European Cells and Materials Vol.51 2025 (pages 83–102) DOI: 10.22203/eCM.v051a05 ISSN 1473-2262

Review

STEM CELL HOMING AS A PROMISING STRATEGY FOR BONE REGENERATION: FOCUS ON BIOMATERIALS

S.B. Liu[1], Y. Liu[1], Z.Z. Zheng[1], B.L. Li[1], J.J. Shao[1], X. Liu[1], E. Luo[1,*] and H.H. Liu[1,*]

[1]State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, 610041 Chengdu, Sichuan, China

Abstract

Bone regeneration, predominantly orchestrated via stem cell, holds significant implications for orthopedic and reconstructive surgery. Owing to the inherent limitations associated with stem cell transplantation and related modalities, the strategy of biomaterial-mediated endogenous stem cell homing has emerged as a promising alternative, which has garnered substantial interest from both the academic and clinical communities. This innovative approach employs chemokines and other molecular cues to direct the recruitment of endogenous stem cells to the site of bone defect, thereby promoting bone regeneration in a more physiologically relevant manner. Bone marrow is recognized as the primary niche and a major reservoir for a diverse array of stem cells. In this comprehensive review, we meticulously delineate the endogenous stem cell homing paradigm and describe the biological factors affecting stem cell homing. Moreover, we provide an in-depth analysis of the latest developments in functionally enriched biomaterials that are specifically designed to facilitate the homing, survival, and functional integration of stem cell at the site of bone injury.

Keywords: Stem cell homing, biomaterials, bone regeneration, bone tissue engineering, bioactive factors.

***Address for correspondence**: E. Luo, State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, 610041 Chengdu, Sichuan, China. Email: luoen521125@sina.com; H.H. Liu, State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, 610041 Chengdu, Sichuan, China. Email: hanghangliu_hx@foxmail.com.

Introduction

The skeletal system serves a dual function within the body, offering mechanical integrity and protection, and concurrently serves as a critical site for bone marrow residence and calcium homeostasis regulation [1,2]. In clinical scenarios, bone defects arise from a spectrum of pathological states, encompassing severe trauma, tumor resection, infectious processes, and osteoporosis [3]. The suboptimal repair of these defects can amplify the physical, psychological, and economic burdens faced by patients [4]. Autografts and allografts have been considered as the benchmark of treatment and demonstrated efficacy [5]. However, their limited donor availability, immunogenicity, and the additional surgical risks associated with the acquisition of donor material impede their broader clinical adoption [6–8]. In the last several years, bone tissue engineering has garnered heightened interest because of its distinctive benefits in the regeneration of bone lesions, devoid of consequential injury and the need for *ex vivo* cultivation [9–11]. Yet, the quest for a convenient and efficient utilization of tissue engineering to overcome the challenges of bone regeneration remains a significant challenge in both clinical and basic research domains.

Stem cells are a unique type of cell known for their ability to regenerate and differentiate into various cell types [12]. These cells play a crucial role in numerous biological processes, including development, tissue repair, and immune regulation [13,14]. Stem cell-based therapies have shown great promise in the field of regenerative medicine, providing new treatment options for a range of conditions where the body's natural ability to heal is compromised [15,16]. Stem cell transplantation within the traumatic zone has been previously applied to augment bone formation through direct injection. Tissue engineering has further seeded stem cells into biological scaffolds to mimic the micro-environment of bone rebuilding and achieve *in situ* regeneration [17,18]. Hydroxyapatite/polyacrylonitrile (HA/PAN) composite scaffolds showed excellent biocompatibility. Culture of bone marrow mesenchymal stem cells (BM-MSCs) on the three-dimensional (3D) HA/PAN com-

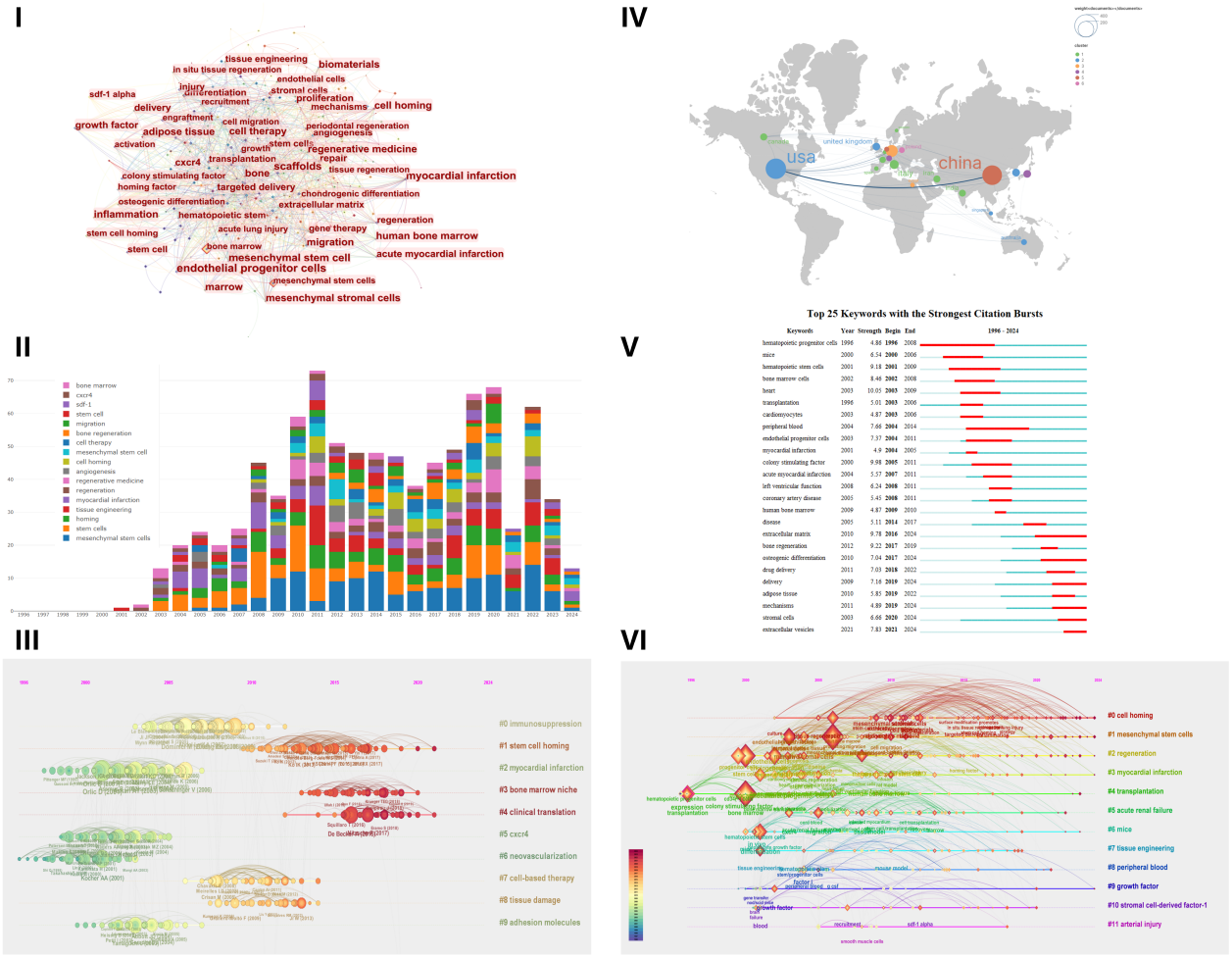

Fig. 1. Bibliometric analysis of relevant publications on stem cell homing and bone tissue engineering. The figure, visualized with CiteSpace, VOSviewer, and Scimago Graphica, captures the multifaceted aspects of the research terrain. (**I**) The keyword co-occurrence map visualizes the concurrent appearance of terms occurring at least 15 times, with font size indicating frequency. (**II**) A bar chart depicts the annual publication trends from 1996 to 2024. (**III**) Visualization of influential authors publishing articles associated with the selected keywords provides insight into the key contributors in the field. (**IV**) An international collaboration map highlights countries/regions with related publications. (**V**) The top 25 keywords with significant citation bursts are shown, marked by red bars indicating peak citation periods. (**VI**) A co-citation reference map with a timeline provides insights into the seminal works influencing this field. SDF-1, stromal cell-derived factor-1.

posite scaffolds has revealed enhanced cellular proliferation, increased osteogenic differentiation, and augmented mineralization capacity [19]. However, several challenges still exist in the transplantation process, such as difficulties in obtaining, storing, manipulating, immune rejection and uncontrolled cell growth [20]. Therefore, the strategy of activating the body's endogenous stem cells to substitute for cell transplantation has garnered considerable interest among researchers.

For these reasons, *in situ* tissue regeneration approaches reliant on endogenous stem cells homing have emerged. Stem cell homing describes the capability of mobilization and migration of endogenous cells within the body. Tissues and organs have the natural ability to regenerate due to the attraction and homing of host-derived stem cells [21–23]. Following bone injury, dormant stem cells are activated and transformed into specific cell types, secreting various biological factors (such as chemokines, cytokines, and enzymes) in order to maintain tissue balance and meet the body's repair needs [24]. Due to its reliance on the fine-tuned micro-regulation of the internal environment, the endogenous stem cell homing strategy independent of cell transplantation has increasingly captured public attention and garnered widespread interest [24,25]. Furthermore, the regenerative capability is impaired under pathological conditions such as aging [26], inflammation [27], osteoporosis [28] and diabetes [29]. A strategy dependent on endogenous stem cell homing may provide a

Table 1. Characterization and function of primary bone marrow-derived stem cells involved in cell homing.

Stem cells type	Definition	Functions in bone regeneration	Reference
Mesenchymal stem cells (MSCs)/ skeletal stem cells (SSCs)	CD73+/CD105+/CD90+/CD34–/CD45–; PDPN+/CD73+/CD164/CD146–	Self-renew/ differentiation/paracrine	[39,40]
Hematopoietic stem cells (HSCs)	Long-term HSCs (LT-HSCs): CD34+/CD38–/ CD90+/ CD45RA–; Short-term-HSCs (ST-HSCs): CD34+/CD38–/ CD90–/ CD45RA–	Self-renew/ differentiation/paracrine	[41]
Endothelial progenitor cells (EPCs)	Myeloid angiogenic cells (MACs): CD45+/CD14+/CD31+/VEGFR2+/CD146–/CD34–; Endothelial colony-forming cells (ECFCs): CD31+/CD146+/VEGFR2+/CD45–/CD14–	Self-renew/ differentiation/paracrine	[42]
Muse cell	SSEA3+/CD105+	Differentiation/paracrine	[43]
Myeloid progenitor cells (MPCs)	CD34+/CD33+	Paracrine	[44]
Very small embryonic-like stem cells (VSELs)	SSEA-4+/CD133+/CXCR4+/Lin–/CD45–	Differentiation	[45]

VEGFR2, vascular endothelial growth factor receptor 2; Muse, multilineage-differentiating stress-enduring.

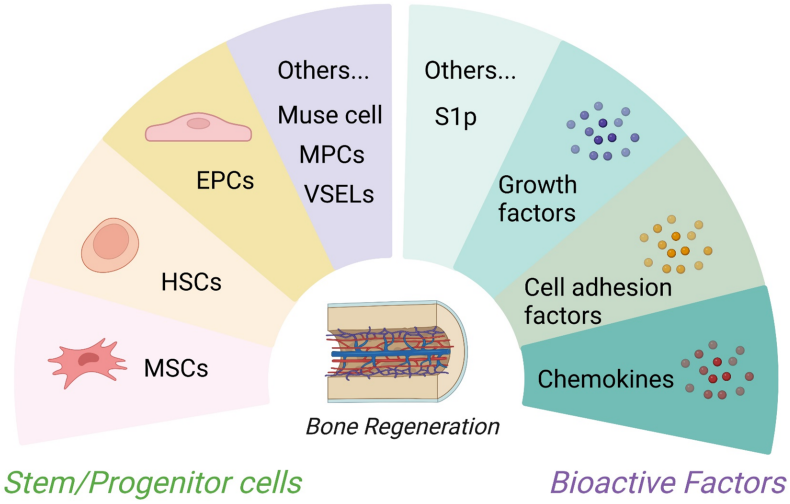

Fig. 2. The types of stem cells and factors implicated in the homing process within the bone microenvironment. MSCs, mesenchymal stem cells; HSCs, hematopoietic stem cells; EPCs, endothelial progenitor cells; S1P, sphingosine-1-phosphate; MPCs, myeloid progenitor cells; VSELs, very small embryonic-like stem cells.

promising method to fully harness the body's regenerative potential. As exported, biomaterials have become a critical asset in orchestrating the homing of stem cells and fostering the regeneration of bone tissue. Biomaterials not only facilitate cell homing and provide scaffold for the growth of nascent tissue but also integrate with chemokines and additional bioactive compounds [30–32], providing a promising option for the development of acellular scaffolds that can effectively recruit stem cells. In this comprehensive review, we provide an in-depth examination of the current research advancements in bone regeneration mediated by stem cell homing. We performed a comprehensive bibliometric analysis on the themes of stem cell homing and bone tissue regeneration, through the Web of Science Core Collection (WoSCC) database. An overlay visualization map of keyword co-occurrence was created, revealing hotspots such as "biomaterials" emerged (Fig. 1**I**). An increase in publication volumes of the field was also observed (Fig. 1**II**). The study reflects the enthusiastic participation of scholars from various institutions and countries in bone tissue engineer-

Table 2. Factors involved in stem cells homing.

Factors type	Composition	Function	Reference
Chemokines	Stromal cell-derived factor-1 (SDF-1), interleukin (IL)-8, monocyte chemotactic protein (MCP)-1, etc.	Mobilize and promote stem cell migration	[71–73]
Cell adhesion factors	Intercellular adhesion molecule (ICAM)-1, integrins, E-/L-selectin cadherins, etc.	Mediate cell-cell and cell-ECM adhesion	[74–77]
Growth factors	Vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), insulin-like growth factors (IGFs), bone morphogenetic proteins (BMPs), etc.	Promote the growth and differentiation of stem cells	[78–81]
Others	Sphingosine-1-phosphate (S1P), etc.	Promote stem cell migration and differentiation	[82]

ECM, extracellular matrix.

ing, with a focus on stem cell homing. This underscores the influence and pressing demand for advanced developments in this critical area (Fig. 1**III,IV**). A more detailed analysis of keywords experiencing citation bursts and co-cited references over the past five years highlights the growing prominence and significance of "cell homing" and "MSCs" in contemporary research advancements (Fig. 1**V,VI**).

Then we categorized the various types of bone marrow-derived stem cells that have been shown to contribute to bone repair, highlighting their distinct homing behaviors and regenerative potential within the scope of bone tissue engineering. Additionally, we delved into the factors that influence stem cell homing, discussed their importance in guiding stem cell migration and homing process (Fig. 2). Furthermore, we surveyed the latest developments in biomaterials that have been engineered to enhance stem cell homing to bone defects. This includes growth factors and cytokines carried by the materials, as well as the molecular mechanisms by which these biomaterials and their associated factors facilitate bone regeneration. Throughout the review, we emphasize the translational potential of these findings and highlight areas where further research is needed to optimize stem cell homing strategies for clinical applications in bone regeneration.

Bone Marrow-Derived Stem Cells Involved in Cell Homing

Stem cells are characterized by their multipotency and self-renewal capacity, which enables them to develop into a diverse spectrum of cellular lineages and ensures the continuous replenishment of their population [33]. They are widely found across diverse tissues, including bone, skin, adipose and other organs [34]. It is well recognized that bone constitutes an intricate amalgamation of various cell types, with stem cells playing a crucial role in preserving bone homeostasis. Stem cells reside in the bone marrow niche in a quiescent condition, within a microenvironment that sustains vital growth factors and extracellular matrix (ECM) for their survival and function [35]. Generally, they maintain a state of low proliferation and a semi-dormant condition. The engagement between the stromal cell-derived factor-1 (SDF-1)-CXCR4 axis and the very late antigen-4 (VLA-4) complex, along with its binding partner vascular adhesion molecule-1 (VCAM-1), underlies the occurrence of this particular phenomenon. However, when triggered by external stimuli (mechanical stress, injury cues), the stem cells are activated from repose, beginning to proliferate and migrate to locations where they exhibit the regenerative capabilities [36–38]. Initially, the structural integrity of the SDF-1 and CXCR4 complexes, as well as the VCAM-1 and VLA-4 proteins, is subject to degradation by various proteolytic enzymes, including metalloproteinases and cathepsin G, which are released by immune cells such as monocytes. Subsequently, an increase in vascular permeability triggers the mobilization of stem cells from the bone marrow into the peripheral circulation. The VLA-4 molecules on the surface of these stem cells then bind to VCAM-1 ligands expressed on endothelial cells, thereby facilitating their adhesion and subsequent transmigration across the vascular endothelial barrier. Ultimately, the homing stem cells successfully engraft at the site of injury and initiate differentiation into osteoblasts or chondrocytes, secreting bone matrix to foster the generation of new bone tissue [24]. A detailed illustration of this process is provided in Fig. 3.

In this overview, we discuss the main types of stem cells found in the bone marrow microenvironment, including mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs) and others. We also highlight the functional roles of these cell types in the homing process (Table 1, Ref. [39–45]).

Table 3. The effects of various physical properties on stem cell function.

Physical properties	Classification	Effects	Reference
Stiffness	Soft	Tend to provide a microenvironment for the adipogenic differentiation of stem cells	[102–104]
	Stiff	More conducive to stem cell adhesion and migration, with a greater tendency towards osteogenic differentiation	
Pore size	Micropores (less than 2 nm) Mesopores (between 2 to 50 nm) Macropores (larger than 50 nm)	The effects of different pore sizes on the migration and proliferation of various stem cells are not the same	[105]
Topography	Continuous	Affect the shape and orientation of cells	[111]
	Discontinuous	Regulate osteogenic capacity	[112]
	Random	Not conducive to the differentiation of stem cells	[110]
	Hierarchically patterned	Show great advantages in promoting cell adhesion and osteogenic differentiation	[113]
Surface charge	Positively Negatively Neutral charged	A positively charged surface is more favorable for cell adhesion, spreading, and migration	[107]

MSCs/Skeletal Stem Cells (SSCs)

MSCs represent a distinct subpopulation of spindle-shaped cells endowed with multipotent proliferative capacity and a fibroblastic phenotype. These cells were initially isolated from bone marrow and named "stromal cells" [46] and subsequently characterized in 1991 [47]. MSCs are capable of undergoing adipogenesis, chondrogenesis, and osteogenesis. They are earlier recognized to present specific surface markers, including CD73, CD105 and CD90, while lacking the expression of CD34 and CD45 [39]. In recent years, advanced lineage tracing techniques have delineated various subpopulations of bone MSCs *in vivo*, encompassing those that are positive for platelet-derived growth factor receptor (PDGFR)α, PDGFR-β, Prx1, Nestin, leptin receptor (LepR) and myxovirus resistance 1 (Mx-1) [48]. Moreover, these subpopulations may also vary due to different pathological conditions.

SSCs were identified and isolated as stem cells for the first time in 2015 [40]. They represent a more primitive origin compared to MSCs. SSCs are distinguished as a cohort of cells that are positive for PDPN, CD73, and CD164 and negative for CD146. They possess the ability to differentiate into early osteogenic, chondrogenic and stromal progenitors, followed by differentiating into bone, cartilage, and stromal cells. Furthermore, SSCs are able to respond to bone injury by local expansion, thereby contributing to bone repair and regeneration processes [49].

HSCs

HSCs constitute a pivotal component of bone marrow cellularity. The bone marrow microenvironment furnishes an ideal milieu for the sustenance and expansion of HSCs, exerting a critical effect on the functional manifestation and developmental trajectory of these cells [50]. The lifelong maintenance of functional hematopoiesis is guaranteed to depend on the self-renewal and pluripotent properties of HSCs [51]. Similar to MSCs, HSCs are not homogeneous but exist in varied forms. The immature, long-term HSCs (LT-HSCs) are specialized in self-renewal and sustaining the stem cell population, whereas short-term HSCs (ST-HSCs) have the capacity to develop into cells with multilineage potential [41]. The canonical surface markers utilized to define HSCs and their lineage-committed descendants are CD34, CD38, CD90, and CD45RA [41,52].

HSCs play a crucial role in regulating bone metabolism and the process of bone regeneration. The endosteal and perivascular niches within the bone marrow house a complex array of cellular components, which are essential for the proper functioning of HSCs [53]. These specialized cells guide HSCs by releasing cytokines such as angiopoietin-I (Ang-I), osteopontin (OPN), CXC-chemokine ligand 12 (CXCL12), and Ang-II, which are crucial for the homing and migration of HSCs [54–56]. HSCs can transition from a dormant to a proliferative state to regenerate the hematopoietic system and contribute to bone regeneration after injury [57].

EPCs

EPCs constitute a unipotent progenitor population distinguished by their self-renewal capacity, clonogenic potential, and differentiation ability [58,59]. Initially purified by Asahara *et al.* [60], these cells have been proposed to enhance the development of collateral blood vessels. Bone marrow serves as a bountiful source of EPCs.

Table 4. Bioactive factors-loaded biomaterials for bone regeneration via promoting stem cell homing.

Bioactive factors	Biomaterials	Targeting function	Animal models	Reference
SDF-1	Silk fibroin/broussonetia kazinoki composite scaffolds	MSCs migration, homing, osteogenesis and vascularization	Rats, calvaria defects	[114]
	PLGA 3D scaffolds	MSCs proliferation, osteogenesis	/	[115]
	PLEOF hydrogels	MSCs migration	/	[116]
	3D collagen scaffolds infiltrated with intrafibrillar silica	Osteogenesi, vascularization, MSCs homing	Mice, ectopic ossification	[117]
	Nanoparticles/hydrogels composites	Osteogenesi, cell homing	Rats, calvaria defects	[118]
	Hydroxyapatite/polyacrylonitrile composite scaffolds	Osteogenesi, cell homing	Mice, ectopic ossification	[119]
SDF-1 + BMP-7	Poly-epsilon-caprolactone /hydroxyapatite hybrid scaffolds	Osteogenesi, vascularization	Rats, mandibular incisor extraction	[120]
SDF-1 + antimiRNA-138	Chitosan/β-sodium glycerol phosphate	Osteogenesi, MSCs homing	Rats, calvaria defects	[121]
SDF-1 + dexamethasone	Encapsulated hydroxypropyl-β-cyclodextrin microspheres	Osteogenesi, vascularization, MSCs homing	Dogs, dorsal muscles dogs	[122]
VEGF	Chitosan/collagen sponge	Vascularization, osteogenesi, cell proliferation	Rats, femur defect/mice, calvaria defects	[123,124]
	Gelatin/alginate/β-TCP	Proliferation and adhesion	/	[125]
	PLGA scaffold	Vascularization, osteogenesis	Rats, calvarial defect	[126]
	Silk fibroin/CaP/PLGA	Vascularization, osteogenesis	Rabbits, calvarial defect	[127]
	PLGA spheres and fibrin	Angiogenesi, osteogenesis	Dogs, femoral neck defect	[128]
VEGF + BMP-2	PLGA/gelatin hydrogel complex	Angiogenesi, osteogenesis	Rats, ectopic ossification	[129]
	SiO_2–/HA-GelMA	Angiogenesi, osteogenesis and cell migration	Rats, cranial defect	[81]
BMP-2/7 heterodimeric complex	Collagen-hydroxyapatite scaffold	Angiogenesi, osteogenesis	Rats, femoral defect	[130]
BMP-2 + PDGF-BB	Fibronectin genetically engineered scaffold	Cell homing, osteogenesis	Rats, calvaria defects	[131]
BMP-2 + SDF-1	Acoustically responsive scaffold embedded into hydrogel	Host stem cells recruitment	Rats, femoral defect	[132]
RGD motifs	Gelatin sponge	MSCs homing	Mice, calvaria defects	[133]

Table 4. Continued.

Bioactive factors	Biomaterials	Targeting function	Animal models	Reference
Integrin $\alpha4\beta1$	Polymeric electrospun platforms	MSCs homing	/	[134]
Peptide	PCL electrospun meshes	MSCs adhesion, spreading, homing, survival	Rats, femoral defect	[135]
Aptamer	Nanoparticles	MSCs homing	Rats, femoral defect	[136]
SP + simvastatin	PCL/gelatin (PCL/GEL) co-electrospun membrane	MSCs homing	Rats, calvaria defect	[137]
MicroRNAs	Self-assembling peptide nanofiber hydrogel	Stem cell homing, suppress senescence	Rats, osteoarthritis	[138]

PLGA, poly (D, L-lactide-co-glycolide); PLEOF, poly (lactide ethylene oxide fumarate); RGD, arginine-glycine-aspartic acid; HA, hydroxyapatite; GelMA, gelatin methacryloyl; 3D, three-dimensional; PCL, polycaprolactone; SP, substance P; TCP, tricalcium phosphate.

As research advances incrementally, EPCs are categorized into two primary groups according to their origin from hematopoietic or endothelial lineages: myeloid angiogenic cells (MACs, CD45+/CD14+/CD31+/vascular endothelial growth factor receptor 2 (VEGFR2)+/CD146–/CD34–), and endothelial colony-forming cells (ECFCs, CD31+/CD146+/VEGFR2+/CD45–/CD14–) [42]. MACs lack the capacity to differentiate into endothelial cells but promote angiogenesis through secreted factors, whereas ECFCs primarily exert their function by differentiating into endothelial cells [61].

Bone is a highly vascularized tissue that relies on neovascularization with adequate blood supply for successful bone regeneration [62]. EPCs are indispensable contributors to bone vascularization, as they can be activated and directed to sites of injury to engage in the healing process [63]. These cells possess the ability to differentiate into endothelial cells and secrete cytokines that facilitate vascular formation. Furthermore, EPCs exert regulatory functions on other cells within the bone microenvironment. H-type endothelial cells, a subtype characterized in 2014, are coupled with osteoprogenitor cells and play a role in bone remodeling [64]. Additionally, EPCs secrete cytokines such as CXCL12, bone morphogenetic protein (BMP)-2, platelet-derived growth factor (PDGF)-BB, and others, which interact with MSCs, macrophages, and osteoclasts, influencing osteogenesis and osteoclastogenesis [65]. These mechanisms collectively underpin the establishment of an osteogenic-angiogenic coupling system.

Other Stem Cells

Beyond the well-characterized populations of MSCs, HSCs, and EPCs, bone marrow harbors a complement of less abundant stem cells that still contribute to tissue regeneration. Specifically, multilineage-differentiating stress-enduring (Muse) cells, a subset of MSCs with enhanced tolerance, exhibit pluripotent-like and macrophage-like characteristics [43]. These cells express pluripotency-associated genes such as *Nanog*, *Oct3/4*, and *Sox2* and migrate selectively to sites of injury by detecting sphingosine-1-phosphate (S1P) released from damaged or apoptotic cells [66–68]. Upon arrival, Muse cells engulf compromised cells. In essence, Muse cells participate in tissue repair through rapid and selective homing to damaged sites, replacement of cells through differentiation, and the exertion of bystander effects. Additionally, myeloid progenitor cells (MPCs) are integral to bone regeneration, particularly during the inflammatory and repair stages [44]. MPCs contribute to immune regulation, osteogenesis, and angiogenesis. Furthermore, bone marrow has been found to contain very small embryonic-like stem cells (VSELs) [45], which are rare, early developmental cells capable of crossing germlines upon activation.

Factors and Potential Mechanisms for Achieving Efficient Homing of Stem Cells

The bone marrow microenvironment, characterized by an intricate network of surrounding tissues, cells, and the multitude of factors they secrete, collectively serves as a nurturing "cradle" that safeguards the cells within. Among these, signaling factors are crucial for preserving the equilibrium of the bone marrow's microenvironment [69,70]. Upon bone injury, a plethora of different factors are locally expressed. These diverse signals alter the original tissue microenvironment, subsequently initiating the stem cell homing effect. In this part, we offer a synopsis of the primary signaling factors that influence stem cell homing, including chemokines, growth factors, adhesion molecules, and other signal molecules (Table 2, Ref. [71–82]). It is essential to acknowledge that these factors function interactively rather

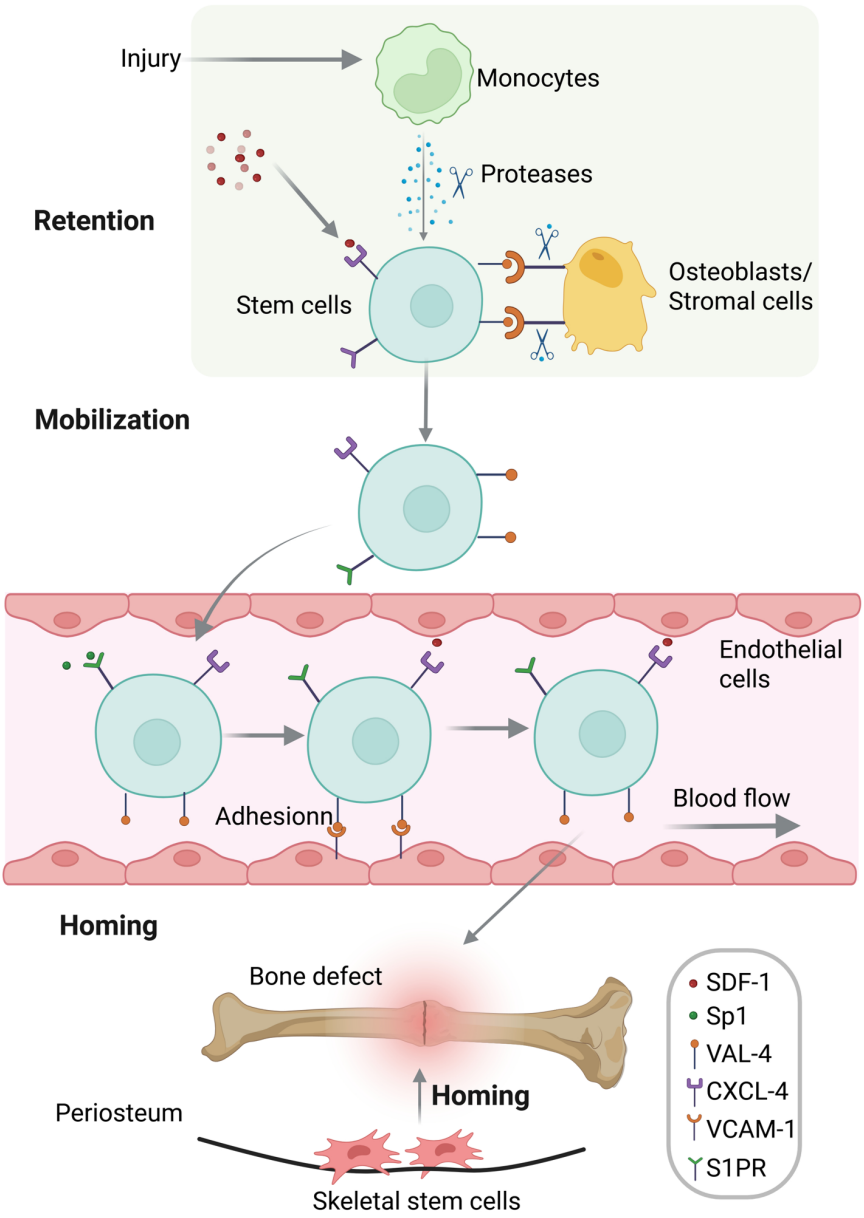

Fig. 3. Stem cell homing in bone regeneration. SP, substance P; CXCL-4, CXC-chemokine ligand 4; S1PR, S1P receptor; VCAM-1, vascular adhesion molecule-1.

than independently, engaging in a dialogue of mutual regulation and collectively contributing to the homing of stem cells.

Chemokines

Chemokines comprise a group of small cytokines or signaling proteins that are released by cells. The molecules are tissue-specific, with each tissue emitting unique chemokines to establish concentration gradients [83]. The gradients act as attractants for cells with chemokine receptors, guiding them towards their original tissue. SDF-1, also known as CXCL12, is a key chemokine that plays a significant role in directing the migration and homing of stem cells [84]. SDF-1 strongly binds to CXCR4 receptors which are commonly found in various stem cell populations such as MSCs, HSCs, and EPCs [71,85]. The SDF-1/CXCR4 pathway is involved in triggering a cascade of downstream signals, including the PI3K/AKT or Rac/Rho signaling pathway, thereby promoting the mobilization of stem cells [86,87]. As a result, the processes of stem cell expansion, migration, bone formation, and blood vessel growth were enhanced to improve bone healing. Activation of CXCR4 has been shown to accelerate the bone repair and mineralization processes [88]. Additionally, interleukin (IL)-8, and monocyte chemotactic protein (MCP)-1 have been shown to promote the multiplication and homing of stem cells during bone regeneration [72,73].

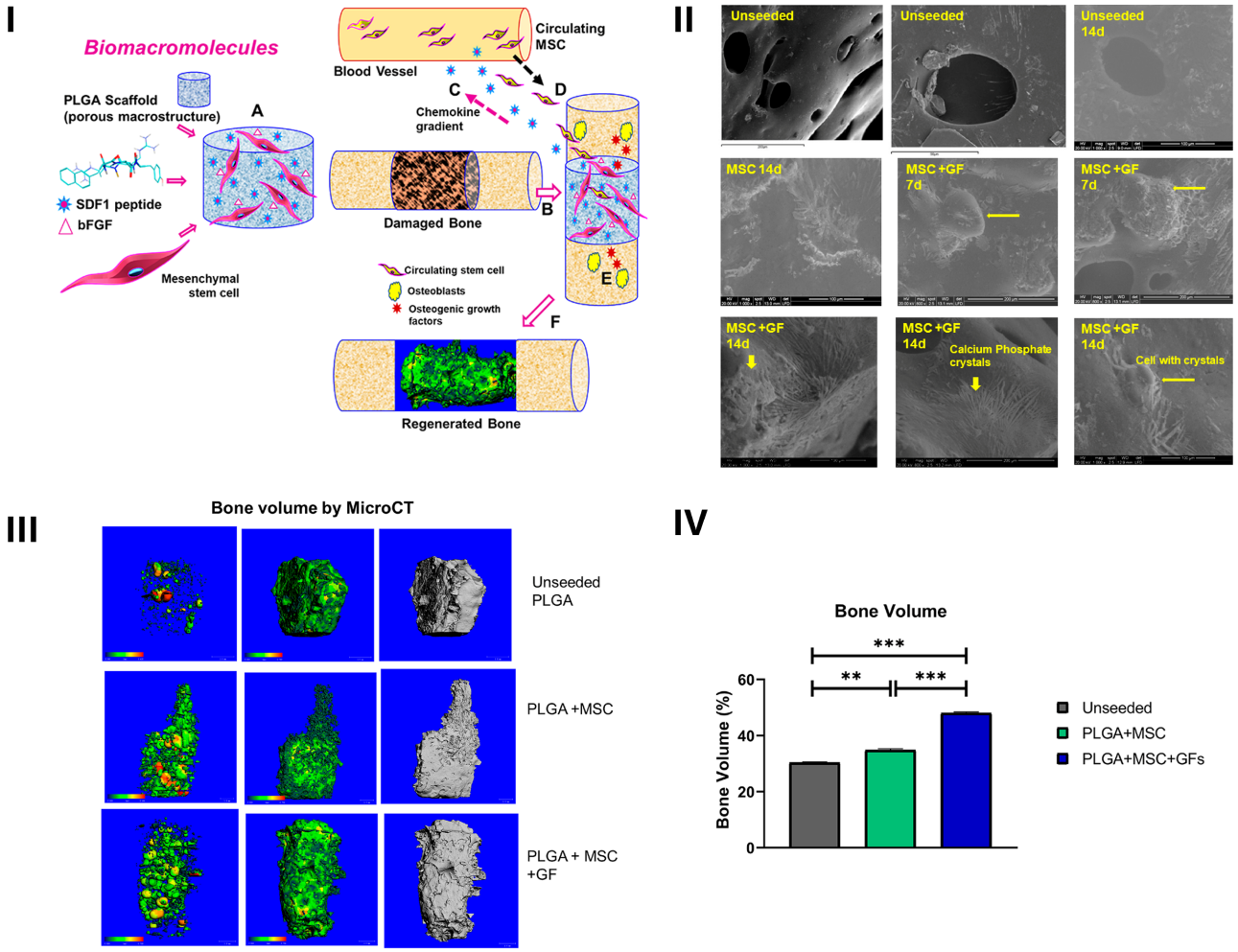

Fig. 4. SDF-1 mediated bone regeneration using biodegradable PLGA 3D scaffolds and BM-MSCs. (**I**) The diagram of the strategy. (**II**) Analysis of cell adhesion, growth, morphology, and mineralization in construct cultures by environmental scanning electron microscopy. For Fig. 4(**II**), scale bars = 200 μm, 50 μm, 100 μm, 100 μm, 200 μm, 200 μm,100 μm, 200 μm, 100 μm, following left-to-right and top-to-bottom sequence. (**III,IV**) Bone volume evaluation by MicroCT analysis of PLGA constructs. Data are presented as means ± SD. Statistical analysis was performed using Student's *t*-test. $^{**}p < 0.01$ and $^{***}p < 0.001$. Figures reproduced with permission from [115] Copyright 2020, American Chemical society. PLGA, poly (D, L-lactide-co-glycolide); 3D, three-dimensional; bFGF, basic-fibroblast growth factor; GF, growth factor; MicroCT, Micro computed tomography; BM-MSCs, bone marrow mesenchymal stem cells.

Cell Adhesion Factors

Cell adhesion molecules (CAMs) include a multifaceted array of proteins that encourage vital interactions between cells and ECM. These molecular mediators are instrumental in the significant forms of connection, movement, and differentiation of stem cells during their homing stage. CAMs include members of the immunoglobulin superfamily individuals, integrins, selectins, and cadherins. Intercellular adhesion molecule (ICAM)-1 acts as a ligand that can bind to leukocyte function-associated antigen-1 (LFA-1) and is a type of transmembrane glycoprotein with a single polypeptide chain expressed on the cell surface [74]. The engagement of ICAM-1 with LFA-1 is connected to cell homing [89]. As HSCs are mobilized from the bone marrow by granulocyte-colony-stimulating factor (G-CSF), neutrophil elastase and cathepsin G can cleave the VCAM-1 molecules shown on stromal cell surfaces [90]. This cleavage decreases the attachment of stromal cells to HSCs, thereby enhancing the migration of stem cells. Integrins are heterodimers composed of α and β subunits, with multiple subtypes available [75]. Integrin signaling transcriptionally regulates SDF-1α expression, thereby affecting the homing of HSCs. Integrin $\alpha4\beta1$ plays pivotal roles in regulating MSCs homing, adhesion, migration, and differentiation [91,92]. E-/L-selectin, both belonging to the selectin family and expressed on the surface of endothelial cells, is capable of binding to specific ligands on the surface of stem cells [76]. This interaction facilitates the migration of stem cells to targeted locations. Similar to the above ad-

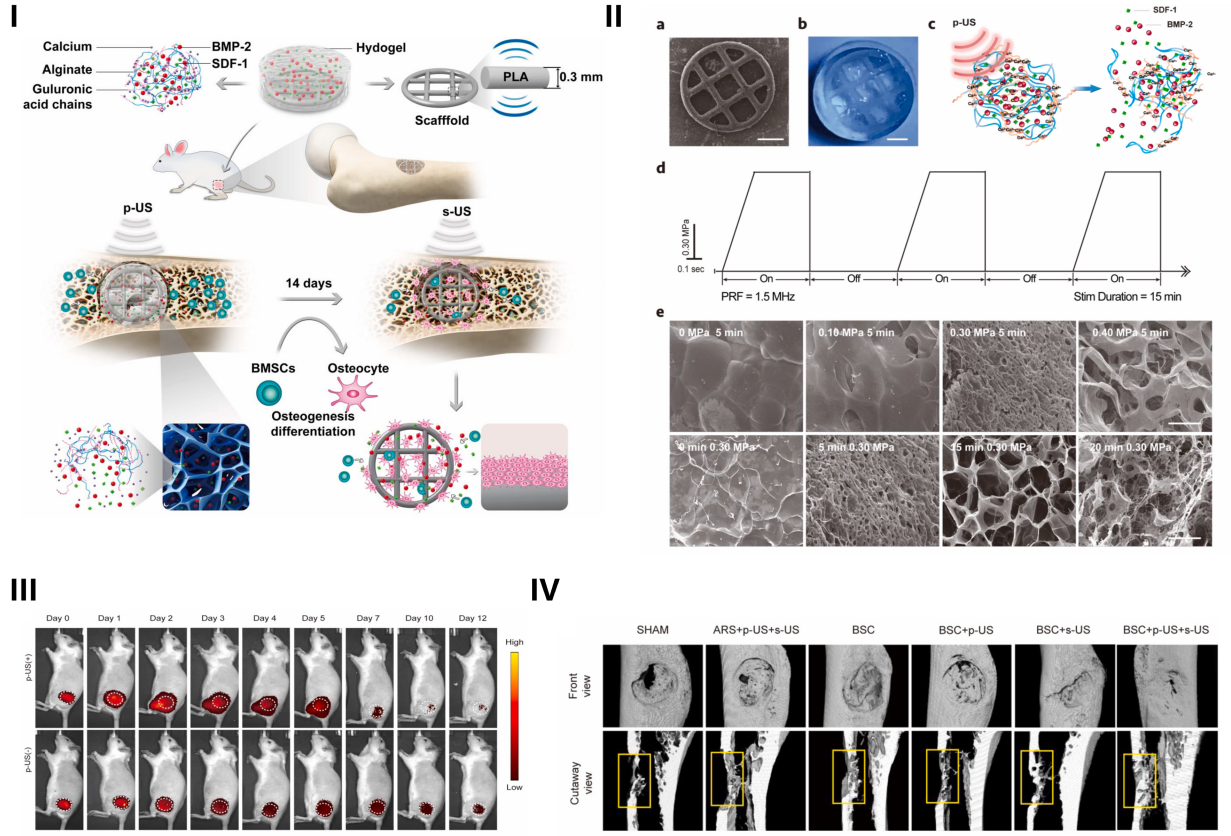

Fig. 5. Control of the recruitment and capture of endogenous stem cells for bone defects repair utilizing ultrasound-dependent biomimetic hydrogel scaffold complexes loaded with SDF-1 and BMP-2. (**I**) Schematic design of BSC-mediated endogenous BMMSCs repairing bone defects using US. (**II**) Acoustically-controlled chemokine release from BSC. For Fig. 5(**II**)a, scale bar = 1 mm; for Fig. 5(**II**)b, scale bar = 1 mm; for Fig. 5(**II**)e, scale bar = 100 μm. (**III**) *In vivo* fluorescence images of rats treated with or without daily 20-min p-US irradiation for 12 days, revealing gradually increased fluorescent areas in the rats that received with p-US irradiation from day 0 to day 5 and indicating the accelerated degradation of alginate hydrogel in rats that received with p-US irradiation. (**IV**) Representative μCT 3D reconstructed images (top row) and sagittal images (bottom row) of femoral defects in rats received with different treatment groups. Figures reproduced with permission from [132] Copyright under a Creative Commons license. BMP, bone morphogenetic protein; PLA, polylactic acids; p-US, pulsed ultrasound; s-US, sinusoidal continuous wave ultrasound; PRF, pulse repetition frequency; ARS, acoustically responsive scaffold; BSC, biomimetic hydrogel scaffold complexes.

hesion factors, cadherins affect stem cell homing by connecting with cytoskeletal proteins, affecting the stem cell's ability to survive and self-renew [77].

Growth Factors

In addition to the aforementioned two primary categories of signaling molecules, growth factors are instrumental in directing the migration and promoting the regenerative potential of stem cells within the bone matrix. This collection of factors includes a diverse array of molecules such as vascular endothelial growth factor (VEGF) [78], PDGF [79], fibroblast growth factors (FGFs) [93], insulin-like growth factors (IGFs) [80], and BMPs [81]. VEGF can stimulate the expression of cell adhesion molecules on endothelial cells, thereby enhancing the adhesion between stem cells and endothelial cells [94]. In addition, VEGF has the ability to promote the migration of stem cells and regulate the formation of new blood vessels. The reported components of PDGFs are intervened through the actuation of the PI3K/AKT signaling cascades, which coordinate cytoskeletal remodeling, in this way cultivating stem cell movement and reasonability [95,96]. In addition, VEGF and BMPs can actuate the expression of qualities that protect the stem cell properties and help in their homing and differentiation [81].

Other Factors

With the enhancement of our understanding of the homing behavior of stem cells, a plethora of regulatory factors have been successively identified. Sphingosine-1-phosphate (S1P), which is expressed in both MSCs and HSCs, has been demonstrated to promote stem cell homing and differentiation through the stimulation of S1P receptor 3 (S1PR3) and S1PR1 [82].

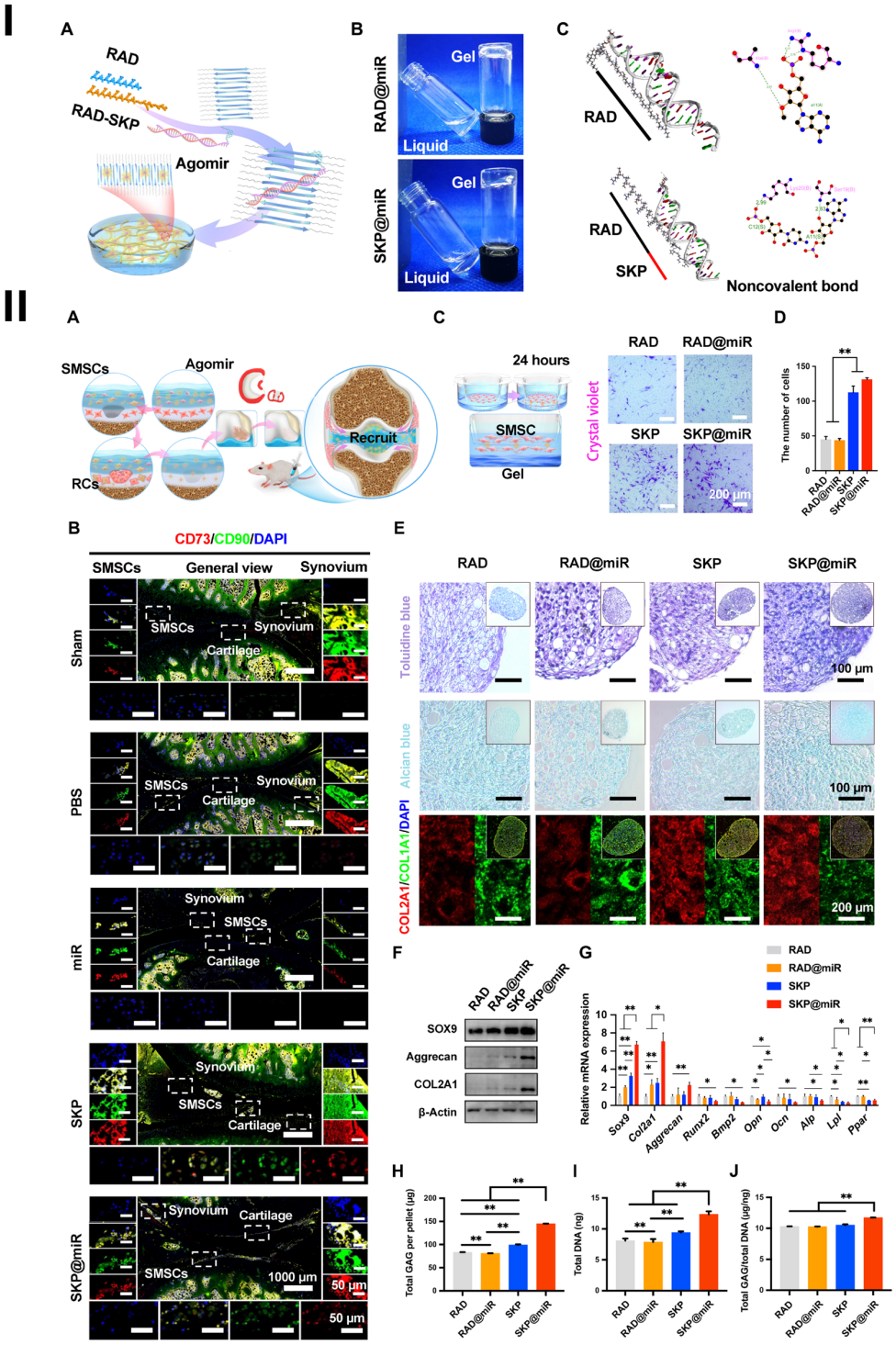

Fig. 6. Stem cell-homing hydrogel-based miR-29b-5p delivery promotes cartilage regeneration. (**I**) Schematic illustration of SKP@miR. RAD and SKP peptides self-assemble to form a nanofiber hydrogel with agomir-29b-5p distributed inside. (**II**) The miR-29b-5p delivery system induces synovial stem cell recruitment and promotes chondrogenic differentiation. For Fig. 6(**II**)B, scale bar = 1000 μm and 50 μm, respectively; for Fig. 6(**II**)C, scale bar = 200 μm; for Fig. 6(**II**)E, scale bar = 100 μm, 100 μm and 200 μm, from top to bottom. Data are presented as means ± SD. Statistical analysis was performed using one-way ANOVA. *$p < 0.05$ and **$p < 0.01$. Figures reproduced with permission from [138] Copyright under the terms of the Creative Commons Attribution-NonCommercial license. ANOVA, one-way analysis of variance; RAD, self-assembling peptide (Ac-(RADA)$_4$-NH$_2$); SKP, stem cell–homing sequence SKPPGTSS; sMSC, synovium-derived mesenchymal stem cells; RCs, rat chondrocytes; DAPI, 4′,6-diamidino-2-phenylindole; PBS, phosphate-buffered saline; GAG, glycosaminoglycan.

Table 5. Summary of bioactive factor release strategies.

Strategies	Method	Rates/durations	Advantages	Disadvantage	Representative examples	Reference
Physical encapsulation	Single scaffold	Slow release/ duration varies (3–5 weeks)	Simple preparation process; improved sequestration and effective delivery	Low release efficiency and single functionality; difficult dose control	BMP-2/7-loaded collagen-hydroxyapatite scaffold; SDF-1-loaded silk-collagen sponge scaffold	[130,139]
	Composite delivery system	Slowly,15 d–nearly several weeks	Controlled release with sequential release of different factors.	Complex preparation process with unstable release rate;	Silk fibroin/broussonetia kazinoki composite scaffolds; Microsphere coating-decorated HA scaffolds; BMP-2/SDF-1-loaded acoustically responsive scaffold embedded into hydrogel	[114,122] [132]
Chemical crosslinking	Receptor-ligand binding	/	High stability *in vivo*; specific binding capability	*In vivo* feasibility still needs to be explored; low dose of growth factors	LLP2A-modified electrospun scaffolds; polycaprolactone electrospun mesh conjugated with an MSC affinity peptide	[133,134]
	Self-assembled nanoparticles	Slowly/40 d	Non-invasive; higher feasibility; limited synthesis cost; no batch-to-batch variability; MSCs specificity	Unclear pharmacokinetics; frequent injections	Aptamer-functionalized nanoparticles; microRNA-loaded peptide nanofiber hydrogel	[136,138]

Biomaterial-Guided Stem Cell Homing in Bone Regeneration

Over the course of the past several decades, significant advancements have been made in the field of bone tissue engineering. This innovative technique aims to repair or regenerate bone tissue with the aid of biofunctional materials that possess distinctive physicochemical and mechanical properties. To date, a plethora of biomaterials have been utilized bone tissue engineering dependent on their capacity for osteoconductivity, osteoinductivity, and immune regulation. Researchers have reviewed and summarized a diverse array of biomaterials and advanced techniques for bone therapy and regeneration, including ceramics, polymers, metals, layered double hydroxides, and composites [97]. As a fundamental part of the bone regeneration process, fostering the attraction of endogenous stem and progenitor cells to injured tissues is a critical component in the development of innovative tissue engineering approaches. In this section, we outline the current biomaterial-driven strategies that have been suggested to govern the homing of host stem cells.

Biomaterials in Stem Cell Homing

A diverse array of biomaterials has been developed and investigated to guide stem cell homing, including porous/nanofiber scaffolds, coating materials, magnetic nanoparticles, thermo/light-responsive materials, and framework nucleic acids. Chitosan-based hybrid scaffolds, in particular, have shown promise in the restoration of damaged bone and cartilage tissue, owing to their favorable osteoconductivity, porosity, and appropriately distributed pore sizes, as well as their capacity to attract stem cells [98]. Iron oxide nanoparticles have been demonstrated to enhance MSCs proliferation and migration and VEGF secretion, thereby improving homing and anti-inflammatory properties [99]. MSCs have been observed to migrate from the bone marrow to a non-osseous bioceramic implant via the bloodstream, leading to the development of ectopic bone in a canine model [100]. An electrospun poly(3-hydroxybutyrate-co-4-hydroxybutyrate)/graphene oxide nanofibrous scaffold has been developed with a straightforward fabrication process, a desirable porous structure, enhanced stem cell homing properties, and rapid osteogenic potential [101]. Furthermore, calcium phosphate has been found to enhance MSC homing by activating the immune system to secrete chemokines (CCL2, CXCL10,16, etc.) through the ERK signaling pathway [73].

The physical properties of biomaterials, such as stiffness, are recognized as influential factors in regulating stem

cell homing due to their impact on cell adhesion. The impact of culture substrate stiffness on stem cell recruitment, proliferation, and differentiation is varied, and no unified standards have yet been established [30]. Generically, cells seeded on a substrate with a gradient of stiffness exhibited a tendency to migrate from the soft to the stiffer side. Moreover, cells generate a larger force in stiffer surfaces at the focal adhesion and osteogenesis is advanced [102]. Therefore, rigid materials such as alginate, polycaprolactone (PCL), polylactic acid, and polydimethylsiloxane are more appropriate for cartilage and bone tissue engineering applications than softer materials like hydrogels [103,104]. Pore size is one of the important physical characteristics of biomaterials. According to the internal width, pores can be classified into micropores (less than 2 nm), mesopores (between 2 to 50 nm) and macropores (larger than 50 nm) [105]. Size approximately equivalent to or marginally larger than the average cell diameter has been demonstrated to facilitate initial cellular adherence, establishing a conducive substratum for subsequent cellular migration and proliferation. Scaffolds with smaller pores offered enhanced structural support and initial cellular adhesion but imposed constraints on cellular proliferation. In contrast, larger pore sizes accommodate sufficient space for cellular migration and intercellular communication, albeit with a trade-off of reduced mechanical integrity [106]. Certainly, the porosity requirements for different stem cells to perform their respective physiological functions vary. It is essential to select the appropriate pore size tailored to the specific needs of each cell type. Surface charge also plays an important role in stem cell function. Typically, nanoparticles with positively charged surfaces tend to adsorb negatively charged cell surface molecules, thereby promoting cell attachment and adhesion [107]. In recent years, the roles of topography have also gained significant attention, with evidence emphasizing their profound effects on stem cell adhesion, migration, and differentiation [108]. This conceptual framework is informed by the exemplary role of the ECM in cell biology, which provides a three-dimensional space for stem cells to engage in physical and chemical signaling essential for their functions [109]. Consequently, the topological structure of biological scaffolds is indispensable for the modulation of stem cell homing. Surface topography can be categorized as continuous, discontinuous, random, and hierarchically patterned surfaces. Manufacturing techniques such as electrospinning, 3D printing, and soft lithography are used [110]. Stem cells recognize topographical cues by forming lamellipodia, filopodia, and changing membrane curvature, leading to downstream signaling transmission [110]. Biomaterials designed with the intricate topography of the ECM are increasingly being utilized to enhance stem cell homing. Here, we summarize the effects of various physical properties on stem cell function as shown in Table 3 (Ref. [102–105,107,110–113]).

Application of Bioactive Factors

Modulating the physical and biological attributes of biomaterials aids in regulating the sequential processes underlying bone regeneration. Various delivery scaffolds have been explored and designed to achieve local release of bioactive factors based on natural and synthetic polymers for stem cell homing (Table 4, Ref. [81,114–138]).

SDF-1, as a primary chemokine for stem cell homing, has been the subject of extensive research aimed at the design of biomaterials capable of delivering it to target sites. The SDF-1-loaded silk fibroin/broussonetia kazinoki composite scaffolds has demonstrated a sustained, controlled release profile, effectively stimulating MSC migration, homing and vascularization, thereby exhibiting robust bone regeneration potential in bone defects [114]. Similarly, positive outcomes have been observed with SDF-1 encapsulated within various biomaterials, including biodegradable poly (D, L-lactide-co-glycolide) (PLGA) 3D scaffolds [115] (Fig. 4), poly (lactide ethylene oxide fumarate) (PLEOF) hydrogels [116], knitted silk-collagen sponge scaffolds [139], 3D collagen scaffolds infiltrated with intrafibrillar silica [117], nanoparticles/hydrogels composites [118], and hydroxyapatite/polyacrylonitrile composite scaffolds [119]. Furthermore, the combined application of SDF-1 with other factors or drugs has been explored. For instance, SDF-1 and BMP-7 were incorporated into a scaffold composed of a poly-epsilon-caprolactone and hydroxyapatite hybrid, which includes interconnected microchannels with a diameter of 200 micrometers, to facilitate stem cell migration and enhance their homing capacity [120]. Additionally, the integration of SDF-1 into chitosan/tripolyphosphate/hyaluronic acid/antimiRNA-138 nanoparticle-modified chitosan/β-sodium glycerol phosphate hydrogel has demonstrated potential in facilitating the regeneration of critical-size calvaria bone defects by enhancing MSCs homing and promoting osteogenic differentiation [121]. Furthermore, *in vitro* culture experiments with dexamethasone-encapsulated hydroxypropyl-β-cyclodextrin microspheres coated with SDF-1 have revealed that the initial release of SDF-1 markedly enhances the migration of MSCs towards the inner regions of the scaffold [122].

VEGF and BMP-2 have been extensively studied and utilized in tissue engineering and regenerative medicine to promote angiogenesis and facilitate osteogenesis. As previously discussed, VEGF primarily participates in angiogenesis during bone repair and also exerts a substantial influence on MSCs and EPCs homing. Controlled release of VEGF has been achieved in various materials, including chitosan/collagen sponge [123,124], gelatin/alginate/β-tricalcium phosphate (TCP) [125], PLGA scaffold [126], silk fibroin/CaP/PLGA [127], PLGA spheres and fibrin [128], to advance stem cell homing. Similarly, BMP-2, a multifunctional growth factor belonging to the TGF-β superfamily, not only regulates osteogenic differentiation but

also mobilizes, captures, and adheres stem cells, promoting their homing and participating in the repair of bone tissue. The synergistic application of both VEGF and BMP-2 has been demonstrated to elicit the directed migration of MSCs and EPCs towards subcutaneously implanted silk scaffolds in nude mice and PLGA/gelatin hydrogel complex in rats [129]. The dual-factor strategy has led to a marked enhancement in neovascularization and osteogenesis when compared to either growth factor used in isolation. The controlled release of a BMP-2/7 heterodimeric complex through a collagen-hydroxyapatite scaffold has demonstrated enhanced osteo-inductive capabilities, a phenomenon attributed to its beneficial influence on the recruitment of progenitor cells to the site of implantation [130]. A recombinant fragment of fibronectin was genetically engineered to feature dual-binding domains, enabling specific affinity for both PDGF-BB and BMP-2, thereby creating a multifunctional molecular construct. Similar outcome was demonstrated in the combined application of BMP-2 and SDF-1 [132] (Fig. 5). The scaffold was evaluated in a rat model for its efficacy in bone repair, where it demonstrated enhanced recruitment of MSCs [131]. This demonstrates the potential of biomaterials to guide stem cell homing for improved bone regeneration and highlights the synergistic effects of growth factor combinations in tissue engineering applications.

Cellular adhesion plays a crucial role in facilitating stem cell recruitment. To tackle this issue, challenges have been identified and addressed by modifying biomaterial surfaces with specific biomolecules. The attachment of cell adhesive arginine-glycine-aspartic acid (RGD) motifs to gelatin sponge frameworks through enzymatic conjugation has been shown to attract MSCs and promote vigorous osteogenic differentiation. This phenomenon relies on the specific interactions between RGD and integrin receptors [133]. Moreover, modifying the surface of polymeric electrospun platforms with ligands for integrin $\alpha 4\beta 1$ has been found to improve MSCs attachment, spreading, and homing abilities [134]. A specific peptide sequence, known as E7, has been identified and successfully attached to PCL electrospun meshes, creating a platform that works as an efficient "MSC-homing device", improving the recruitment of MSCs [135]. Additionally, the application of aptamer coatings on biomaterial surfaces has demonstrated to be a promising approach to increasing the recruitment of stem cells. Aptamers, which are synthetic single-stranded DNA or RNA molecules, serve as versatile targeting ligands capable of binding to a variety of cell types. Research introduced a novel nanoparticle system functionalized with aptamers that has the potential to enhance stem cell recruitment and facilitate bone repair [136]. The effectiveness of this methodology was validated using an aptamer (Apt19s)-modified framework, created by incorporating a silk fibroin scaffold within a silk fibroin/hyaluronic acid-tyramine hydrogel framework [140].

Beyond the aforementioned factors, the integration of drugs, microRNAs (miRNAs), and exosomes (EXOs) within biomaterials has increasingly garnered the attention of researchers. Particularly, a progressively organized PCL/gelatin co-electrospun membrane was created, consolidating gelatin filaments stacked with substance P (SP) and polycaprolactone strands stacked with simvastatin [137]. This layer is designed to inspire a quick discharge of SP at the beginning, followed by a delayed, relentless discharge of simvastatin over a month. This process facilitates the mobilization of stem cells and promoting angiogenesis, while also stimulating persistent osteogenesis. MicroRNAs (miRNAs) are a category of short non-coding RNA species that play a significant part in the post-transcriptional regulation of gene expression. miRNAs function by binding to complementary regions within target messenger RNAs (mRNAs), resulting in either the inhibition of protein synthesis or the promotion of mRNA. In the context of stem cell homing, miRNAs play a crucial role in regulating key processes such as stem cell migration, proliferation, differentiation, and survival [141]. An injectable self-assembling peptide nanofiber hydrogel, enhanced with a stem cell recruitment peptide, was utilized to deliver agomir-29b-5p. This combination was intended to promote the recruitment of endogenous synovial stem cells to the infusion site [138] (Fig. 6). Furthermore, miRNA-delivery systems have been incorporated into hydrogel, collagen, hyaluronic acid, and PCL matrices [142]. Exosomes (EXOs) are endosome-derived extracellular vesicles that represent a diverse population of nanoscale particles (ranging from 30 to 150 nm) released by a variety of cell types [143]. They are irreplaceable in intercellular signaling, encouraging the exchange of genetic material, proteins, and lipids among cells. EXOs, named a "stellar" player in tissue engineering, are esteemed for their exceptional biocompatibility and versatile capabilities. The carrier biomaterials for exosomes incorporate nanohydrogels, little intestinal submucosa/bioactive glass, gelatin methacryloyl (GelMA) hydrogels, and others [144].

Additionally, this review summarizes various delivery and release strategies for biomaterials loaded with the above bioactive factors that target stem cell homing during bone regeneration. We also compare the differences among these strategies, as illustrated in the Table 5 (Ref. [114,122,130,132–134,136,138,139]).

Conclusions and Perspectives

Stimulating the homing of endogenous stem cells has become a cutting-edge approach for fostering bone regeneration within the field of contemporary bone tissue engineering. In this review, we delineate the stem cell populations within the bone marrow microenvironment, provide an overview of the factors influencing stem cell homing and compile the state-of-the-art in biomaterials and methodologies that harness this homing phenomenon to enhance bone regenerative processes. The insights gained

from these technologies offer critical foundational knowledge and have profound implications for the translation of stem cell-based therapies into clinical practice.

Within the domain of skeletal restoration, the progression of biomaterials demonstrates multifaceted advancements and dynamic trends. Presently, stem cell-based biomaterials have revolutionized the field of tissue regeneration. Significant research initiatives have focused on designing biomaterials possessing a wide array of biological and physical attributes, such as the creation of cellular niches with precisely tuned pore dimensions that prompt stem cells to transfer from an engineered microenvironment to a biological one. Furthermore, biomaterials engineered to improve stem cell recruitment through "bone immunomodulatory" functions are increasingly becoming the subject of research and innovation [145].

Despite the promising progress, challenges still remain. Initially, the development of biomaterials requires further refinement to enhance their mechanical properties in order to effectively support the recovery of weight-bearing bone. Materials must demonstrate excellent biocompatibility to prevent any abnormal inflammatory reactions or other negative effects, and their degradation rate should be carefully synchronized with the pace of bone regeneration to ensure long-term safety. Stem cell homing during bone regeneration is a complex biological process, and effectively controlling this process alongside bone repair presents a significant challenge. Moreover, pathologies such as senile osteoporosis may contribute to a significant lessening in both the amount and viability of stem cells, underscoring the need for proceeded examination into techniques to powerfully upgrade the enlistment and differentiation of senescent stem cells under pathological conditions. Finally, the transition from the knowledge gained in mouse models to its application in other animal species and, ultimately, to the treatment of human bone defects represents a significant and ongoing challenge that requires further research.

In summary, the approach of guiding stem cell homing with biomaterials harbors tremendous promise in the domain of bone regeneration, with more innovative biomaterials poised to become a cornerstone in the field of bone tissue engineering.

List of Abbreviations

HA/PAN, hydroxyapatite/polyacrylonitrile; BM-MSCs, bone marrow mesenchymal stem cells; ECM, extracellular matrix; VLA-4, very late antigen-4; VCAM-1, vascular adhesion molecule-1; PDGFR, platelet-derived growth factor receptor; LepR, leptin receptor; Mx-1, myxovirus resistance 1; SSCs, skeletal stem cells; HSCs, hematopoietic stem cells; EPCs, endothelial progenitor cells; LT-HSCs, long-term hematopoietic stem cells; ST-HSCs, short-term hematopoietic stem cells; BMP, bone morphogenetic protein; Ang-I, angiopoietin-I; OPN, osteopontin; CXCL12, CXC-chemokine ligand 12; MACs, myeloid angiogenic cells; ECFCs, endothelial colony-forming cells; MPCs, myeloid progenitor cells; VSELs, very small embryonic-like stem cells; SDF-1, stromal cell-derived factor-1; IL-8, interleukin-8; MCP, monocyte chemotactic protein; CAMs, cell adhesion molecules; ICAM, intercellular adhesion molecule; FGFs, fibroblast growth factors; IGFs, insulin-like growth factors; LFA-1, leukocyte function-associated antigen-1; G-CSF, granulocyte-colony-stimulating factor; S1P, sphingosine-1-phosphate; PLGA, poly (D, L-lactide-co-glycolide); PLEOF, poly (lactide ethylene oxide fumarate); RGD, arginine-glycine-aspartic acid; PCL, polycaprolactone; SP, substance P; WoSCC, Web of Science Core Collection; VEGFR2, vascular endothelial growth factor receptor 2; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; miRNAs, microRNAs; EXOs, exosomes; GelMA, gelatin methacryloyl; MSCs, mesenchymal stem cells; S1PR, S1P receptor; 3D, three-dimensional; Muse, multilineage-differentiating stress-enduring; bFGF, basic-fibroblast growth factor; GF, growth factor; MicroCT, Micro computed tomography; PLA, polylactic acids; p-US, pulsed ultrasound; s-US, sinusoidal continuous wave ultrasound; PRF, pulse repetition frequency; ARS, acoustically responsive scaffold; BSC, biomimetic hydrogel scaffold complexes; ANOVA, one-way analysis of variance; RAD, self-assembling peptide ($Ac\text{-}(RADA)_4\text{-}NH_2$); SKP, stem cell–homing sequence SKPPGTSS; sMSC, synovium-derived mesenchymal stem cells; RCs, rat chondrocytes; DAPI, 4′,6-diamidino-2-phenylindole; PBS, phosphate-buffered saline; GAG, glycosaminoglycan; TCP, tricalcium phosphate; mRNAs, messenger RNAs.

Availability of Data and Materials

Not Applicable.

Author Contributions

SBL contributed to the material preparation, data collection and analysis, manuscript-writing. YL and ZZZ contributed to the conceptualization and data collection. BLL and JJS contributed to the conceptualization and investigation. XL contributed to the investigation, methodology, and writing-review. EL and HHL contributed to the conceptualization, supervision, funding acquisition, writing-review and editing. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not Applicable.

Acknowledgments

The authors would like to thank Yinghui Wen (State Key Laboratory of Oral Diseases, West China Hospital of Stomatology, Sichuan University) for helpful advice.

Funding

The National Natural Science Foundation of China (82370932, 82401072); the Program of Science and Technology Department of Sichuan Province (2024YFFK0204); Natural Science Foundation of Sichuan Province (2023NSFSC1512, 2023NSFSC1517, 2024NSFSC1588), China Postdoctoral Science Foundation (2024M752269); and Special Funding of the Sichuan Province Postdoctoral Science Fund (TB2024082).

Conflict of Interest

The authors declare that they have no conflicts of interest with the contents of this article.

References

[1] Chen S, He T, Zhong Y, Chen M, Yao Q, Chen D, *et al*. Roles of focal adhesion proteins in skeleton and diseases. Acta Pharmaceutica Sinica. B. 2023; 13: 998–1013. https://doi.org/10.1016/j.apsb.2022.09.020.

[2] Saponaro F, Ferrisi R, Gado F, Polini B, Saba A, Manera C, *et al*. The Role of Cannabinoids in Bone Metabolism: A New Perspective for Bone Disorders. International Journal of Molecular Sciences. 2021; 22: 12374. https://doi.org/10.3390/ijms222212374.

[3] Ambrosi TH, Longaker MT, Chan CKF. A Revised Perspective of Skeletal Stem Cell Biology. Frontiers in Cell and Developmental Biology. 2019; 7: 189. https://doi.org/10.3389/fcell.2019.00189.

[4] Borgström F, Karlsson L, Ortsäter G, Norton N, Halbout P, Cooper C, *et al*. Fragility fractures in Europe: burden, management and opportunities. Archives of Osteoporosis. 2020; 15: 59. https://doi.org/10.1007/s11657-020-0706-y.

[5] Xue N, Ding X, Huang R, Jiang R, Huang H, Pan X, *et al*. Bone Tissue Engineering in the Treatment of Bone Defects. Pharmaceuticals. 2022; 15: 879. https://doi.org/10.3390/ph15070879.

[6] Baldwin P, Li DJ, Auston DA, Mir HS, Yoon RS, Koval KJ. Autograft, Allograft, and Bone Graft Substitutes: Clinical Evidence and Indications for Use in the Setting of Orthopaedic Trauma Surgery. Journal of Orthopaedic Trauma. 2019; 33: 203–213. https://doi.org/10.1097/BOT.0000000000001420.

[7] Schmidt AH. Autologous bone graft: Is it still the gold standard? Injury. 2021; 52: S18–S22. https://doi.org/10.1016/j.injury.2021.01.043.

[8] Xu ZJ, He RX. Selection of allografts for impaction bone grafting for bone defect reconstruction on the acetabular side. Chinese Medical Journal. 2010; 123: 3143–3147.

[9] Sivakumar PM, Yetisgin AA, Sahin SB, Demir E, Cetinel S. Bone tissue engineering: Anionic polysaccharides as promising scaffolds. Carbohydrate Polymers. 2022; 283: 119142. https://doi.org/10.1016/j.carbpol.2022.119142.

[10] Li JJ, Ebied M, Xu J, Zreiqat H. Current Approaches to Bone Tissue Engineering: The Interface between Biology and Engineering. Advanced Healthcare Materials. 2018; 7: e1701061. https://doi.org/10.1002/adhm.201701061.

[11] Roseti L, Parisi V, Petretta M, Cavallo C, Desando G, Bartolotti I, *et al*. Scaffolds for Bone Tissue Engineering: State of the art and new perspectives. Materials Science & Engineering. C, Materials for Biological Applications. 2017; 78: 1246–1262. https://doi.org/10.1016/j.msec.2017.05.017.

[12] Sarkar A, Saha S, Paul A, Maji A, Roy P, Maity TK. Understanding stem cells and its pivotal role in regenerative medicine. Life Sciences. 2021; 273: 119270. https://doi.org/10.1016/j.lfs.2021.119270.

[13] Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. Stem Cell Research & Therapy. 2019; 10: 68. https://doi.org/10.1186/s13287-019-1165-5.

[14] Krieger T, Simons BD. Dynamic stem cell heterogeneity. Development. 2015; 142: 1396–1406. https://doi.org/10.1242/dev.101063.

[15] Grayson WL, Bunnell BA, Martin E, Frazier T, Hung BP, Gimble JM. Stromal cells and stem cells in clinical bone regeneration. Nature Reviews. Endocrinology. 2015; 11: 140–150. https://doi.org/10.1038/nrendo.2014.234.

[16] Qin Y, Guan J, Zhang C. Mesenchymal stem cells: mechanisms and role in bone regeneration. Postgraduate Medical Journal. 2014; 90: 643–647. https://doi.org/10.1136/postgradmedj-2013-132387.

[17] Lin J, Shao J, Juan L, Yu W, Song X, Liu P, *et al*. Enhancing bone regeneration by combining mesenchymal stem cell sheets with β-TCP/COL-I scaffolds. Journal of Biomedical Materials Research. Part B, Applied Biomaterials. 2018; 106: 2037–2045. https://doi.org/10.1002/jbm.b.34003.

[18] Sun K, Lin H, Tang Y, Xiang S, Xue J, Yin W, *et al*. Injectable BMP-2 gene-activated scaffold for the repair of cranial bone defect in mice. Stem Cells Translational Medicine. 2020; 9: 1631–1642. https://doi.org/10.1002/sctm.19-0315.

[19] Wu S, Wang J, Zou L, Jin L, Wang Z, Li Y. A three-dimensional hydroxyapatite/polyacrylonitrile composite scaffold designed for bone tissue engineering. RSC Advances. 2018; 8: 1730–1736. https://doi.org/10.1039/c7ra12449j.

[20] Mason C, Dunnill P. A brief definition of regenerative medicine. Regenerative Medicine. 2008; 3: 1–5. https://doi.org/10.2217/17460751.3.1.1.

[21] Liesveld JL, Sharma N, Aljitawi OS. Stem cell homing: From physiology to therapeutics. Stem Cells. 2020; 38: 1241–1253. https://doi.org/10.1002/stem.3242.

[22] Yin Y, Li X, He XT, Wu RX, Sun HH, Chen FM. Leveraging Stem Cell Homing for Therapeutic Regeneration. Journal of Dental Research. 2017; 96: 601–609. https://doi.org/10.1177/0022034517706070.

[23] Sordi V. Mesenchymal stem cell homing capacity. Transplantation. 2009; 87: S42–S45. https://doi.org/10.1097/TP.0b013e3181a28533.

[24] Lin W, Xu L, Zwingenberger S, Gibon E, Goodman SB, Li G. Mesenchymal stem cells homing to improve bone healing. Journal of Orthopaedic Translation. 2017; 9: 19–27. https://doi.org/10.1016/j.jot.2017.03.002.

[25] Chen Y, Li Y, Lu F, Dong Z. Endogenous Bone Marrow-Derived Stem Cell Mobilization and Homing for *In Situ* Tissue Regeneration. Stem Cells. 2023; 41: 541–551. https://doi.org/10.1093/stmcls/sxad026.

[26] Kushioka J, Chow SK, Toya M, Tsubosaka M, Shen H, Gao Q, *et al*. Bone regeneration in inflammation with aging and cell-based immunomodulatory therapy. Inflammation and Regeneration. 2023; 43: 29. https://doi.org/10.1186/s41232-023-00279-1.

[27] Goodman SB, Pajarinen J, Yao Z, Lin T. Inflammation and Bone Repair: From Particle Disease to Tissue Regeneration. Frontiers in Bioengineering and Biotechnology. 2019; 7: 230. https://doi.org/10.3389/fbioe.2019.00230.

[28] Patel D, Wairkar S. Bone regeneration in osteoporosis: opportunities and challenges. Drug Delivery and Translational Research. 2023; 13: 419–432. https://doi.org/10.1007/s13346-022-01222-6.

[29] Cai F, Liu Y, Liu K, Zhao R, Chen W, Yusufu A, *et al*. Diabetes mellitus impairs bone regeneration and biomechanics. Journal of Orthopaedic Surgery and Research. 2023; 18: 169. https://doi.org/10.1186/s13018-023-03644-5.

[30] Dalir Abdolahinia E, Safari Z, Sadat Kachouei SS, Zabeti Jahromi R, Atashkar N, Karbalaeihasanesfahani A, *et al*. Cell homing strat-

egy as a promising approach to the vitality of pulp-dentin complexes in endodontic therapy: focus on potential biomaterials. Expert Opinion on Biological Therapy. 2022; 22: 1405–1416. https://doi.org/10.1080/14712598.2022.2142466.

[31] Herrmann M, Verrier S, Alini M. Strategies to Stimulate Mobilization and Homing of Endogenous Stem and Progenitor Cells for Bone Tissue Repair. Frontiers in Bioengineering and Biotechnology. 2015; 3: 79. https://doi.org/10.3389/fbioe.2015.00079.

[32] Chen FM, Wu LA, Zhang M, Zhang R, Sun HH. Homing of endogenous stem/progenitor cells for *in situ* tissue regeneration: Promises, strategies, and translational perspectives. Biomaterials. 2011; 32: 3189–3209. https://doi.org/10.1016/j.biomaterials.2010.12.032.

[33] Ding DC, Shyu WC, Lin SZ. Mesenchymal Stem Cells. Cell Transplantation. 2011; 20: 5–14. https://doi.org/10.3727/096368910X.

[34] Jo H, Brito S, Kwak BM, Park S, Lee MG, Bin BH. Applications of Mesenchymal Stem Cells in Skin Regeneration and Rejuvenation. International Journal of Molecular Sciences. 2021; 22: 2410. https://doi.org/10.3390/ijms22052410.

[35] Lewis EE, Wheadon H, Lewis N, Yang J, Mullin M, Hursthouse A, *et al*. A Quiescent, Regeneration-Responsive Tissue Engineered Mesenchymal Stem Cell Bone Marrow Niche Model via Magnetic Levitation. ACS Nano. 2016; 10: 8346–8354. https://doi.org/10.1021/acsnano.6b02841.

[36] Wei X, Yang X, Han ZP, Qu FF, Shao L, Shi YF. Mesenchymal stem cells: a new trend for cell therapy. Acta Pharmacologica Sinica. 2013; 34: 747–754. https://doi.org/10.1038/aps.2013.50.

[37] de Morree A, Rando TA. Regulation of adult stem cell quiescence and its functions in the maintenance of tissue integrity. Nature Reviews. Molecular Cell Biology. 2023; 24: 334–354. https://doi.org/10.1038/s41580-022-00568-6.

[38] Li L, Bhatia R. Stem cell quiescence. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2011; 17: 4936–4941. https://doi.org/10.1158/1078-0432.CCR-10-1499.

[39] Baker N, Boyette LB, Tuan RS. Characterization of bone marrow-derived mesenchymal stem cells in aging. Bone. 2015; 70: 37–47. https://doi.org/10.1016/j.bone.2014.10.014.

[40] Chan CKF, Seo EY, Chen JY, Lo D, McArdle A, Sinha R, *et al*. Identification and specification of the mouse skeletal stem cell. Cell. 2015; 160: 285–298. https://doi.org/10.1016/j.cell.2014.12.002.

[41] Oliveira CS, Carreira M, Correia CR, Mano JF. The Therapeutic Potential of Hematopoietic Stem Cells in Bone Regeneration. Tissue Engineering. Part B, Reviews. 2022; 28: 379–392. https://doi.org/10.1089/ten.TEB.2021.0019.

[42] Medina RJ, Barber CL, Sabatier F, Dignat-George F, Melero-Martin JM, Khosrotehrani K, *et al*. Endothelial Progenitors: A Consensus Statement on Nomenclature. Stem Cells Translational Medicine. 2017; 6: 1316–1320. https://doi.org/10.1002/sctm.16-0360.

[43] Wakao S, Oguma Y, Kushida Y, Kuroda Y, Tatsumi K, Dezawa M. Phagocytosing differentiated cell-fragments is a novel mechanism for controlling somatic stem cell differentiation within a short time frame. Cellular and Molecular Life Sciences: CMLS. 2022; 79: 542. https://doi.org/10.1007/s00018-022-04555-0.

[44] Molstad DHH, Zars E, Norton A, Mansky KC, Westendorf JJ, Bradley EW. Hdac3 deletion in myeloid progenitor cells enhances bone healing in females and limits osteoclast fusion via Pmepa1. Scientific Reports. 2020; 10: 21804. https://doi.org/10.1038/s41598-020-78364-5.

[45] Havens AM, Shiozawa Y, Jung Y, Sun H, Wang J, McGee S, *et al*. Human very small embryonic-like cells generate skeletal structures, *in vivo*. Stem Cells and Development. 2013; 22: 622–630. https://doi.org/10.1089/scd.2012.0327.

[46] Friedenstein AJ, Chailakhyan RK, Latsinik NV, Panasyuk AF, Keiliss-Borok IV. Stromal cells responsible for transferring the microenvironment of the hemopoietic tissues. Cloning *in vitro* and retransplantation *in vivo*. Transplantation. 1974; 17: 331–340. https://doi.org/10.1097/00007890-197404000-00001.

[47] Caplan AI. Mesenchymal stem cells. Journal of Orthopaedic Research: Official Publication of the Orthopaedic Research Society. 1991; 9: 641–650. https://doi.org/10.1002/jor.1100090504.

[48] Ning K, Yang B, Chen M, Man G, Liu S, Wang DE, *et al*. Functional Heterogeneity of Bone Marrow Mesenchymal Stem Cell Subpopulations in Physiology and Pathology. International Journal of Molecular Sciences. 2022; 23: 11928. https://doi.org/10.3390/ijms231911928.

[49] Feng H, Jiang B, Xing W, Sun J, Greenblatt MB, Zou W. Skeletal stem cells: origins, definitions, and functions in bone development and disease. Life Medicine. 2022; 1: 276–293. https://doi.org/10.1093/lifemedi/lnac048.

[50] Omatsu Y. Cellular niches for hematopoietic stem cells in bone marrow under normal and malignant conditions. Inflammation and Regeneration. 2023; 43: 15. https://doi.org/10.1186/s41232-023-00267-5.

[51] Kasbekar M, Mitchell CA, Proven MA, Passegué E. Hematopoietic stem cells through the ages: A lifetime of adaptation to organismal demands. Cell Stem Cell. 2023; 30: 1403–1420. https://doi.org/10.1016/j.stem.2023.09.013.

[52] Cimato TR, Furlage RL, Conway A, Wallace PK. Simultaneous measurement of human hematopoietic stem and progenitor cells in blood using multicolor flow cytometry. Cytometry. Part B, Clinical Cytometry. 2016; 90: 415–423. https://doi.org/10.1002/cyto.b.21354.

[53] Mendelson A, Frenette PS. Hematopoietic stem cell niche maintenance during homeostasis and regeneration. Nature Medicine. 2014; 20: 833–846. https://doi.org/10.1038/nm.3647.

[54] Kumar S, Geiger H. HSC Niche Biology and HSC Expansion *Ex Vivo*. Trends in Molecular Medicine. 2017; 23: 799–819. https://doi.org/10.1016/j.molmed.2017.07.003.

[55] Ellis SL, Nilsson SK. The location and cellular composition of the hemopoietic stem cell niche. Cytotherapy. 2012; 14: 135–143. https://doi.org/10.3109/14653249.2011.630729.

[56] Lawal RA, Calvi LM. The niche as a target for hematopoietic manipulation and regeneration. Tissue Engineering. Part B, Reviews. 2011; 17: 415–422. https://doi.org/10.1089/ten.TEB.2011.0197.

[57] Iaquinta MR, Mazzoni E, Bononi I, Rotondo JC, Mazziotta C, Montesi M, *et al.* Adult Stem Cells for Bone Regeneration and Repair. Frontiers in Cell and Developmental Biology. 2019; 7: 268. https://doi.org/10.3389/fcell.2019.00268.

[58] Li J, Ma Y, Miao XH, Guo JD, Li DW. Neovascularization and tissue regeneration by endothelial progenitor cells in ischemic stroke. Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2021; 42: 3585–3593. https://doi.org/10.1007/s10072-021-05428-3.

[59] Matsumoto T, Kuroda R, Mifune Y, Kawamoto A, Shoji T, Miwa M, *et al*. Circulating endothelial/skeletal progenitor cells for bone regeneration and healing. Bone. 2008; 43: 434–439. https://doi.org/10.1016/j.bone.2008.05.001.

[60] Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, *et al*. Isolation of putative progenitor endothelial cells for angiogenesis. Science. 1997; 275: 964–967. https://doi.org/10.1126/science.275.5302.964.

[61] Shi H, Zhao Z, Jiang W, Zhu P, Zhou N, Huang X. A Review Into the Insights of the Role of Endothelial Progenitor Cells on Bone Biology. Frontiers in Cell and Developmental Biology. 2022; 10: 878697. https://doi.org/10.3389/fcell.2022.878697.

[62] Lafage-Proust MH, Prisby R, Roche B, Vico L. Bone vascularization and remodeling. Joint Bone Spine. 2010; 77: 521–524. https://doi.org/10.1016/j.jbspin.2010.09.009.

[63] Liu H, Jiao Y, Zhou W, Bai S, Feng Z, Dong Y, *et al*. Endothelial progenitor cells improve the therapeutic effect of mesenchymal stem cell sheets on irradiated bone defect repair in a rat model. Journal of Translational Medicine. 2018; 16: 137. https://doi.org/10.1186/s12967-018-1517-4.

[64] Kusumbe AP, Ramasamy SK, Adams RH. Coupling of angiogenesis and osteogenesis by a specific vessel subtype in bone. Nature. 2014; 507: 323–328. https://doi.org/10.1038/nature13145.

[65] Bouland C, Philippart P, Dequanter D, Corrillon F, Loeb I, Bron D, *et al*. Cross-Talk Between Mesenchymal Stromal Cells (MSCs) and Endothelial Progenitor Cells (EPCs) in Bone Regeneration. Frontiers in Cell and Developmental Biology. 2021; 9: 674084. https://doi.org/10.3389/fcell.2021.674084.

[66] Kuroda Y, Kitada M, Wakao S, Nishikawa K, Tanimura Y, Makinoshima H, *et al*. Unique multipotent cells in adult human mesenchymal cell populations. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107: 8639–8643. https://doi.org/10.1073/pnas.0911647107.

[67] Wakao S, Kitada M, Kuroda Y, Shigemoto T, Matsuse D, Akashi H, *et al*. Multilineage-differentiating stress-enduring (Muse) cells are a primary source of induced pluripotent stem cells in human fibroblasts. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108: 9875–9880. https://doi.org/10.1073/pnas.1100816108.

[68] Yamada Y, Wakao S, Kushida Y, Minatoguchi S, Mikami A, Higashi K, *et al*. S1P-S1PR2 Axis Mediates Homing of Muse Cells Into Damaged Heart for Long-Lasting Tissue Repair and Functional Recovery After Acute Myocardial Infarction. Circulation Research. 2018; 122: 1069–1083. https://doi.org/10.1161/circresaha.117.311648.

[69] Kwon HM, Hur SM, Park KY, Kim CK, Kim YM, Kim HS, *et al*. Multiple paracrine factors secreted by mesenchymal stem cells contribute to angiogenesis. Vascular Pharmacology. 2014; 63: 19–28. https://doi.org/10.1016/j.vph.2014.06.004.

[70] Galliera E, Locati M, Mantovani A, Corsi MM. Chemokines and bone remodeling. International Journal of Immunopathology and Pharmacology. 2008; 21: 485–491. https://doi.org/10.1177/039463200802100301.

[71] Zhang H, Li X, Li J, Zhong L, Chen X, Chen S. SDF-1 mediates mesenchymal stem cell recruitment and migration via the SDF-1/CXCR4 axis in bone defect. Journal of Bone and Mineral Metabolism. 2021; 39: 126–138. https://doi.org/10.1007/s00774-020-01122-0.

[72] Cai B, Lin D, Li Y, Wang L, Xie J, Dai T, *et al*. N2-Polarized Neutrophils Guide Bone Mesenchymal Stem Cell Recruitment and Initiate Bone Regeneration: A Missing Piece of the Bone Regeneration Puzzle. Advanced Science. 2021; 8: e2100584. https://doi.org/10.1002/advs.202100584.

[73] Wang M, Chen F, Wang J, Chen X, Liang J, Yang X, *et al*. Calcium phosphate altered the cytokine secretion of macrophages and influenced the homing of mesenchymal stem cells. Journal of Materials Chemistry. B. 2018; 6: 4765–4774. https://doi.org/10.1039/c8tb01201f.

[74] Makgoba MW, Sanders ME, Luce GEG, Dustint ML, Springer TA, Clark EA, *et al*. ICAM-1 a ligand for LFA-1-dependent adhesion of B, T and myeloid cells. Nature. 1988; 331: 86–88. https://doi.org/10.1038/331086a0.

[75] Takada Y, Ye X, Simon S. The integrins. Genome Biology. 2007; 8: 215. https://doi.org/10.1186/gb-2007-8-5-215.

[76] Thankamony SP, Sackstein R. Enforced hematopoietic cell E- and L-selectin ligand (HCELL) expression primes transendothelial migration of human mesenchymal stem cells. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108: 2258–2263. https://doi.org/10.1073/pnas.1018064108.

[77] Soncin F, Ward CM. The function of e-cadherin in stem cell pluripotency and self-renewal. Genes. 2011; 2: 229–259. https://doi.org/10.3390/genes2010229.

[78] Mesnieres M, Böhm AM, Peredo N, Trompet D, Valle-Tenney R, Bajaj M, *et al*. Fetal hematopoietic stem cell homing is controlled by VEGF regulating the integrity and oxidative status of the stromal-vascular bone marrow niches. Cell Reports. 2021; 36: 109618. https://doi.org/10.1016/j.celrep.2021.109618.

[79] Zhang M, Yu W, Niibe K, Zhang W, Egusa H, Tang T, *et al*. The Effects of Platelet-Derived Growth Factor-BB on Bone Marrow Stromal Cell-Mediated Vascularized Bone Regeneration. Stem Cells International. 2018; 2018: 3272098. https://doi.org/10.1155/2018/3272098.

[80] Youssef A, Aboalola D, Han VKM. The Roles of Insulin-Like Growth Factors in Mesenchymal Stem Cell Niche. Stem Cells International. 2017; 2017: 9453108. https://doi.org/10.1155/2017/9453108.

[81] Cao H, He S, Wu M, Hong L, Feng X, Gao X, *et al*. Cascaded controlled delivering growth factors to build vascularized and osteogenic microenvironment for bone regeneration. Materials Today. Bio. 2024; 25: 101015. https://doi.org/10.1016/j.mtbio.2024.101015.

[82] Ogle ME, Olingy CE, Awojoodu AO, Das A, Ortiz RA, Cheung HY, *et al*. Sphingosine-1-Phosphate Receptor-3 Supports Hematopoietic Stem and Progenitor Cell Residence within the Bone Marrow Niche. Stem Cells. 2017; 35: 1040–1052. https://doi.org/10.1002/stem.2556.

[83] Ahmadzadeh A, Kast RE, Ketabchi N, Shahrabi S, Shahjahani M, Jaseb K, *et al*. Regulatory effect of chemokines in bone marrow niche. Cell and Tissue Research. 2015; 361: 401–410. https://doi.org/10.1007/s00441-015-2129-4.

[84] Askari AT, Unzek S, Popovic ZB, Goldman CK, Forudi F, Kiedrowski M, *et al*. Effect of stromal-cell-derived factor 1 on stem-cell homing and tissue regeneration in ischaemic cardiomyopathy. Lancet. 2003; 362: 697–703. https://doi.org/10.1016/s0140-6736(03)14232-8.

[85] Alvarez P, Carrillo E, Vélez C, Hita-Contreras F, Martínez-Amat A, Rodríguez-Serrano F, *et al*. Regulatory systems in bone marrow for hematopoietic stem/progenitor cells mobilization and homing. BioMed Research International. 2013; 2013: 312656. https://doi.org/10.1155/2013/312656.

[86] Yu J, Li M, Qu Z, Yan D, Li D, Ruan Q. SDF-1/CXCR4-mediated migration of transplanted bone marrow stromal cells toward areas of heart myocardial infarction through activation of PI3K/Akt. Journal of Cardiovascular Pharmacology. 2010; 55: 496–505. https://doi.org/10.1097/FJC.0b013e3181d7a384.

[87] Tan W, Martin D, Gutkind JS. The Galpha13-Rho signaling axis is required for SDF-1-induced migration through CXCR4. The Journal of Biological Chemistry. 2006; 281: 39542–39549. https://doi.org/10.1074/jbc.M609062200.

[88] Kumar S, Ponnazhagan S. Mobilization of bone marrow mesenchymal stem cells *in vivo* augments bone healing in a mouse model of segmental bone defect. Bone. 2012; 50: 1012–1018. https://doi.org/10.1016/j.bone.2012.01.027.

[89] Buffone A Jr, Anderson NR, Hammer DA. Migration against the direction of flow is LFA-1-dependent in human hematopoietic stem and progenitor cells. Journal of Cell Science. 2018; 131: jcs205575. https://doi.org/10.1242/jcs.205575.

[90] Greenbaum AM, Link DC. Mechanisms of G-CSF-mediated hematopoietic stem and progenitor mobilization. Leukemia. 2011; 25: 211–217. https://doi.org/10.1038/leu.2010.248.

[91] Marie PJ. Targeting integrins to promote bone formation and repair. Nature Reviews. Endocrinology. 2013; 9: 288–295. https://doi.org/10.1038/nrendo.2013.4.

[92] Roy IM, Anu PV, Zaunz S, Reddi S, Giri AM, Sankar RS, *et al*. Inhibition of SRC-mediated integrin signaling in bone marrow niche enhances hematopoietic stem cell function. iScience. 2022; 25: 105171. https://doi.org/10.1016/j.isci.2022.105171.

[93] Yun YR, Won JE, Jeon E, Lee S, Kang W, Jo H, *et al*. Fibroblast growth factors: biology, function, and application for tissue regeneration. Journal of Tissue Engineering. 2010; 2010: 218142. https://doi.org/10.4061/2010/218142.

[94] Abhinand CS, Raju R, Soumya SJ, Arya PS, Sudhakaran PR. VEGF-

A/VEGFR2 signaling network in endothelial cells relevant to angiogenesis. Journal of Cell Communication and Signaling. 2016; 10: 347–354. https://doi.org/10.1007/s12079-016-0352-8.

[95] Xu S, Wei J, Liu Y, Zhang L, Duan M, Li J, *et al*. PDGF-AA guides cell crosstalk between human dental pulp stem cells *in vitro* via the PDGFR-α/PI3K/Akt axis. International Endodontic Journal. 2024; 57: 549–565. https://doi.org/10.1111/iej.14038.

[96] Popielarczyk TL, Huckle WR, Barrett JG. Human Bone Marrow-Derived Mesenchymal Stem Cells Home via the PI3K-Akt, MAPK, and Jak/Stat Signaling Pathways in Response to Platelet-Derived Growth Factor. Stem Cells and Development. 2019; 28: 1191–1202. https://doi.org/10.1089/scd.2019.0003.

[97] Bai Y, Wang Z, He X, Zhu Y, Xu X, Yang H, *et al*. Application of Bioactive Materials for Osteogenic Function in Bone Tissue Engineering. Small Methods. 2024; 8: e2301283. https://doi.org/10.1002/smtd.202301283.

[98] Qi P, Ning Z, Zhang X. Synergistic effects of 3D chitosan-based hybrid scaffolds and mesenchymal stem cells in orthopaedic tissue engineering. IET Nanobiotechnology/IET. 2023; 17: 41–48. https://doi.org/10.1049/nbt2.12103.

[99] Li X, Wei Z, Lv H, Wu L, Cui Y, Yao H, *et al*. Iron oxide nanoparticles promote the migration of mesenchymal stem cells to injury sites. International Journal of Nanomedicine. 2019; 14: 573–589. https://doi.org/10.2147/ijn.s184920.

[100] Song G, Habibovic P, Bao C, Hu J, van Blitterswijk CA, Yuan H, *et al*. The homing of bone marrow MSCs to non-osseous sites for ectopic bone formation induced by osteoinductive calcium phosphate. Biomaterials. 2013; 34: 2167–2176. https://doi.org/10.1016/j.biomaterials.2012.12.010.

[101] Zhou T, Li G, Lin S, Tian T, Ma Q, Zhang Q, *et al*. Electrospun Poly(3-hydroxybutyrate-co-4-hydroxybutyrate)/Graphene Oxide Scaffold: Enhanced Properties and Promoted *in Vivo* Bone Repair in Rats. ACS Applied Materials & Interfaces. 2017; 9: 42589–42600. https://doi.org/10.1021/acsami.7b14267.

[102] Engler AJ, Sen S, Sweeney HL, Discher DE. Matrix elasticity directs stem cell lineage specification. Cell. 2006; 126: 677–689. https://doi.org/10.1016/j.cell.2006.06.044.

[103] Markert CD, Guo X, Skardal A, Wang Z, Bharadwaj S, Zhang Y, *et al*. Characterizing the micro-scale elastic modulus of hydrogels for use in regenerative medicine. Journal of the Mechanical Behavior of Biomedical Materials. 2013; 27: 115–127. https://doi.org/10.1016/j.jmbbm.2013.07.008.

[104] Nemir S, West JL. Synthetic materials in the study of cell response to substrate rigidity. Annals of Biomedical Engineering. 2010; 38: 2–20. https://doi.org/10.1007/s10439-009-9811-1.

[105] Su T, Xu M, Lu F, Chang Q. Adipogenesis or osteogenesis: destiny decision made by mechanical properties of biomaterials. RSC Advances. 2022; 12: 24501–24510. https://doi.org/10.1039/d2ra02841g.

[106] Tytgat L, Kollert MR, Van Damme L, Thienpont H, Ottevaere H, Duda GN, *et al*. Evaluation of 3D Printed Gelatin-Based Scaffolds with Varying Pore Size for MSC-Based Adipose Tissue Engineering. Macromolecular Bioscience. 2020; 20: e1900364. https://doi.org/10.1002/mabi.201900364.

[107] Sun Y, Lu Y, Yin L, Liu Z. The Roles of Nanoparticles in Stem Cell-Based Therapy for Cardiovascular Disease. Frontiers in Bioengineering and Biotechnology. 2020; 8: 947. https://doi.org/10.3389/fbioe.2020.00947.

[108] Shi H, Zhou K, Wang M, Wang N, Song Y, Xiong W, *et al*. Integrating physicomechanical and biological strategies for BTE: biomaterials-induced osteogenic differentiation of MSCs. Theranostics. 2023; 13: 3245–3275. https://doi.org/10.7150/thno.84759.

[109] Vining KH, Mooney DJ. Mechanical forces direct stem cell behaviour in development and regeneration. Nature Reviews. Molecular Cell Biology. 2017; 18: 728–742. https://doi.org/10.1038/nrm.2017.108.

[110] Xiao L, Sun Y, Liao L, Su X. Response of mesenchymal stem cells to surface topography of scaffolds and the underlying mechanisms. Journal of Materials Chemistry. B. 2023; 11: 2550–2567. https://doi.org/10.1039/d2tb01875f.

[111] Simitzi C, Karali K, Ranella A, Stratakis E. Controlling the Outgrowth and Functions of Neural Stem Cells: The Effect of Surface Topography. Chemphyschem: a European Journal of Chemical Physics and Physical Chemistry. 2018; 19: 1143–1163. https://doi.org/10.1002/cphc.201701175.

[112] Wilkinson A, Hewitt RN, McNamara LE, McCloy D, Dominic Meek RM, Dalby MJ. Biomimetic microtopography to enhance osteogenesis *in vitro*. Acta Biomaterialia. 2011; 7: 2919–2925. https://doi.org/10.1016/j.actbio.2011.03.026.

[113] Zhang H, Zhang H, Xiong Y, Dong L, Li X. Development of hierarchical porous bioceramic scaffolds with controlled micro/nano surface topography for accelerating bone regeneration. Materials Science & Engineering. C, Materials for Biological Applications. 2021; 130: 112437. https://doi.org/10.1016/j.msec.2021.112437.

[114] Kim JI, Kieu TTT, Lee JC. A Novel Strategy to Enhance the Bone Healing Efficacy of Composite Scaffolds via Induction of Cell Recruitment and Vascularization. Biomaterials Research. 2025; 29: 0185. https://doi.org/10.34133/bmr.0185.

[115] Mukherjee S, Agarwal M, Bakshi A, Sawant S, Thomas L, Fujii N, *et al*. Chemokine SDF1 Mediated Bone Regeneration Using Biodegradable Poly(D,L-lactide-*co*-glycolide) 3D Scaffolds and Bone Marrow-Derived Mesenchymal Stem Cells: Implication for the Development of an "Off-the-Shelf" Pharmacologically Active Construct. Biomacromolecules. 2020; 21: 4888–4903. https://doi.org/10.1021/acs.biomac.0c01134.

[116] He X, Ma J, Jabbari E. Migration of marrow stromal cells in response to sustained release of stromal-derived factor-1alpha from poly(lactide ethylene oxide fumarate) hydrogels. International Journal of Pharmaceutics. 2010; 390: 107–116. https://doi.org/10.1016/j.ijpharm.2009.12.063.

[117] Niu L, Jiao K, Qi Y, Nikonov S, Yiu CKY, Arola DD, *et al*. Intrafibrillar silicification of collagen scaffolds for sustained release of stem cell homing chemokine in hard tissue regeneration. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2012; 26: 4517–4529. https://doi.org/10.1096/fj.12-210211.

[118] Mi L, Liu H, Gao Y, Miao H, Ruan J. Injectable nanoparticles/hydrogels composite as sustained release system with stromal cell-derived factor-1α for calvarial bone regeneration. International Journal of Biological Macromolecules. 2017; 101: 341–347. https://doi.org/10.1016/j.ijbiomac.2017.03.098.

[119] Wang J, Li J, Lu Y, Yang H, Hong N, Jin L, *et al*. Incorporation of Stromal Cell-Derived Factor-1α in Three-Dimensional Hydroxyapatite/Polyacrylonitrile Composite Scaffolds for Bone Regeneration. ACS Biomaterials Science & Engineering. 2019; 5: 911–921. https://doi.org/10.1021/acsbiomaterials.8b01146.

[120] Kim K, Lee CH, Kim BK, Mao JJ. Anatomically shaped tooth and periodontal regeneration by cell homing. Journal of Dental Research. 2010; 89: 842–847. https://doi.org/10.1177/0022034510370803.

[121] Wu G, Feng C, Quan J, Wang Z, Wei W, Zang S, *et al*. *In situ* controlled release of stromal cell-derived factor-1α and antimiR-138 for on-demand cranial bone regeneration. Carbohydrate Polymers. 2018; 182: 215–224. https://doi.org/10.1016/j.carbpol.2017.10.090.

[122] Zhang B, Li H, He L, Han Z, Zhou T, Zhi W, *et al*. Surface-decorated hydroxyapatite scaffold with on-demand delivery of dexamethasone and stromal cell derived factor-1 for enhanced osteogenesis. Materials Science & Engineering. C, Materials for Biological Applications. 2018; 89: 355–370. https://doi.org/10.1016/j.msec.2018.04.008.

[123] De la Riva B, Nowak C, Sánchez E, Hernández A, Schulz-Siegmund M, Pec MK, *et al*. VEGF-controlled release within a bone defect from alginate/chitosan/PLA-H scaffolds. European Journal of

Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V. 2009; 73: 50–58. https://doi.org/10.1016/j.ejpb.2009.04.014.

[124] Behr B, Sorkin M, Lehnhardt M, Renda A, Longaker MT, Quarto N. A comparative analysis of the osteogenic effects of BMP-2, FGF-2, and VEGFA in a calvarial defect mode. Tissue Engineering. Part A. 2012; 18: 1079–1086. https://doi.org/10.1089/ten.TEA.2011.0537.

[125] Fahimipour F, Rasoulianboroujeni M, Dashtimoghadam E, Khoshroo K, Tahriri M, Bastami F, *et al*. 3D printed TCP-based scaffold incorporating VEGF-loaded PLGA microspheres for craniofacial tissue engineering. Dental Materials: Official Publication of the Academy of Dental Materials. 2017; 33: 1205–1216. https://doi.org/10.1016/j.dental.2017.06.016.

[126] Kaigler D, Wang Z, Horger K, Mooney DJ, Krebsbach PH. VEGF scaffolds enhance angiogenesis and bone regeneration in irradiated osseous defects. Journal of Bone and Mineral Research: the Official Journal of the American Society for Bone and Mineral Research. 2006; 21: 735–744. https://doi.org/10.1359/jbmr.060120.

[127] Farokhi M, Mottaghitalab F, Shokrgozar MA, Ai J, Hadjati J, Azami M. Bio-hybrid silk fibroin/calcium phosphate/PLGA nanocomposite scaffold to control the delivery of vascular endothelial growth factor. Materials Science & Engineering. C, Materials for Biological Applications. 2014; 35: 401–410. https://doi.org/10.1016/j.msec.2013.11.023.

[128] Zhang L, Zhang L, Lan X, Xu M, Mao Z, Lv H, *et al*. Improvement in angiogenesis and osteogenesis with modified cannulated screws combined with VEGF/PLGA/fibrin glue in femoral neck fractures. Journal of Materials Science. Materials in Medicine. 2014; 25: 1165–1172. https://doi.org/10.1007/s10856-013-5138-4.

[129] Kempen DHR, Lu L, Heijink A, Hefferan TE, Creemers LB, Maran A, *et al*. Effect of local sequential VEGF and BMP-2 delivery on ectopic and orthotopic bone regeneration. Biomaterials. 2009; 30: 2816–2825. https://doi.org/10.1016/j.biomaterials.2009.01.031.

[130] Liu Y, Puthia M, Sheehy EJ, Ambite I, Petrlova J, Prithviraj S, *et al*. Sustained delivery of a heterodimer bone morphogenetic protein-2/7 via a collagen hydroxyapatite scaffold accelerates and improves critical femoral defect healing. Acta Biomaterialia. 2023; 162: 164–181. https://doi.org/10.1016/j.actbio.2023.03.028.

[131] Martino MM, Tortelli F, Mochizuki M, Traub S, Ben-David D, Kuhn GA, *et al*. Engineering the growth factor microenvironment with fibronectin domains to promote wound and bone tissue healing. Science Translational Medicine. 2011; 3: 100ra89. https://doi.org/10.1126/scitranslmed.3002614.

[132] He Y, Li F, Jiang P, Cai F, Lin Q, Zhou M, *et al*. Remote control of the recruitment and capture of endogenous stem cells by ultrasound for *in situ* repair of bone defects. Bioactive Materials. 2023; 21: 223–238. https://doi.org/10.1016/j.bioactmat.2022.08.012.

[133] Li J, Zhang Y, Zhou X, Wang S, Hao R, Han J, *et al*. Enzymatically functionalized RGD-gelatin scaffolds that recruit host mesenchymal stem cells *in vivo* and promote bone regeneration. Journal of Colloid and Interface Science. 2022; 612: 377–391. https://doi.org/10.1016/j.jcis.2021.12.091.

[134] Hao D, Ma B, He C, Liu R, Farmer DL, Lam KS, *et al*. Surface modification of polymeric electrospun scaffolds via a potent and high-affinity integrin $\alpha4\beta1$ ligand improved the adhesion, spreading and survival of human chorionic villus-derived mesenchymal stem cells: a new insight for fetal tissue engineering. Journal of Materials Chemistry. B. 2020; 8: 1649–1659. https://doi.org/10.1039/c9tb02309g.

[135] Shao Z, Zhang X, Pi Y, Wang X, Jia Z, Zhu J, *et al*. Polycaprolactone electrospun mesh conjugated with an MSC affinity peptide for MSC homing *in vivo*. Biomaterials. 2012; 33: 3375–3387. https://doi.org/10.1016/j.biomaterials.2012.01.033.

[136] Wang M, Wu H, Li Q, Yang Y, Che F, Wang G, *et al*. Novel Aptamer-Functionalized Nanoparticles Enhances Bone Defect Repair By Improving Stem Cell Recruitment. International Journal of Nanomedicine. 2019; 14: 8707–8724. https://doi.org/10.2147/ijn.s223164.

[137] Al-Baadani MA, Xu L, Cai K, Yie KHR, Shen Y, Al-Bishari AM, *et al*. Preparation of co-electrospinning membrane loaded with simvastatin and substance P to accelerate bone regeneration by promoting cell homing, angiogenesis and osteogenesis. Materials Today. Bio. 2023; 21: 100692. https://doi.org/10.1016/j.mtbio.2023.100692.

[138] Zhu J, Yang S, Qi Y, Gong Z, Zhang H, Liang K, *et al*. Stem cell-homing hydrogel-based miR-29b-5p delivery promotes cartilage regeneration by suppressing senescence in an osteoarthritis rat model. Science Advances. 2022; 8: eabk0011. https://doi.org/10.1126/sciadv.abk0011.

[139] Shen W, Chen X, Chen J, Yin Z, Heng BC, Chen W, *et al*. The effect of incorporation of exogenous stromal cell-derived factor-1 alpha within a knitted silk-collagen sponge scaffold on tendon regeneration. Biomaterials. 2010; 31: 7239–7249. https://doi.org/10.1016/j.biomaterials.2010.05.040.

[140] Wang X, Song X, Li T, Chen J, Cheng G, Yang L, *et al*. Aptamer-Functionalized Bioscaffold Enhances Cartilage Repair by Improving Stem Cell Recruitment in Osteochondral Defects of Rabbit Knees. The American Journal of Sports Medicine. 2019; 47: 2316–2326. https://doi.org/10.1177/0363546519856355.

[141] He L, Zhang H. MicroRNAs in the Migration of Mesenchymal Stem Cells. Stem Cell Reviews and Reports. 2019; 15: 3–12. https://doi.org/10.1007/s12015-018-9852-7.

[142] Leng Q, Chen L, Lv Y. RNA-based scaffolds for bone regeneration: application and mechanisms of mRNA, miRNA and siRNA. Theranostics. 2020; 10: 3190–3205. https://doi.org/10.7150/thno.42640.

[143] Zou J, Yang W, Cui W, Li C, Ma C, Ji X, *et al*. Therapeutic potential and mechanisms of mesenchymal stem cell-derived exosomes as bioactive materials in tendon-bone healing. Journal of Nanobiotechnology. 2023; 21: 14. https://doi.org/10.1186/s12951-023-01778-6.

[144] Khazaei F, Rezakhani L, Alizadeh M, Mahdavian E, Khazaei M. Exosomes and exosome-loaded scaffolds: Characterization and application in modern regenerative medicine. Tissue & Cell. 2023; 80: 102007. https://doi.org/10.1016/j.tice.2022.102007.

[145] Luo Y, Liu H, Chen M, Zhang Y, Zheng W, Wu L, *et al.* Immunomodulatory nanomedicine for osteoporosis: Current practices and emerging prospects. Acta Biomaterialia. 2024; 179: 13–35. https://doi.org/10.1016/j.actbio.2024.03.011.

Editor's note: The Scientific Editor responsible for this paper was Fergal O' Brien.

Received: 30th April 2024; **Accepted**: 9th December 2024; **Published**: 26th June 2025