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Review Paper

Extracellular Vesicles in Bone Regeneration: Mechanisms, Innovations, and Clinical Prospective

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ABSTRACT

Background: Bone regeneration remains a major challenge in regenerative medicine because successful repair requires the coordinated regulation of osteogenesis, angiogenesis, and immune responses within complex defect microenvironments. Extracellular vesicles (EVs), including exosomes and microvesicles, have emerged as promising acellular therapeutic agents capable of reproducing many of the regenerative effects of stem and progenitor cells while reducing the risks associated with cell-based therapies.

Methods: This narrative review synthesizes current evidence on the biological functions, cellular sources, engineering strategies, and therapeutic applications of EVs in bone regeneration. Relevant studies published between 2015 and 2025 were reviewed, focusing on molecular mechanisms, bioengineering approaches, disease-specific applications, and translational challenges associated with EV-based therapies.

Results: EVs derived from diverse sources, including bone marrow, adipose tissue, dental pulp, muscle cells, and gut microbiota, were shown to promote bone regeneration through the delivery of bioactive proteins, lipids, nucleic acids, and metabolites. These vesicles regulate key regenerative pathways, including PI3K/AKT, BMP/Smad/RUNX2, Wnt/β-catenin, TGF-β1/Smad/MAPK, and microRNA-mediated signaling. EVs enhance osteogenesis, stimulate angiogenic–osteogenic coupling, modulate macrophage polarization toward a reparative M2 phenotype, and improve bone healing under aging, diabetic, and osteoporotic conditions. Advanced bioengineering strategies, such as scaffold functionalization, hydrogels, nanoparticle conjugation, and genetic engineering, further improve EV targeting, retention, and controlled release. Preclinical studies demonstrate substantial regenerative benefits across a range of musculoskeletal disorders.

Conclusion: EV-based therapies represent a promising and versatile platform for bone regeneration by integrating osteogenic, angiogenic, and immunomodulatory functions within a cell-free therapeutic framework. Although significant challenges remain, including standardization of EV isolation, scalable manufacturing, potency assessment, and clinical reproducibility, ongoing advances in bioengineering and precision medicine may accelerate the translation of EV-based therapeutics into clinical practice for musculoskeletal repair.

Keywords: Extracellular vesicles (EVs), Exosome, Bone regeneration, Mesenchymal stem cells (MSC), Tissue engineering, Regenerative medicine

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Highlights

● EVs represent a promising cell-free therapeutic alternative to stem cell-based approaches, reducing the risks of immune rejection and tumorigenicity in bone regeneration.

● The regenerative efficacy of EVs is largely attributed to their capacity to coordinate osteogenesis, angiogenesis, and immunomodulation through the regulation of key molecular signaling pathways.

● Advanced bioengineering platforms, including scaffolds and hydrogels, play a pivotal role in optimizing EV delivery, enhancing therapeutic efficacy, and facilitating clinical translation.

Plain Language Summary

Bone regeneration remains a significant clinical challenge, particularly in older adults and individuals affected by conditions such as diabetes, osteoporosis, and chronic inflammatory diseases. This review highlights the emerging potential of extracellular vesicles (EVs), nanoscale particles naturally released by cells that carry a diverse range of biological signals involved in tissue repair and regeneration. Unlike conventional cell-based therapies, EVs provide a cell-free therapeutic approach, potentially reducing concerns related to immune rejection, tumor formation, and the complexity of cell transplantation. Current evidence indicates that EVs can support bone healing through multiple complementary mechanisms. They promote the activity and differentiation of bone-forming cells, stimulate the formation of new blood vessels required for tissue repair, and regulate immune responses to create a more favorable healing environment. Importantly, the biological effects of EVs are strongly influenced by their cellular source. EVs derived from healthy or young cells often exhibit enhanced regenerative properties, whereas those originating from aged or diseased cells may have diminished or even adverse effects. To improve therapeutic performance, researchers are developing advanced delivery platforms, including biomaterial scaffolds, hydrogels, and nanoparticle-based systems. These technologies help retain EVs at the injury site, protect their bioactive cargo, and enable controlled release over time, thereby enhancing their regenerative potential. The clinical importance of this field lies in its potential to address bone injuries and defects that heal poorly and often result in chronic pain, disability, and reduced quality of life. Although significant challenges remain before widespread clinical adoption, EV-based therapies represent a promising frontier in regenerative medicine and may provide innovative treatment options for patients with complex and difficult-to-heal skeletal disorders.

Introduction

Bone regeneration represents one of the most challenging aspects of regenerative medicine, particularly in cases involving critical-size defects, aging-related bone loss, and pathological conditions such as diabetes mellitus and osteoporosis [1-3]. The intricate process of bone healing requires precise coordination of multiple cellular mechanisms, including osteogenesis, angiogenesis, and immunomodulation, all occurring within a complex microenvironmental milieu [4, 5]. Traditional therapeutic approaches, while having shown clinical success, often fall short in addressing the multifaceted nature of bone repair, necessitating the development of innovative strategies that can orchestrate these interconnected biological processes more effectively [6, 7].

The emergence of mesenchymal stem cell (MSC)-based therapies has revolutionized bone tissue engineering, offering promising avenues for enhancing bone regeneration [8, 9]. However, the clinical translation of MSC-based treatments has been hindered by several limitations, including immune rejection, tumorigenicity risks, and the substantial loss of transplanted cells due to apoptosis in the hostile microenvironment of damaged tissues [10-12]. These challenges have prompted researchers to explore alternative cell-free therapeutic approaches that can harness the regenerative potential of stem cells while circumventing the associated risks and limitations [13, 14]. This progression from cell-based to cell-free therapeutics is not merely a change in delivery mode but reflects a deeper paradigm shift—one that focuses on harnessing the complex signaling repertoire of cells without the logistical, immunological, and safety burdens of live-cell transplantation. In essence, EV-based strategies can be seen as a distilled form of stem cell therapy, preserving multifaceted regenerative signals while offering greater clinical feasibility.

In recent years, EVs have emerged as pivotal mediators of intercellular communication and tissue regeneration, representing a paradigm shift in regenerative medicine [15, 16]. These membrane-bound nanoparticles, ranging from 30 to 1000 nanometers in diameter, are secreted by virtually all cell types and carry diverse cargo, including proteins, lipids, nucleic acids, and metabolites [17, 18]. The therapeutic potential of EVs lies in their ability to recapitulate many of the beneficial effects of their parent cells while offering significant advantages in terms of safety, stability, and scalability for clinical applications [19, 20].

Extracellular vesicles (EVs) are membrane-bound particles released by cells and mainly include exosomes (30–150 nm), microvesicles (100–1000 nm), and apoptotic bodies (>1000 nm). These vesicles differ in size, content, and biogenesis mechanisms [21]. In many studies, the isolated EVs may represent a mixture of these subtypes, unless specific isolation and characterization methods are applied. In the referenced studies, most EVs were isolated by ultracentrifugation or precipitation methods without full characterization of subtypes. Therefore, the term EVs refers to a mixed population that may include exosomes, microvesicles, and apoptotic bodies. A major advantage of EV-based therapy is its potential to overcome challenges in aging-related bone regeneration. Aging disrupts bone homeostasis by reducing stem cell osteogenic capacity, impairing angiogenesis, and altering immune responses [8, 14]. Recent studies show that EVs from young or rejuvenated cells can reverse cellular senescence, restore osteogenesis, and enhance regeneration in aged bone environments [14, 22], offering a promising approach for age-related bone diseases in the growing elderly population [23, 24].

EVs from various sources, such as bone marrow MSC (BMMSCs), adipose-derived stem cells (ADSCs), dental pulp stem cells (DPSCs), and muscle cells exhibit strong therapeutic potential by promoting osteogenesis, enhancing angiogenesis, and modulating immune responses essential for bone healing [17, 25, 26]. The therapeutic efficacy of EVs can be further enhanced through various strategies, including hypoxic preconditioning, genetic engineering, or surface functionalization to optimize cargo and targeting [3, 27].

The interplay between angiogenesis and osteogenesis is vital for bone regeneration, with EVs demonstrating strong potential by supporting new blood vessel formation essential for bone healing; disruption of this coupling often leads to poor outcomes [3, 6]. EVs also exhibit key immunomodulatory effects, effectively shifting macrophages from pro-inflammatory M1 to anti-inflammatory M2 phenotypes, thus enhancing bone repair [28]. However, challenges remain for clinical translation, including the need for standardized EV isolation and characterization, optimal dosing, effective delivery systems, and reproducibility across patients.

This review summarizes current knowledge and recent advances in extracellular vesicle (EV)-based therapeutics for bone regeneration. We critically evaluate various cellular sources—including MSCs, bone cells, and emerging alternatives—highlighting their benefits and mechanisms. Key molecular pathways are discussed, focusing on microRNA regulation, protein transfer, and immunomodulation. The review also examines engineering strategies, such as surface modification, drug loading, and novel delivery systems to enhance EV efficacy and clinical translation. Therapeutic applications, including fracture repair, critical-size defects, aging-related bone loss, diabetes, and periodontal/osteoporotic damage are assessed. We present recommendations for future research, emphasizing precision medicine, advanced engineering, combination approaches, and digital integration to accelerate the clinical adoption of EV-based bone therapies. This framework aims to inform research directions and support translation into clinical practice, addressing critical gaps in musculoskeletal regenerative medicine.

Search Study

Because research on EV-based bone regeneration covers multiple disciplines, we designed a search strategy that was both broad and focused. The aim was not only to collect as many studies as possible, but also to choose those that are truly relevant for understanding both the mechanisms and the clinical potential of EVs. A comprehensive literature search was conducted across PubMed, Web of Science, Scopus, and Embase to identify studies on EV-based therapeutics for bone regeneration. The search strategy utilized a combination of relevant keywords and MeSH terms, including “extracellular vesicles,” “exosomes,” “small extracellular vesicles,” “EVs,” “microvesicles,” “mesenchymal stem cells,” “MSC,” “bone regeneration,” “bone repair,” “osteogenesis,” “angiogenesis,” “immune modulation,” “bone healing,” “fracture healing,” “osteoporosis,” “bone tissue engineering,” “biomaterials,” “hydrogel,” “EV-based therapy.” Only full-text English articles were saved, covering original lab studies, animal experiments, and clinical pilot trials, as well as high-quality review papers with mechanistic discussion. We excluded abstracts, opinion pieces, and papers that did not confirm the vesicles’ identity with standard methods. This process

improves reliability but might exclude some valuable research from non-English-speaking countries. To better organize the evidence, studies were grouped by both clinical problem (e.g. osteoporosis, diabetic bone loss, infection-related defects, aging-related decline, large defects) and research stage (cell-based lab work, animal models, human studies). This approach shows which areas are rich in mechanistic evidence and which still lack translation to the clinic. The scope of this review focused on studies published between 2015 and 2025, ensuring a comprehensive evaluation of the most recent and relevant advancements in the field. The temporal filter (2015–2025) was applied to reflect the surge of bioengineering-enabled EV research in the past decade, consciously excluding earlier, pre-standardization era studies whose isolation methods often lacked ISEV-compliant reporting. While this process increases the applicability of mechanistic and delivery platform advances to present-day translational design, it may underrepresent the historical evolution of the field and early conceptual hypotheses. Studies were stratified not only by clinical context—aging-related bone loss, osteoporosis, diabetic bone complications, infection-induced defects, large or complex injuries—but also by evidence maturity level (in vitro mechanistic, preclinical proof-of-concept, early-phase human).

Molecular Mechanisms and Signaling Pathways

EVs contribute to bone repair through multiple, interconnected molecular pathways (Table 1). The PI3K/AKT signaling cascade plays a central role in cell survival, angiogenesis, and proliferation, while the BMP-2/Smad1/RUNX2 axis is essential for osteogenic differentiation. Evidence from BMMSC-derived exosomes in rat femoral nonunion models confirms that activating BMP-2/Smad1/RUNX2 not only promotes osteogenesis and angiogenesis but also shortens the healing timeline—a parameter rarely reported but critical for clinical translation [29]. Similarly, DPSC-derived EVs drive osteogenic gene expression in jawbone marrow-derived MSCs with outcomes comparable to recombinant BMP-2 [4]. EVs from DPSCs also activate TGF-β1/Smad/MAPK pathways in HERS cells, suggesting that their effects extend beyond classical osteogenic routes [30]. Both BMMSC- and HUVEC-derived EVs enhance angiogenesis, endothelial proliferation, and migration through the PTEN/PI3K/AKT axis [31]. However, comparative potency data between these two EV sources are scarce, making it difficult to determine optimal cell origins for pro-angiogenic therapies.

The Wnt/β-catenin pathway is another critical driver of bone formation and remodeling. ADSC-derived exosomes promote fracture healing in diabetic models by activating Wnt3a/β-catenin and enhancing BMSC osteogenesis [32]. Since diabetes alters osteoblast signaling responsiveness, these findings support Wnt pathway targeting as a potentially condition-specific intervention. Inflammatory regulation is equally important: TNF-α-preconditioned MSC-EVs can reduce pro-inflammatory M1 markers and increase reparative M2 markers [28], aligning local immune profiles with tissue regeneration needs. Likewise, EVs from juvenile mouse serum activate the Pink1/Parkin pathway, improving mitochondrial function and rejuvenating aged bone microenvironments [9]. The JAK2/STAT3 pathway also appears relevant, contributing indirect neuroprotective effects that could benefit fracture healing via enhanced systemic recovery. A critical limitation is that most of these mechanistic insights are from rodent models under controlled conditions, where healing environments are more uniform than in human patients with comorbidities. Moreover, the field lacks head-to-head studies comparing the therapeutic weight of these mechanisms across different pathologies. For example, whether PI3K/AKT dominance in diabetic bone loss truly outweighs Wnt/β-catenin activation in osteoporotic repair. This gap complicates target prioritization. This means mechanistic studies should not be divorced from source-comparison analyses if the goal is to design condition-tailored EV therapies.

However, most of these insights are derived from rodent models under controlled laboratory conditions, which may not fully capture the complexity of human bone healing processes. Moreover, comparative studies directly evaluating the relative importance of these pathways in different pathological conditions (e.g. diabetes vs osteoporosis) are still lacking, limiting our ability to prioritize therapeutic targets. Future research should integrate multi-pathway analyses using standardized EV isolation and quantification methods to ensure data comparability. While the above pathways illustrate the molecular diversity of EV-mediated bone regeneration, their actual contribution to therapeutic outcomes is strongly influenced by the cellular origin of the EVs. For example, MSC-derived EVs may preferentially activate osteogenic cascades, whereas endothelial cell-derived EVs could be more potent in promoting angiogenesis. This underscores the need to evaluate EV sources in parallel with mechanistic studies, rather than in isolation. The diversity outlined above is distilled in Table 1.

Table 1. Key molecular mechanisms and signaling pathways in EV-mediated bone regeneration

Signaling Pathway	Key Molecules/miRNAs	Cellular Effects	Ref.
PTEN/PI3K/AKT	miR-210-3p, EFNA3, HIF-1α	Enhanced angiogenesis, cell survival	[3]
	miR-23a-3p, PTEN	Vascularized bone regeneration	[33]
	miR-29b-3p	Enhanced angiogenesis, fracture healing	[31]
BMP-2/Smad1/RUNX2	BMP-2, RUNX2, Smad1	Osteogenesis, bone formation	[29]
TGF-β1/Smad/MAPK	TGF-β1, Smad proteins	Osteogenic differentiation	[30]
Wnt/β-catenin	Wnt3a, β-catenin	Bone formation, diabetic bone healing	[32]
	β-catenin, COL2A1, SOX-9	Osteochondral defect repair	[34]
NF-κB/ERK1/2	Connexin 43 (Cx43)	Senescence induction, inflammation	[35]
NRON/NFATc1	lncRNA NRON, NFATc1	Osteoclast inhibition	[14]
Pink1/Parkin mitophagy	Tomm7, Pink1, Parkin	Mitochondrial function, anti-aging	[9]
NRF2 signaling	NRF2, Cordycepin	Cell rejuvenation, anti-senescence	[5]
JAK2/STAT3	miR-21, JAK2, STAT3	Neuroprotection, astrocyte conversion	[36]
FOXO4/CBL targeting	miR-328a-3p, miR-150-5p	Osteogenesis promotion	[37]
MIF/M1-M2 polarization	miR-451a, MIF	Immunomodulation	[26]
TNF-α/inflammatory	TNF-α, M1/M2 markers	Enhanced immunomodulation	[28]
IRAK1/TRAF6/NF-Kb	miR-146a, IRAK1, TRAF6	Anti-inflammatory, neural repair	[38]
BMP4 signaling	BMP4, M1/M2 macrophages	Tendon-bone healing	[39]
miR-331-3p/FGF23/DKK1	miR-331-3p, FGF23, DKK1	Osteoblast function enhancement	[40]
Adenosine receptor/AKT-ERK	Adenosine receptors, AKT, ERK1/2	Cell proliferation, migration	[41]
proliferating cell nuclear antigen (PCNA) transfer	PCNA protein	Anti-aging, cell rejuvenation	[7]
Myosin-10–targeted signaling	Nidogen-1 (NID1), Myosin-10	Migration, angiogenesis and vascularization	[42]
VEGF-mediated signaling	*VEGF* gene	Angiogenesis and vascularization	[43]
Nitric oxide synthase (NOS)–related signaling	Endothelial nitric oxide synthase (eNOS), VEGFa	Migration, angiogenesis and vascularization	[44]
Cytoskeleton stiffness–mediated signaling	Tropomyosin-1 (TPM1)	Osteogenesis and bone formation	[15]
NRON/NFATc1 signaling	lncRNA NRON, NFATc1	Osteogenesis and bone formation	[14]
Osteoinductive EV cargo–mediated signaling	ALP enzyme, calcium	Osteogenesis and bone formation	[8]

Sources and Types of EVs

MSC-derived EVs

MSC-derived EVs remain the most extensively studied for bone regeneration due to their consistent. Osteogenic, angiogenic, and immunomodulatory properties demonstrated across multiple preclinical models. These EVs originate from diverse MSC sources: bone marrow, adipose tissue, umbilical cord, dental pulp, synovium, and periodontal ligament. Each has distinct molecular cargo profiles that are shaped by their tissue microenvironment and culture conditions.

Comparative studies highlight that EVs from the same MSC type can vary significantly in potency depending on donor age, health status, or preconditioning method. However, the literature largely focuses on isolated single-source evaluations, limiting insights into which MSC source offers superior outcomes under specific pathological contexts (e.g. diabetic fracture vs osteoporotic defect). This knowledge gap has direct implications for clinical source selection and manufacturing optimization.

A detailed summary of representative MSC-derived EVs, application contexts, mechanisms, and principal outcomes is provided in Table 2, which should be interpreted not only as a repository of findings but also as an opportunity to detect patterns in source–mechanism–effect relationships that remain underexplored.

Non-MSC cellular sources

Besides MSCs, various other cell types secrete EVs with clinically relevant regenerative effects (Figure 1). These cell types include osteoblasts, endothelial cells, immune cells, neurons, and even osteoclasts subjected to bioactive compound conditioning. While such diversity expands the regenerative toolkit, research on non-MSC

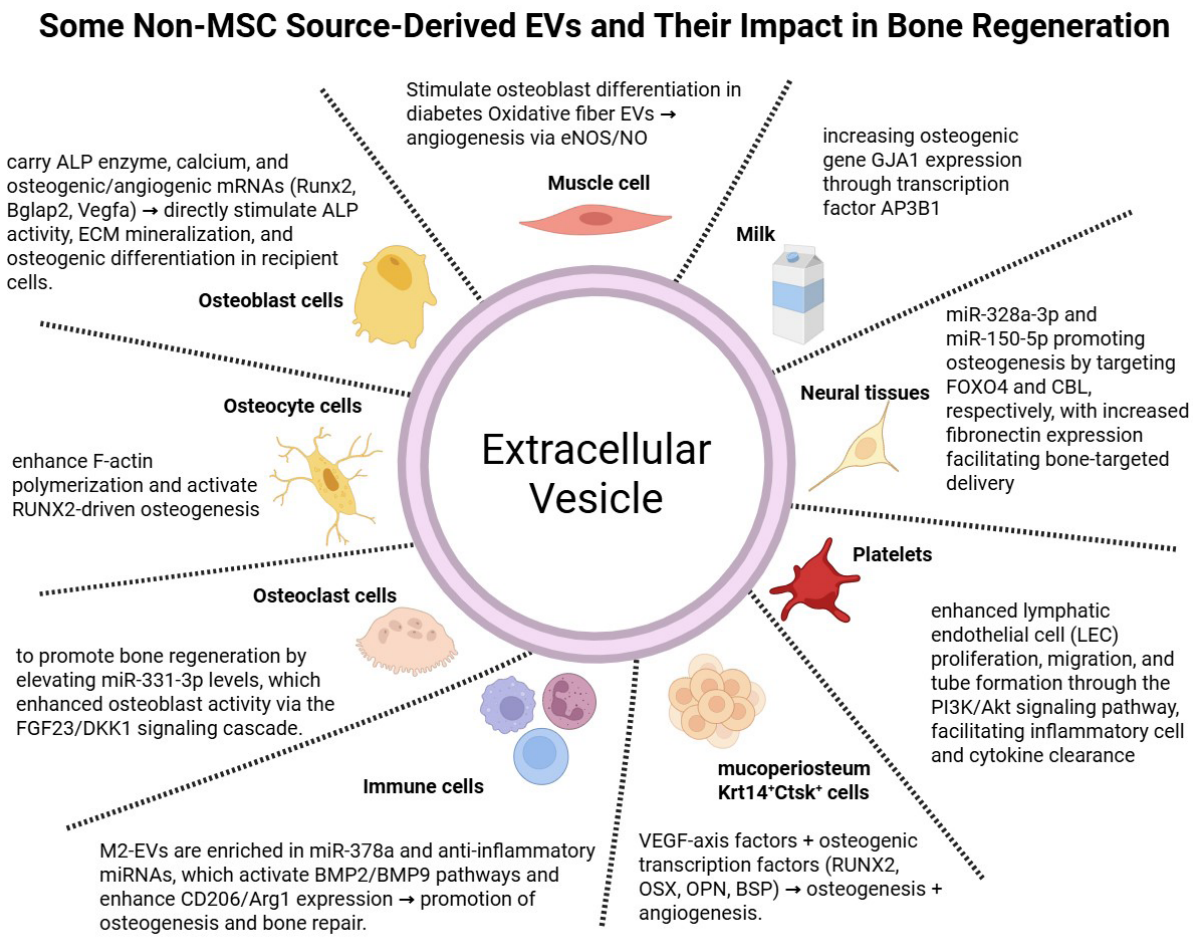

Figure 1. Non-MSC source-derived EVs and their impact on bone regeneration through osteogenesis, angiogenesis, and immunomodulation

Table 2. Representative MSC-derived EVs and their applications in bone regeneration, highlighting key findings, mechanisms, and therapeutic outcomes

MSC Source	Key Findings	Application	Mechanism	Ref.
Bone marrow MSCs	Enhanced fracture healing via BMP-2/Smad1/RUNX2 pathway	Femoral nonunion	Osteogenesis and angiogenesis promotion	[29]
Bone marrow MSCs	miR-29b-3p promoted angiogenesis via PTEN/PI3K/AKT	Fracture healing	Neovascularization enhancement	[31]
Bone marrow MSCs	BGN+BMSC-EVs inhibited osteoclast differentiation	Osteoporosis	lncRNA NRON-mediated NFATc1 inhibition	[14]
Bone marrow MSCs	PMN-EVs enhanced BMSC proliferation and osteogenesis	Bone regeneration	SOD2 and GJA1 protein upregulation	[7]
Bone marrow MSCs	Oxygen-supplying composite with calcium peroxide	Bone defect repair	Hypoxia relief and inflammation regulation	[45]
Bone marrow MSCs	Lithium-stimulated exosomes promoted M2 polarization	Glucocorticoid-induced osteonecrosis	Pro-osteogenic and pro-angiogenic activity	[46]
Bone marrow MSCs	miR-668-3p enrichment enhanced osteoblast function	Osteonecrosis of femoral head	Enhanced CD63 and CD9 expression	[47]
Bone marrow MSCs	Fe3O4 nanoparticle and static magnetic field preconditioning	Bone tissue engineering	miR-1260a enrichment, HDAC7/COL4A2 inhibition	[48]
Bone marrow MSCs	BMSC-sEVs modulated OPG-RANKL signaling	Periodontal tissue regeneration	Macrophage polarization and inflammation reduction	[49]
Bone marrow MSCs	Mutant HIF-1α carrying exosomes with β-TCP scaffolds	Critical-sized bone defects	Enhanced neovascularization	[50]
Adipose-derived MSCs	Immunomodulatory effects via miR-451a targeting MIF	Traumatic bone defects	M1/M2 macrophage polarization regulation	[26]
Adipose-derived MSCs	Promoted fracture healing via Wnt3a/β-catenin pathway	Diabetic fractures	BMSC osteogenic differentiation enhancement	[32]
Adipose-derived MSCs	Hypoxic apoptotic EVs with 3D-printed ECM scaffolds	osteochondral regeneration	M2 macrophage polarization and stem cell proliferation	[16]
Adipose-derived MSCs	MHA containing sEVs	Osteoporotic tendon-to-bone healing	Biomechanical strength improvement (2x)	[51]
Adipose-derived MSCs	Circadian rhythm-regulated sEVs via triphasic microneedles	Rotator cuff repair	M1 macrophage polarization inhibition	[52]
Adipose-derived MSCs	CGRP-enriched EVs with PLGA/pDA scaffolds	Alveolar bone defect repair	Periodontal ligament stem cell osteogenesis	[53]
Adipose-derived MSCs	miR-486-5p delivery for wound healing	Skin wound repair	*Sp5* gene targeting, fibroblast/endothelial enhancement	[54]
Adipose-derived MSCs	Anti-inflammatory responses and matrix preservation	ACL repair	Type I collagen fiber increase, biomechanical improvement	[55]
Umbilical cord MSCs	Rejuvenated senescent BMSCs by transferring PCNA	Aging-related bone loss	Anti-aging effects and wound healing	[7]
Umbilical cord MSCs	miR-23a-3p activated PTEN/AKT signaling	Critical-size bone defects	Vascularized bone regeneration on bioglass scaffolds	[33]
Dental pulp MSCs	Cordycepin-loaded exosomes activated NRF2 signaling	Aged bone regeneration	Senescent cell rejuvenation	[5]
Dental pulp MSCs	Comparable effects to BMP-2 on osteogenic genes	Mandibular defect repair	Faster wound closure and increased bone density	[4]
Dental pulp MSCs	Osteoinductive EVs in adhesive hydrogels	Bone regeneration	2.23-fold BMP2 expression increase	[56]
Dental pulp MSCs	TGF-β1/Smad/MAPK pathway activation	Alveolar bone defect regeneration	HERS cell osteogenic gene expression	[30]
Synovial MSCs	Enhanced osteochondral repair via Wnt/β-catenin pathway	Osteochondral repair	Chondrogenic gene expression (*COL2A1*, *SOX-9*, *RUNX2*)	[34]
Periodontal ligament MSCs	P-EVs in matrigel enhanced BMSC function	Calvarial bone defect repair	AKT and ERK1/2 phosphorylation via adenosine signaling	[41]

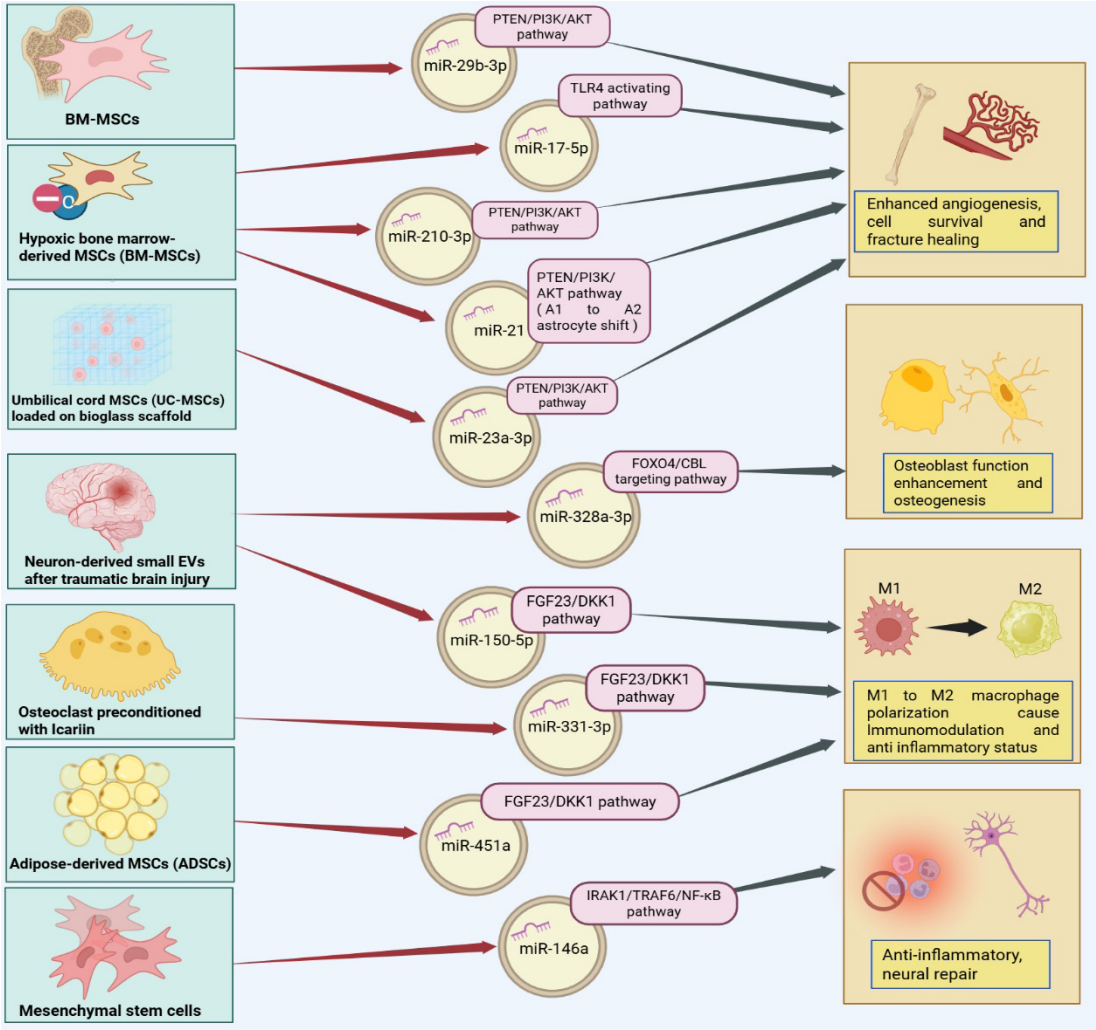

Figure 2. Graphical summary of the signaling pathways and Key MicroRNAs carried by EVs from various cellular sources, highlighting their roles in promoting angiogenesis, osteogenesis, immune modulation, and anti-inflammatory effects during bone regeneration

EVs is scattered and frequently lacks standardization in isolation, characterization, and dosing protocols. Consequently, cross-study comparisons are difficult, and claims of superiority over MSC-derived EVs should be interpreted with caution until verified by head-to-head functional studies.

MicroRNA-mediated pathways in EV-based bone regeneration

Figure 2 illustrates the major microRNA (miRNA)-mediated pathways through which EVs from various sources influence bone repair. EVs from BMMSCs, hypoxic preconditioned MSCs, umbilical cord MSCs, neuron-derived cells, icariin-treated osteoclasts, and adipose MSCs regulate key cascades, such as PTEN/PI3K/AKT, FOXO4/CBL, FGF23/DKK1, and IRAK1/TRAF6/NF-κB. These targeted interactions produce functional outcomes, including angiogenesis enhancement, improved cell survival, osteoblast activation, macrophage phenotype switching (M1 to M2), anti-inflammatory effects, and neural repair. Although the figure integrates multiple datasets, it should be noted that most mechanistic evidence comes from reductionist models where one pathway is studied in isolation. In vivo, these pathways interact within a complex and dynamic signaling network, meaning the therapeutic contribution of any single miRNA may differ markedly in a clinical setting. Addressing this gap will require multi-pathway and multi-source analyses with standardized EV profiling. As such, Figure 2 is most valuable when used as a hypothesis-generating tool, guiding future studies toward integrative rather than single-axis mechanistic exploration.

Delivery Systems and Scaffolds

The clinical translation of EVs for bone regeneration depends on more than just producing therapeutic vesicles. It requires delivery systems that protect EV stability, control their spatial and temporal release, and direct them precisely to target tissues. Without these elements, therapeutic efficacy is likely to drop dramatically due to rapid clearance, degradation, or off-target deposition. This section reviews delivery strategies with a view toward their functional strengths, limitations, and scalability for clinical use.

Hydrogel-based delivery systems

Hydrogels remain the most versatile and widely implemented EVs carriers for bone regeneration because of their intrinsic biocompatibility, adjustable physical properties, and ability to mimic aspects of the extracellular matrix (ECM). These characteristics not only protect EVs cargo but also allow fine-tuning of release kinetics. Table 3 classifies hydrogel systems by type, EVs source, therapeutic application, and outcome. The field has evolved from simple, passive hydrogel reservoirs toward multi-functional biomaterials that address specific physiological barriers to repair. For instance, oxygen-releasing composites mitigate local hypoxia—a key impediment to healing in large defects or dual-drug releasing systems synchronize EVs delivery with pro-angiogenic or osteoinductive molecules, producing synergistic effects. Nevertheless, the translation of these advanced hydrogels remains hindered by challenges, such as batch-to-batch variability in natural polymers, potential cytotoxicity of crosslinking agents, and the need for scalable sterilization processes that preserve EVs bioactivity. These issues are rarely discussed in preclinical studies but will be decisive for regulatory approval.

Microparticles and nanoparticles

Microparticle- and nanoparticle-based scaffolds provide high surface area and tunable release profiles, making them attractive carriers for EVs. Affinity-modified PLGA microscaffolds, such as biomineralized PDA variants, have demonstrated EVs loading capacities exceeding 20 μg/mg with sustained release for up to 21 days, resulting in substantial bone repair in rat cranial defect models [33], while electrospun SF/PCL nanofibers functionalized with polydopamine have further improved EV retention and scaffold mechanical strength, enabling near-complete regeneration of critical-size calvarial defects within 8 weeks [34]. Collectively, these findings highlight micro/nanostructured scaffolds as efficient and scalable bioactive systems for controlled EVs delivery and accelerated bone regeneration.

Table 3. Hydrogel-based EV delivery systems

Hydrogel Type	EV Source	Application	Key Benefits	Ref.
Oxygen-releasing thermosensitive	BMMSC-derived small EVs	Periodontal bone defects	Pathogen inhibition, infection relief, periodontal regeneration	[1]
Chitosan-collagen	Osteoblast-derived EVs	Bone regeneration	Enhanced EV release kinetics, dose-dependent mineralization	[57]
Gelatin nanoparticles	Adipose-derived stem cell (ADSC)-derived exosomes	Traumatic bone defects	Immunomodulatory effects, M1/M2 macrophage regulation	[26]
Hyaluronic acid	Platelet-derived EVs	Implant biocompatibility	Improved titanium integration, reduced fibrotic response	[58]
GelMA-LAP	TSA-enhanced osteoblast EVs	Bone regeneration	Enhanced proliferation, migration, and mineralization	[59]
Matrigel	PDSC-derived small EVs	Bone defect repair	Enhanced BMSC proliferation via AKT/ERK1/2 signaling	[41]
MHA	ADSC-derived small EVs	Osteoporotic tendon-bone healing	2x biomechanical strength improvement, aligned architecture	[51]
Adhesive hydrogels	Dental pulp stem cell (DPSC)-derived osteoinductive EVs	Bone regeneration	2.23-fold increased BMP2 expression, tissue mineralization	[52]
Collagen hydrogels	Li-stimulated BMSC exosomes	Glucocorticoid-induced osteonecrosis	Macrophage M2 polarization, enhanced angiogenesis	[46]
Oxygen-supplying composite	BMSC-derived exosomes	Bone defect repair	Tissue hypoxia relief, inflammation regulation	[45]
PEG/HA composite	BMSC-derived small EVs	Bone defect repair	Enhanced small EV retention, sustained release	[60]
Injectable dual-drug releasing	DPSC-derived exosomes	Calvarial defects	Sequential VEGF/exosome release, biomimetic healing	[61]

Hydrogel Type	EV Source	Application	Key Benefits	Ref.
Sodium alginate	Krt14+Ctsk+ cell exosomes	Vascularized bone regeneration	Enhanced osteogenesis and angiogenesis coupling	[62]
CSMA hydrogel (injectable)	Electrical stimulation-pretreated BMSC exosomes (Elec-exo)	Rat femur defect repair	Accelerated osteogenesis via PI3K/AKT & MAPK activation; BV/TV ↑ to 83%	[63]
HAMA-CPC injectable composite hydrogel	3D-cultured ADSC-derived small EVs	Rat tibial bone defect repair	Promoted proliferation, migration & osteogenic differentiation of BMSCs; enhanced angiogenesis via NAMPT → S1PR1 → VEGF; ↑ BV/TV, BV, Tb.Th at 4 weeks	[64]
ZIF-8-modified GelMA composite hydrogel	MSC-derived exosomes	Cranial bone defect in rat	Sustained release of EV + Zn^{2+}; miR-23a-3p → AKT upregulation; immunomodulation (M2 polarization, NF-κB inhibition); enhanced osteogenesis & angiogenesis in vivo; low inflammation	[65]
GelMA hydrogel (encapsulated exosomes from osteogenic pre-differentiated MSCs)	MSC-derived exosomes (osteogenically pre-differentiated)	Critical-size bone defect repair (animal model)	Sustained delivery; enhanced osteogenesis & angiogenesis; immunomodulation via macrophage polarization; reduction of DNA oxidative damage; better bone regeneration in vivo	[66]
GelMA-CP05 modified hydrogel	Bmp2 mRNA-enriched exosomes (Exo BMP2+NoBody)	Rat calvarial bone defect repair	Sustained release; higher BMP2 mRNA loading; improved osteogenic differentiation & mineralization; increased BV/TV, Tb.N; durable bone regeneration in vivo	[67]
Adhesive hydrogel	$CD133^+$ urine-derived stem cell exosomes (and USC-Exos)	Rotator cuff healing / tendon-bone interface (rat)	Promoted BMSC proliferation, migration, osteogenic differentiation; subchondral bone repair; improved biomechanical strength of tendon-bone interface	[68]
Exosome-encapsulated hydrogel (injectable)	Umbilical MSC-derived exosomes	Rat calvarial critical-sized defect	BV/TV ↑38.4% vs 24.7% (Exo alone) & 11.5% (control); Tb.Th ↑~102 μm; enhanced angiogenesis (2× tube formation); upregulated osteogenic genes (*Runx2*, *OCN*, *ALP*)	[69]
GelMA (photocrosslinked) – plant exosome–loaded	Epimedium-derived sEVs (plant)	Osteogenic/angiogenic support for bone regeneration (in vitro)	**Sustained release up to 7 days; peak MC3T3-E1 proliferation at 195 μg/mL with 5% GelMA; ALP ↑ at day 7 ($^{**}P<0.01$) and day 14 ($^{***}P< 0.001$); osteogenic genes ↑ (*RUNX2*, *Osterix*, *COL1A1*, *ALPL*, *TGF-β1*); HUVEC tube nodes ↑ ($^{*}P<0.001$); PI3K/Akt activation (inhibited by LY294002); reduced SA-β-Gal$^+$ senescent cells.	[70]
Gelatin/Hyaluronic acid (Gel-HA) composite hydrogel	BMSC-derived exosomes (rich in TGF-β)	Rat cranial critical-sized defect repair	Enhanced osteogenesis & angiogenesis via PI3K/Akt activation; upregulated RUNX2, OCN, VEGF; dose-dependent bone formation (BV/TV ↑ to 41.2% vs 15.1% control; BMD ↑1.53 g/cm³); high exosome retention and biocompatibility	[71]
GelMA/Nanoclay (LAP composite)	TSA-treated osteoblast-derived EVs (epigenetically enhanced)	Bone defect repair	Controlled EV release (90% vsF 22% at day 7 in GelMA-LAP), ↑ ALP (1.34–1.89 fold), ↑ collagen (1.3–2.0 fold), ↑ calcium deposition (1.78 fold); improved proliferation & migration	[72]
GelMA/SAMA/β-TCP hydrogel	Yoda1-pretreated BMSC exosomes	Rat cranial bone defect repair	Sustained exosome release (≥21 days); enhanced osteogenesis via ERK/PI3K-AKT activation; ↑ collagen/OCN expression; significant BV/TV increase at 4 & 8 weeks	[73]

Other biodegradable scaffolds

Biodegradable and bioactive scaffolds offer a dual advantage for bone regeneration: they provide mechanical support to fill and stabilize defects while acting as controlled depots for EVs. Across ceramics, natural ECM-derived materials, bioactive glasses, and polymeric systems, a recurring theme emerges—the integration of osteoimmunomodulation, angiogenesis, and osteogenesis while maintaining resorbable, tissue-mimetic architectures. Below, these categories are analyzed in terms of functionality, mechanistic potential, and translational relevance.

Ceramic-based and immunoactive platforms

3D-printed lithium-doped calcium silicate (LiCS) scaffolds illustrate how scaffold chemistry can actively influence immune modulation. These scaffolds reprogram macrophages toward an M2 phenotype and boost the release of miR-145-5p–rich EVs, suppressing pro-inflammatory cytokines (CD86, IL-1β, TNF-α) and upregulating angiogenic and osteogenic markers, such as VEGF, Ang-1, BSP, and OC. In rabbit femoral critical-size defects, LiCS scaffolds significantly outperformed conventional calcium silicate in BV/TV, trabecular thickness, collagen deposition, and mineralization [35]. This evidence underscores the capacity of ceramic chemistry to tune the immune microenvironment and indirectly modulate EV signaling. However, most results come from small-animal defect models, and load-bearing adaptation remains largely untested.

Naturally-derived ECM scaffolds

Natural decellularized matrices inherently provide an ECM-like microenvironment that can synergize with EV therapy. For instance, tannic acid–modified decellularized tendon scaffolds loaded with SCAP-derived nanovesicles ensured controlled release while preserving osteogenic and angiogenic miRNA cargo, improving MSC osteogenesis, human umbilical vein endothelial cells (HUVEC) angiogenesis, and cranial defect repair [36]. Likewise, fish-scale acellular scaffolds enriched with osteogenically differentiated BMSC exosomes achieved ~80% calvarial healing compared with ~53% in scaffold-only and ~6% in controls [37], and bovine osteoid xenografts combined with DPSC exosomes enhanced histopathologic and microstructural bone repair in mandibular defects [38]. The strength of ECM-derived scaffolds lies in their intrinsic bioactivity and host cell compatibility, yet variability in donor source, decellularization methods, and sterilization can alter both the mechanical and bioactive properties, a factor rarely standardized in current studies.

Bioactive glasses and calcium-phosphate scaffolds

Exosome-functionalized 58S bioactive glass scaffolds enhanced osteoblast activity, osteon formation, and angiogenesis, delivering sustained release in calvarial defects. Similarly, nano-hydroxyapatite (nHA) scaffolds loaded with hEnSC-derived exosomes promote osteogenesis and vascularization with extended release (~68% over 164 h). Mineralized osteoblast-derived EVs encapsulated in chitosan–collagen hydrogels drove osteoblast differentiation via miRNA–mRNA regulation and maintained bioactivity for up to 30 days. These findings highlight the ability of ionically active mineral phases to stabilize vesicles, support staged release, and guide bone formation. A key translational challenge here is ensuring scalable manufacturing of such mineral–EV composites while maintaining consistent ion release profiles.

Polymeric and composite systems

Polymeric scaffolds, such as nHA/chitosan/PLGA have been used to deliver ADSC-derived exosomes, stimulating BMSC proliferation, ALP activity, and osteogenic gene expression with a 2-phase release (burst in first 3 days, sustained up to 9 days) that correlated with significant mandibular bone repair. Interpenetrating polymer networks (pectin/chitosan/PVA) mimicked cancellous bone properties (≈83% porosity; 2.9 MPa compressive strength), and when coupled with EVs, improved hMSC proliferation, ALP activity, angiogenesis, and osteogenic differentiation. Functionalized bovine SmartBone® scaffolds loaded with MSC lyosecretome boosted osteoblast differentiation and trabecular bone formation by ~20% .

Further advances in polymeric and composite scaffold systems demonstrate the diverse strategies for enhancing EV-mediated bone regeneration. For instance, 3D-printed PLA scaffolds coated with polydopamine and loaded with hBMSC-derived exosomes have been shown to reduce reactive oxygen species (ROS) levels and promote osteogenesis. It is indicated by elevated ALP activity, calcium deposition, and upregulation of osteogenic markers, such as Runx2, OCN, and IBSP—although their efficacy remains to be validated in vivo [39]. Similarly, zinc-based porous scaffolds incorporating serum-derived exosomes within a poloxamer hydrogel matrix have exhibited dual functionality by enhancing osteogenesis and suppressing osteoclastogenesis through modulation of the p38/STAT1 signaling pathway, achieving notable defect repair in rabbit radius models [40]. Gelatin sponges functionalized with ADSC exosomes further improved femoral defect healing,

with significantly higher BV/TV, BMD, and trabecular thickness, and reduced trabecular separation compared to control gelatin sponges functionalized with ADSC-derived exosomes have also demonstrated significant improvements in bone volume fraction (BV/TV), bone mineral density (BMD), and trabecular architecture compared to scaffold-only controlsls [41]. Moreover, silk fibroin/collagen/nano-hydroxyapatite composites carrying hUCMSC-derived exosomes have been reported to enhance HUVEC migration and angiogenesis in vitro, while increasing BV/TV to approximately 61.9% in rat alveolar defect models, compared with 41.9% in scaffold-only treatments [42]. Polymeric composites offer unmatched tunability in degradation rate, mechanical characteristics, and surface chemistry. However, their inherent synthetic nature often requires careful modification to match the bioactivity levels of natural ECM scaffolds.

Hybrid hydrogel-scaffold platforms

Some platforms bridge solid mechanics and hydrogel dynamics. A gelatin-hyaluronic acid composite loaded with exosomes activated PI3K/Akt signaling, driving BMSC osteogenesis and HUVEC tubulogenesis, raising BV/TV to 41.2% in vivo [43]. Oxygen-releasing hydrogel/PLLA/CaO_2 composites also improved osteogenesis and angiogenesis in calvarial models [44]. These hybrid designs target two common clinical barriers: local hypoxia and poor vesicle retention. However, they add layers of complexity for manufacturing and quality control.

Electrospun nanofibrous scaffolds

ZnO-doped PCL scaffolds both immobilized osteoblast-derived EVs and served as diagnostic interfaces by reflecting extracellular mineralization status via EV cargo [45]. This dual therapeutic–diagnostic potential (theranostics) is promising, but integration into a regulated clinical pipeline will require validation of both efficacy and safety over prolonged use.

Integrative commentary

Collectively, the evidence from ceramics (LiCS) [35], ECM sources (tendon, fish-scale, xenografts [36-38], mineral phases (bioactive glass, nHA [46-48], polymerics (nHA/CS/PLGA [49], IPNs [50], SmartBone [51], PLA [39], Zn scaffolds [40], gelatin/PDA [41], SF/COL-I/nHA [42]) underscores that scaffold chemistry and architecture are not passive carriers but active determinants of EV-mediated bone regeneration. The lack of standardized release profiling, long-term safety assessment, and head-to-head comparisons across categories remains a major bottleneck for clinical adoption. To move forward, integrating quantitative release kinetics, immune-modulatory profiling, and load-bearing performance assessment into preclinical pipelines will be essential.

Implant surface coatings: Enhancing bioactivity via EV functionalization

Titanium (Ti) and its alloys remain the gold standard for orthopedic and dental implants due to their high mechanical strength, corrosion resistance, and proven osseointegration properties. However, their inherently bioinert surfaces limit biological signaling at the tissue–implant interface, which can compromise early-stage healing and long-term integration. Recent advances in surface biofunctionalization with EVs address this limitation by combining mechanical robustness with biologically active cues that promote osteogenesis, angiogenesis, and immunomodulation.

Cui et al. (2025) demonstrated a bioselective approach by engineering 3D-printed porous Ti scaffolds coated with a zwitterionic PMCP layer designed to capture BMSC-derived exosomes [52]. This selective immobilization significantly enhanced osteogenic differentiation and improved bone formation in rabbit femoral defect models. Similarly, nanohydroxyapatite-coated Ti scaffolds functionalized with periodontal ligament stem cell (PDLSC)-derived exosomes achieved sustained vesicle release, elevated cytocompatibility, and demonstrated marked osteogenic enhancement in both in vitro and in vivo settings [53]. Functionalization strategies have also integrated engineered vesicle cargos to modulate host immune environments. In 2022, Ti6Al4V scaffolds were biofunctionalized via polyethylenimine-assisted micro-arc oxidation to immobilize Smurf1-shRNA–engineered BMSC-derived exosomes [54]. This platform not only improved bone formation but also shifted macrophage polarization toward a pro-regenerative M2 phenotype, evidencing the dual role of EV-modified surfaces in bone regeneration and osteoimmunomodulation. Beyond MSC sources, alternative cell-derived vesicles extend the scope of this strategy. Wu et al. (2020) coated Ti6Al4V scaffolds with Schwann cell-derived exosomes, which promoted BMSC proliferation, induced osteogenic differentiation, and enhanced osseointegration in rabbit femoral models [55]. This finding suggests that EV coatings can be tailored for specific regenerative contexts, such as neurovascular support in complex defect environments.

While these findings establish a strong proof-of-concept for EV-coated metallic implants, several translational challenges remain. The stability of vesicle binding under physiological loading, preservation of EV bioactivity during sterilization and storage, and large-scale manufacturing protocols require systematic optimization. Moreover, direct comparative studies between EV coating strategies—standard vs engineered EVs, MSC vs non-MSC sources—are lacking, making it difficult to determine the optimal design for specific clinical scenarios. Integration of quantifiable release kinetics, in vivo immune profiling, and long-term implant performance data will be crucial to validate these systems for regulatory approval and routine clinical application.

Scaffold integration and 3D platforms: From passive supports to active biofactories

3D scaffolds are now a central architecture in bone tissue engineering, providing mechanically competent, biomimetic spaces that can be strategically integrated with EVs. Their design evolution is shifting from static carriers toward dynamic, bioactive platforms that coordinate spatiotemporal EV delivery and mechanical support.

Biomimetic and osteoconductive architectures

PEG/HA composites loaded with BioOss and BMSC-derived sEVs show reinforced mechanical strength, extended EV retention, and continuous osteoinductive signaling [56]. Porous tantalum-based systems with BMSC-EVs exhibit high biocompatibility and augmented new bone deposition in femoral defects [57]. Similarly, PCL-based electrospun membranes enriched with lipocalin-2 exosomes facilitate angiogenesis while suppressing adipogenesis, underscoring cell-lineage specificity [58].

Bioactive co-engineering of EVs and scaffolds

Material-ion crosstalk is emerging as a design axis. For example, magnesium ion-stimulated DPSC-derived EVs in β-TCP/GelMA scaffolds activate AKT/eNOS signaling to enhance vascularized bone formation [59]. 3D-printed Ti designs with hydrogel microsphere domains enabled prolonged release of hypoxia-induced EVs, translating into improved bone volume and neovascularization [60]. Hydroxyapatite-doped poly (lactide-co-glycolide)-b-poly(ethylene glycol)-b-poly(lactide-co-glycolide) (HA-PELGA) scaffolds demonstrate that controlled degradation rate dictates bone morphology, with slower rates favoring compact bulk formation [61].

Similarly, melt electrowritten PCL scaffolds are shown to significantly increase the yield of osteoblast-derived EVs compared to 2D culture, providing a scalable approach for exosome production as well as bone repair applications [62]. Direct integration of mineralized osteoblast-derived exosomes into 3D-printed ceramic scaffolds further enhances osteogenic differentiation and bone formation, confirming the synergistic effect of mineralized cargo with bioactive scaffolds [63].

EV bioactivity amplification via scaffold microarchitecture

Tailored pore geometry in nHA-coated Ti scaffolds boosted osteoblast EV secretion 2.2 fold, producing cargo that enhanced collagen and calcium outputs from hBMSCs [64]. Integration of mineralized osteoblast EVs into HA/TCP gyroids elevated BV/TV in mice from 8.3% to 18.7%, though limited efficacy in rabbits points to species and site-dependence [63].

Multifunctional and cross-tissue regeneration systems

Multifunctional constructs extend beyond pure osteogenesis. hESC-derived EVs incorporated into chitosan-collagen activate the miR-21-5p/YAP1/β-catenin axis [65], while NGF-preconditioned MSC EVs in porous scaffolds support both bone and nerve regeneration [66]. EV-polysaccharide hydrogels and fusion peptide-engineered HA scaffolds improve EV retention, controlled release, and osteogenic yield [67]. Bilayer hydrogel/dECM platforms repair osteochondral defects [68], and strontium-Ti or hybrid bioprint combinations enhanced osteointegration and angiogenesis [69, 70]. Mesoporous bioactive glass with osteoinductive EVs accelerate Smad-mediated repair [71].

Genetic and molecular payload platforms

VEGF plasmid-loaded EVs tethered to PCL scaffolds function as gene-delivery microreactors, stimulating vascularization and bone repair in segmental defects [72]. This action signals a paradigm shift to scaffolds that do not merely carry EVs but program the defect microenvironment.

Evidence consistently shows that scaffold-EV integration supports localized and sustained bioactivity capable of driving multi-lineage regeneration, yet several unresolved challenges constrain its clinical translation. A persistent lack of standardized performance metrics hampers direct comparison between studies, particularly

regarding EV release kinetics, immune modulation, and load-bearing performance. Additionally, the preservation of vesicle bioactivity over extended storage or after sterilization remains insufficiently characterized, creating uncertainty in real-world deployment. Finally, species- and defect-specific variability, as evidenced by inconsistent outcomes in diabetic nonunion and large animal models [63], underscores the need for more predictable systems. Addressing these hurdles through standardized manufacturing and smart delivery platforms is essential for transitioning EV-based therapies into a mainstay of regenerative orthopedics.

Collectively, these findings establish that scaffold integration with EVs enables spatiotemporal control of vesicle release, enhances mechanical and biological performance, and introduces multifunctional capabilities, such as neurogenesis and angiogenesis. By mimicking natural periosteal and trabecular structures, 3D scaffold-EV systems provide one of the most advanced and clinically translatable strategies for complex bone defect repair. Building on the structural and biomechanical advantages of these 3D systems, the next frontier lies in integrating spatiotemporal precision to EV delivery. This action requires moving from passive scaffold-based release towards actively engineered targeting and controlled release systems, as detailed in the following section.

Advanced targeting and controlled release systems

The next generation of EV delivery platforms moves beyond passive release mechanisms, seeking to mitigate rapid EV clearance, burst kinetics, and poor localization through precision spatiotemporal control. Advanced delivery concepts now integrate responsive materials, microarchitectural designs, and bioactive cues to sustain and direct EV function in vivo. Voronoi-designed Ti scaffolds combined with PEGDA/GelMA microspheres enable prolonged release of hypoxia-induced exosomes, resulting in marked enhancements in osteogenesis and angiogenesis in rabbit femoral defects [60]. This design exemplifies how macrolattice geometry can synergize with hydrogel microdomains to achieve concurrent mechanical stability and controlled biofactor release. Such integration of structural and biochemical control underscores a shift toward scaffold systems that actively program the defect microenvironment rather than merely serve as inert carriers.

Alternative strategies include exosome-capturing scaffolds designed to recruit endogenous neutrophil-derived EVs, thereby leveraging innate immune effectors to promote angiogenesis [73]., and hESC-derived EVs enriched in miR-21-5p, when embedded within chitosan-collagen scaffolds, activate YAP1/βcatenin signaling to boost osteogenesis [65]. These examples demonstrate that in situ EV recruitment and genetically or epigenetically primed cargo offer distinct but complementary routes to microenvironment modulation.

Stimuli-responsive and gene-augmented designs further expand functional complexity. Oxygen-releasing hydrogel/PLLACaO_2 composites counteract ischemia to enhance vascularized bone repair [44], while VEGF plasmid-loaded exosomes tethered to PCL scaffolds effectively converted the matrix into a localized gene-delivery factory for vascular remodeling in segmental defects [72]. Likewise, PLGA–PEG–PLGA microspheres embedded in PLLA scaffolds achieve a 10-week sustained release profile, significantly improving bone healing without the need for cell transplantation [74]. These systems collectively highlight the potential of material–cargo codesign in prolonging therapeutic windows.

Highly specific targeting has been achieved using BMSC-derived exosomes functionalized with a BMSC-specific aptamer (STExoAptamer), enabling cell-type-restricted delivery for osteoporosis therapy. In ovariectomized mouse models, this platform increases bone mass and accelerates fracture healing by homing directly to BMMSCs [75]. Similarly, dual-functional aptamerengineered EVs (Apt376bEVs), combining Apt19s for endogenous stem cell recruitment with miR-376b-5p for osteogenic activation, were delivered via GelMA hydrogel (Apt3-76b-EV@GelMA). By targeting Camsap1, this construct achieves sequential and spatially precise modulation of the senescent fracture microenvironment, enabling coordinated recruitment and differentiation in a single platform 17].

Collectively, these innovations signal a maturation of the EV-scaffold paradigm toward actively programmed, disease-responsive systems. However, clinical translation will require standardized potency assays for targeted EV delivery, rigorous in vivo biodistribution profiling, and scalable manufacturing workflows that preserve targeting moieties without compromising EV stability. Only through such integration of engineering precision with biological fidelity can these advanced platforms transition from experimental success to regulatory approval.

Clinical Applications and Disease-specific Approaches

Age-related bone disorders and treatments

Aging exerts a multifaceted and cumulative impact on bone regeneration through interconnected mechanisms: stem cell senescence, dysregulated inflammatory signaling, and diminished metabolic resilience. These changes collectively impair the bone marrow niche, reduce osteoprogenitor availability, and skew cellular differentiation pathways, thereby prolonging or even arresting the healing cascade. EVs have emerged as promising acellular candidates for mitigating these age-related impairments. Unlike systemic growth factor delivery, EVs can encapsulate and deliver complex molecular repertoires—including proteins, lipids, and nucleic acids—capable of simultaneously reactivating osteogenic pathways and tempering chronic inflammation. A critical mechanistic insight is the functional dichotomy between young osteocyte-derived EVs (YO-EVs) and senescent osteocyte-derived EVs (SO-EVs). YO-EVs, enriched in tropomyosin1 (TPM1), promote BMSC osteogenesis [15], whereas SO-EVs bias mesenchymal differentiation toward adipogenesis, reflecting the age-dependent reprogramming of skeletal cell communication. This divergence not only explains the attenuated regenerative response in elderly bone but also underscores the therapeutic rationale for sourcing EVs from young or rejuvenated cells—or engineering senescent-derived EVs to restore TPM1 signaling.

Figure 3 schematically summarizes the spectrum of EV sources and mechanistic targets implicated in bone rejuvenation, highlighting interventions that counteract senescence-driven dysfunction at molecular, cellular,

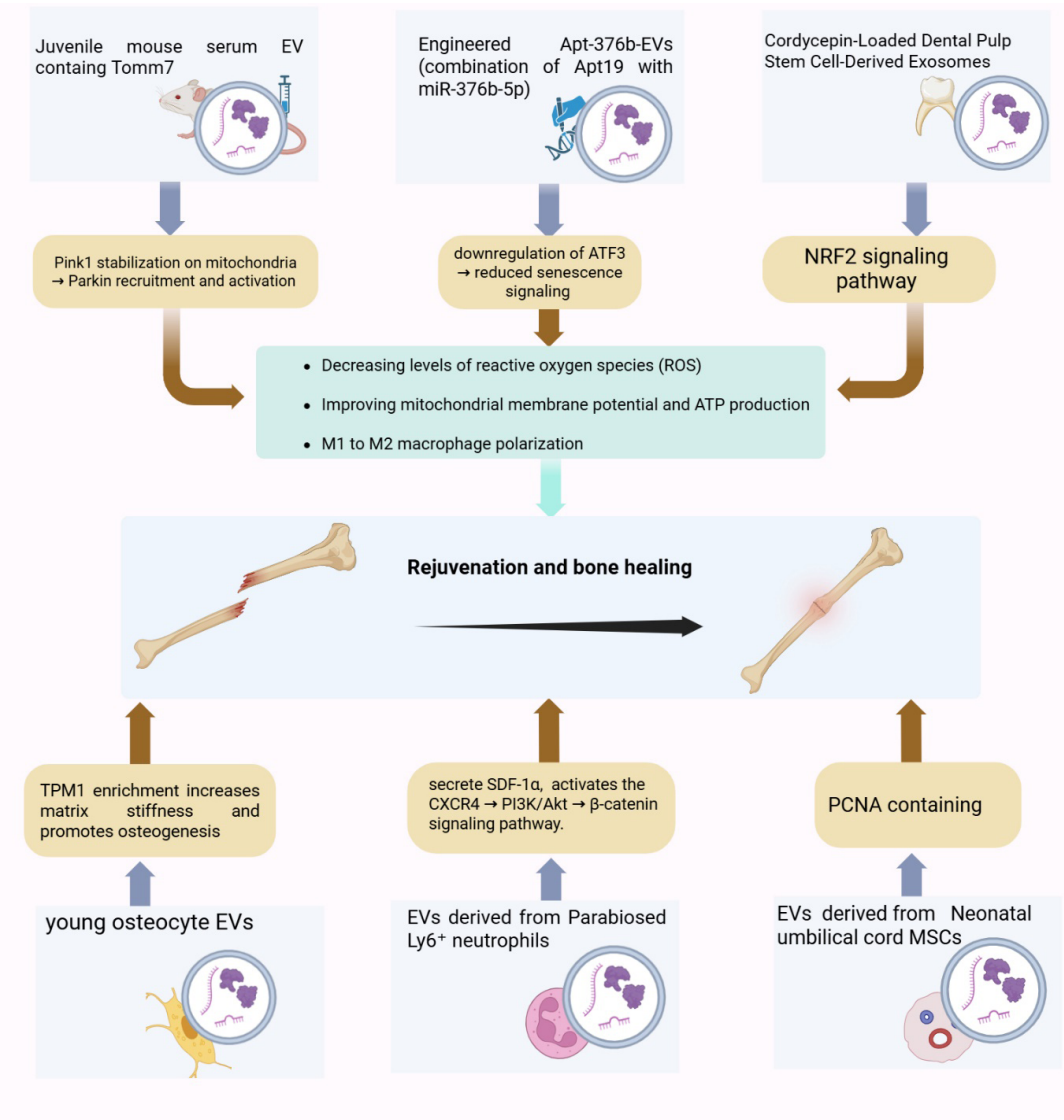

Figure 3. EV-mediated rejuvenation and bone regeneration in aging bone tissue

and tissue levels. While aging-related bone loss provides a highly relevant preclinical platform, it represents only one axis of translation. Metabolic disorders, endocrine dysregulation, and chronic inflammatory conditions can impose more hostile and complex pathophysiological landscapes. Evaluating EV efficacy across these diverse contexts will be crucial to determine whether the regenerative mechanisms effective in aging models are robust enough to withstand these additional biological stressors.

The diagram illustrates how EVs derived from young or engineered cells (e.g. DPSCs, young osteocytes) enhance osteogenesis and reverse senescence in aged bone microenvironments.

Metabolic bone diseases

Diabetes mellitus and bone healing

Diabetes mellitus imposes a sustained and multifactorial burden on bone regeneration, disrupting angiogenesis, skewing immune responses toward a chronic proinflammatory state, and impairing osteoblast and progenitor cell metabolism. These combined effects create a hostile repair microenvironment in which otherwise effective regenerative cues are blunted or lost.

Muscle cell-derived EVs (MyoEVs) can counteract these deficits. In diabetic murine fracture models, MyoEV administration enhanced osteoblastic differentiation, significantly increased bone volume ratio, and restored the pool of Osterix-positive osteoprogenitors suppressed by hyperglycemic conditions [76].

Adipose stem cell-derived exosomes (ASCs-exos) address a complementary mechanistic gap by activating the Wnt3a/βcatenin pathway. In diabetic rat nonunion models, ASCs-exos improves BMMSC osteogenic differentiation and promotes robust fracture bridging, underscoring their capacity to reengage osteogenic programs suppressed by diabetic stress [32]. Conversely, bone marrow stem cell-derived exosomes from diabetic donors (DM-BMS-Cexos) actively impair bone regeneration. Mechanistically, this is linked to downregulation of miR-17, which relieves SMAD7-mediated suppression of osteogenesis. In contrast, nondiabetic BMS-Cexos preserve miR-17 levels, supporting normal osteogenic signaling. The miR-17/SMAD7 axis thus emerges as both a mechanistic explanation for diabetic EV dysfunction and a promising target for therapeutic intervention [77].

Critically, these findings point to 2 nonexclusive strategies: (1) sourcing EVs from healthy or resilient cells capable of resisting diabetic metabolic stress, and (2) engineering diabetic cell-derived EVs to restore pro-osteogenic signaling (e.g. miR-17 enrichment). Both require careful translation into scalable, clinically compliant manufacturing pipelines, as diabetic patients—being a high-risk, high-need population—also demand robust long-term safety data before deployment.

Osteoporosis and hormonal disorders

Osteoporosis reflects a systemic imbalance between bone formation and resorption, where hormonal decline—particularly estrogen loss—exacerbates osteoclast activity and reduces osteoblast function. Recent evidence has broadened this classical paradigm by implicating gut microbiota–host EV interactions. Gut microbiota from children, enriched in *Akkermansia muciniphila*, has been shown to mitigate bone loss in osteoporotic mice by producing EVs that localize to bone tissue, enhance osteogenic activity, and suppress osteoclastogenesis [78]. This finding reframes the gut-bone axis as a clinically actionable target, suggesting that microbiota-derived EVs could serve as bioactive modulators of skeletal metabolism.

Plasma-derived EVs from 54 osteoporotic postmenopausal women revealed quantitative and compositional changes, including elevated total EV counts and an increased proportion of $RANKL^+$ EVs, which correlated with enhanced osteoclastogenesis and suppressed osteoblast differentiation. Distinct miRNA signatures in these EVs further suggest their potential utility as minimally invasive biomarkers for bone loss disorders [79]. Therapeutic innovation has also emerged from stem cell-based sources. Human umbilical cord mesenchymal stromal cell-derived EVs have demonstrated potent bone-protective effects through CLEC11A-mediated regulation of bone metabolism, offering a regenerative approach that directly addresses the molecular basis of osteoporotic bone fragility [80].

Infection-related bone disorders

Bone infections compound regenerative challenges by introducing persistent inflammation, pathogen-mediated cytotoxicity, and disruption of vascularization. Effective therapeutics must combine antimicrobial potency with strategies that restore osteogenesis.

Icariin-treated osteoclast-derived exosomes (ICA-OC-Exo) exemplify this dual-function approach. By upregulating miR-331-3p, ICA-OC-Exo activated osteoblast function via the miR-331-3p/FGF23/DKK1 axis, driving new bone formation even under inflammatory stress [81]. Similarly, an oxygen-releasing thermosensitive hydrogel carrying BMMSC-derived sEVs addressed periodontal bone defects by simultaneously suppressing anaerobic pathogens and promoting regenerative angiogenesis and osteogenesis [1]. A more complex bioengineering strategy employed bacterial EVs co-loaded with BMP2 and VEGF, embedded in IL4–enriched hydrogels, to synergistically enhance immunomodulation, angiogenesis, and osteogenesis, significantly improving osteoporotic fracture repair in murine models [82]. These targeted advances echo a broader clinical imperative: infection itself remains a leading barrier to effective fracture healing. As highlighted in an educational review [83], integrating infection control with regenerative protocols—rather than treating these goals sequentially—may yield superior outcomes in both infection eradication and bone restoration.

Specialized bone regeneration applications

Tendon-bone interface healing

Repairing the tendon-to-bone interface, particularly under osteoporotic or aging conditions, remains clinically challenging due to impaired fibrocartilage formation, chronic inflammation, and altered mechanotransduction. A macroporous hydrogel system (MHA-sEVs) loaded with small EVs from ADSCs significantly enhanced biomechanical integration, achieving roughly a two-fold increase in interface strength compared to controls. Building on this, circadian rhythm–regulated small EVs (CR-sEVs), delivered via triphasic microneedles, improved tendon-to-bone healing by suppressing M1 macrophage polarization and enhancing shoulder function in rotator cuff repair models [84, 85].

Mechanistic dissection of these pathologies has revealed a self-perpetuating inflammatory loop between senescent tendon stem cells (s-TSCs) and M1 macrophages, which exacerbates tissue degeneration in aged individuals. Healthy tendon stem cell-derived exosomes (h-TSC-Exos) disrupted this loop by promoting M2 macrophage polarization, rejuvenating s-TSCs, and enhancing tendon-bone healing through BMP4 signaling [86]. These findings underscore that EV-based modulation of immune-stem cell crosstalk can restore regenerative capacity.

Beyond rotator cuff models, EV therapy in rabbit ACL repair improved anti-inflammatory responses, reduced ECM degradation, increased type I collagen fiber deposition, and markedly enhanced biomechanical failure load [87]. Together, these approaches highlight a translational shift—from purely structural grafting toward immuno-regenerative interface engineering.

Osteochondral defects

Osteochondral lesions demand simultaneous regeneration of articular cartilage and subchondral bone, a task complicated by the divergent biology of these tissues. In one approach, icariin (ICA) was combined with rabbit synovial MSC-derived EVs to synergistically enhance repair. This combination upregulated chondrogenic genes (*COL2A1*, *SOX9*, *RUNX2*) via Wnt/βcatenin signaling, producing superior outcomes versus monotherapies [88]. Hypoxia-induced apoptotic EVs (H-ApoEVs) from ADSCs have also emerged as a potent regenerative modality. Compared to normoxic controls, H-ApoEVs promotes greater tissue repair by stimulating stem cell proliferation and inducing M2 macrophage polarization. When integrated into 3D-printed ECM scaffolds, they provided both a permissive niche and proangiogenic cues [16]. The convergence of hypoxia preconditioning and bioactive scaffolding represents a promising dual-conditioning paradigm for osteochondral interface restoration.

Periodontal and dental applications

The convergence of hypoxia preconditioning and bioactive scaffolding represents a promising dual-conditioning paradigm for osteochondral interface restoration [4]. Osteoinductive EVs embedded in adhesive hydrogels achieved a 2.23-fold increase in BMP2 expression, enhanced tissue mineralization, and stimulated neovascularization in bone defect models [89]. In alveolar bone defect repair, DPSC-EVs activate the TGFβ1/Smad/MAPK pathway in Hertwig's epithelial root sheath (HERS) cells, and when delivered via EV-loaded hydrogels, substantially promoted bone regeneration in rat alveolar socket models [30]. Collectively, these periodontal and maxillofacial strategies indicate that DPSC-EVs can rival or complement standard growth factor therapies, with the added advantages of reduced immunogenicity and multi-factorial signaling. The integration of EV delivery with tissue-adhesive and ECM-mimicking biomaterials appears especially promising for precision regeneration in confined oral and craniofacial defects.

Immune-mediated bone disorders

Immune-mediated bone disorders encompass a spectrum of conditions, such as inflammatory bowel disease (IBD)-related bone loss, autoimmune arthritis, and rare syndromes like SAPHO, where immune dysregulation and skeletal remodeling are tightly interlinked. A growing body of evidence positions EVs as central modulators within this axis, capable of both amplifying pathology and driving repair, depending on their source, molecular cargo, and the immune status of the host.

Microbiota-immune-bone interactions

Bacterial EVs (BEVs) from the gut commensal *Bacteroides thetaiotaomicron* illustrate the bidirectional nature of microbiota–bone communication. These BEVs target dendritic cells, macrophages, and monocytes through Toll-like receptor (TLR) pathways, modulating myeloid differentiation and eliciting divergent responses in healthy versus ulcerative colitis (UC) states. BEV-induced NF-κB activation in monocytes depends strictly on TLR4 and TIRAP signaling, underscoring that microbiota-derived EV efficacy is contingent upon both cell type and disease context, and may be harnessed to recalibrate immune responses in IBD-associated bone damage [90].

Stem-cell-derived immunoregenerative EVs

BMSC-derived EVs and their soluble secretome provide a potent, cell-free avenue for autoimmune and inflammatory bone disorders, notably osteoarthritis (OA). Their cargo—encompassing VEGFA, CCL2, IDO, NO, TIMP1/2, and TGFB1—actively reprograms macrophages toward anti-inflammatory M2 phenotypes, suppresses pro-inflammatory T cells, and maintains ECM homeostasis. Incorporated miRNAs such as hsa-miR-24-3p and hsa-miR-222-3p directly inhibit OA-promoting mediators IL1B and MMPs, representing a multi-pronged attack against inflammation and tissue degeneration [91].

Engineered TIM3 high-expression EVs, designed to reshape early inflammatory microenvironments, extend this principle by enhancing M2 macrophage recruitment, boosting IL10 and TGFβ1 secretion, and activating BMP2 signaling for osseointegration. Sustained release from hydrogels ensured early-phase immune control, a crucial factor in preventing fibrosis and non-union [92].

Bioengineered scaffolds as immune-osteogenic niches

Functional osteogenic bacterial cellulose scaffolds (FOBS), fabricated via aldehyde–dopamine chemistry, integrate immune modulation with bone induction. By increasing hydroxyapatite deposition (+47.1%) and doubling M2 macrophage marker expression (ARG1, Dectin1), FOBS created a pro-regenerative immune milieu that significantly improved bone volume fraction in rat cranial defects [93]. Such "immune-smart" scaffolds exemplify a shift away from purely structural support toward dual-function platforms.

Rare syndromes and immunopathology

In SAPHO syndrome, serum EVs enriched in SAA1 and C-reactive protein emerged as potential biomarkers, while selectively inhibiting osteoclastogenesis during active disease phases—hinting at a temporal therapeutic window for EV interventions [94]. Conversely, EVs from diseased cells can propagate damage: osteoarthritic chondrocyte-derived EVs carrying connexin 43 spread cellular senescence via NFκB and ERK1/2 signaling, contributing to joint degeneration [95]. This duality underscores the necessity for source validation and functional screening in EV-based therapeutics.

Autoimmune arthritis and hybrid nanovesicles

In rheumatoid arthritis (RA), EVs from BMSCs containing miR-378a-5p or miR-34a reduced inflammatory burden via distinct pathways—cyclin I/ATM/ATR/p53 among them—preserving both joint and bone integrity [96, 97]. Conversely, synovial fibroblast-derived small EVs, enriched in miRNA15-29148, promoted chondrocyte apoptosis, revealing an endogenous EV-driven pathogenic route [98]. Innovative delivery formats, such as hybrid EV-mimicking nanovesicles combining M1 macrophage membranes with M2-like nanovesicles, offer targeted immunosuppression when coupled with black phosphorus nanosheets and activated by near-infrared irradiation. In collagen-induced arthritis models, this platform achieved spatiotemporal control over inflammation, a feature highly desirable for autoimmune bone diseases [99].

Collectively, these investigations paint EVs as versatile but double-edged agents in immune-mediated bone pathology. Therapeutic promise lies in precision engineering, disease-context adaptation, and integration with immune-responsive scaffolds or nanomaterials. Nonetheless, heterogeneity in EV bioactivity across patient

populations, the challenge of faithfully modeling human immunopathology, and the long-term consequences of immune modulation remain critical hurdles for clinical translation.

Future Perspectives and Emerging Trends

The trajectory of EV-based bone regeneration is pivoting toward precision medicine, where treatment regimens are tailored to the patient's genetic profile, disease context, and real-time biological responses. Advances in single-EV and single-cell analytic technologies now make it possible to dissect the heterogeneity of EV populations, identifying functional subgroups with superior osteoinductive, angiogenic, or immunomodulatory effectiveness. This resolution paves the way for patient-specific EV formulations, pre-characterized for biomolecular compatibility and projected therapeutic yield, reducing variability in clinical outcomes and overcoming resistance in poorly responsive cases.

Pharmacogenomic approaches are poised to play an equally transformative role. Variations in patient genotypes can affect EV uptake dynamics, intracellular trafficking routes, and the potency of downstream signaling. By incorporating genotype-guided protocols, clinicians could individualize dosing, refine delivery routes, and engineer EV cargo to match specific molecular deficits, thereby maximizing therapeutic efficacy while minimizing off-target activity.

Future EV engineering will likely transition from fixed, one-design vesicles to adaptive "smart" vehicles capable of real-time response to environmental cues within the bone defect microenvironment. Such systems may integrate biosensing materials that alter release kinetics in response to inflammatory mediators, hypoxic gradients, or biomechanical loading. Multi-targeting ligands—such as modular aptamers or peptides—could enable sequential interactions with multiple cellular populations involved in bone repair, while surface moieties engineered for pH or enzyme sensitivity may boost targeting specificity and therapeutic payload activation.

The next frontier will also be defined by rationally designed combination therapies. Gene therapy–EV hybrids could harness EVs as stealth carriers for genetic payloads, amplifying regenerative signaling through both delivered genes and intrinsic vesicle cargo. Immunomodulatory regimens could pair the antiinflammatory macrophage-polarizing effect of EVs with precision immune regulators to optimize early inflammatory phases of bone healing. In the biomaterials sphere, scaffold–EV composites are expected to evolve into programmable, multi-modal delivery platforms that coordinate EV release with growth factors, cytokines, or small molecules in temporally optimized sequences. Similarly, integration with stem cell or tissue engineering approaches could establish bidirectional support, where EVs prepare the host microenvironment for graft acceptance while transplanted cells replenish the EV pool. Targeted delivery of pharmacological bone-anabolic agents via EVs may also improve drug localization and reduce systemic exposure.

Such combination platforms introduce new layers of complexity, underscoring the need for systems biology and computational modeling to predict synergistic response windows, optimize co-therapy timing, and anticipate potential antagonistic interactions. These predictive frameworks should become part of preclinical development to reduce translational attrition and streamline the pathway toward regulatory approval.

As depicted in Figure 4, a structured translational roadmap for EV-based bone regeneration underscores the need for a stage-wise approach—from early-stage discovery and mechanistic validation, through optimization and scalable platform development, to regulatory-aligned preclinical studies and first-in-human trials. This pathway demands attention to scalable manufacturing that preserves EV bioactivity, standardized potency assays, reproducible delivery platforms, and rigorous safety and efficacy evaluation. Without coordinated progress across these domains, even the most compelling preclinical evidence may fail to achieve real-world clinical impact.

Conclusion

EV-based therapies are redefining strategies for bone regeneration by combining the multifactorial benefits of cell-derived signaling with the safety, scalability, and flexibility of acellular platforms. Acting through convergent osteogenic, angiogenic, and immunomodulatory pathways, these vesicles can be tailored via cell source selection, bioengineering, and advanced delivery systems to address diverse pathological contexts. While promising preclinical outcomes and innovative engineering approaches have propelled the field forward, reliable clinical translation will require standardized manufacturing, reproducible potency metrics, and integration of precision medicine principles. Future directions should focus on developing smart, adaptive EV systems and combination regimens that leverage multiple therapeutic modalities. With coordinated innovation and rigorous

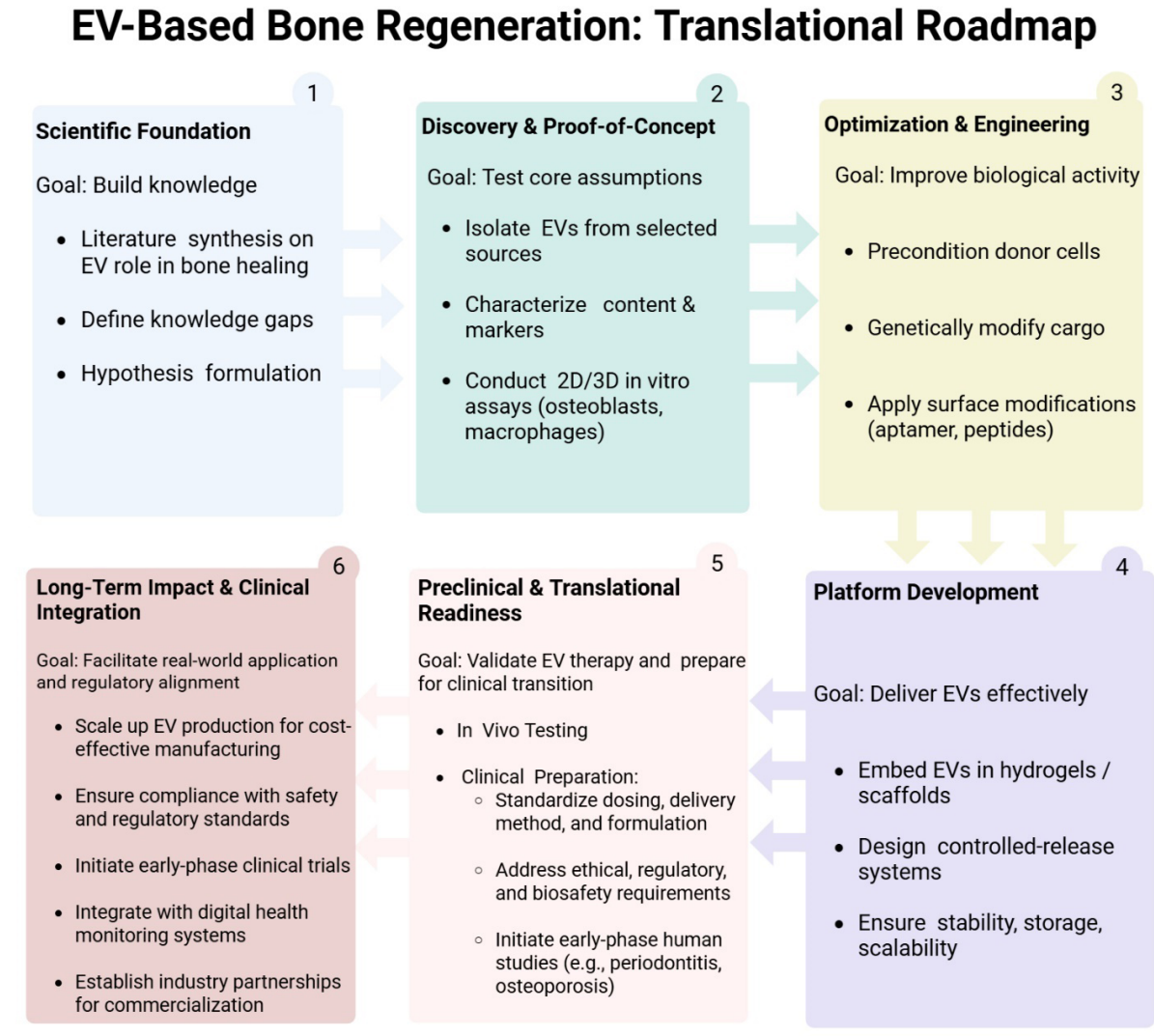

Figure 4. Comprehensive translational roadmap for EV-based bone regeneration, illustrating the sequential phases from scientific foundation to long-term clinical integration

validation, EV-based therapeutics have the potential to become a mainstay in regenerative orthopedics.

The pathway highlights core activities at each stage, including mechanistic discovery, optimization of EV bioactivity, platform development for scalable delivery, and preclinical validation, before advancing to regulatory-aligned clinical trials and widespread adoption. Arrows denote the iterative nature of refinement between stages, underscoring the need for feedback loops linking research, engineering, and clinical evidence to ensure robust, patient-tailored therapeutic strategies.

Ethical Considerations

Compliance with ethical guidelines

This article is a meta-analysis with no human or animal sample.

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Authors' contributions

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Conflict of interest

The authors declared no conflict of interest.

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