field beyond a purely osteogenic and angiogenic interpretation toward a more integrated osteoimmunological model of radiation-injured bone repair. Such a shift may ultimately prove essential to realizing the full therapeutic potential of hAMSC-sEVs as a cell-free strategy for osteoradionecrosis.

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Author Contributions

S.M.: Conceptualization, Investigation (Literature Review), Visualization, Writing - Original draft, and Writing - Review and Editing. The author approved the final manuscript.

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Use of Artificial Intelligence

BioRender AI was used to assist in generating Figure 1, and ChatGPT was used for grammar and language checking. The author reviewed and verified all AI-assisted content and takes full responsibility for the final manuscript.

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