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Biological scaffold as potential platforms for stem cells: Current development and applications in wound healing

Xiang JY *et al.* Biological scaffolds for stem cell-mediated healing

Abstract

Wound repair is a complex challenge for both clinical practitioners and researchers. Conventional approaches for wound repair have several limitations. Stem cell-based therapy has emerged as a novel strategy to address this issue, exhibiting significant potential for enhancing wound healing rates, improving wound quality, and promoting skin regeneration. However, the use of stem cells in skin regeneration presents several challenges. Recently, stem cells and biomaterials have been identified as crucial components of the wound-healing process. Combination therapy involving the development of biocompatible scaffolds, accompanying cells, multiple biological factors, and structures resembling the natural extracellular matrix (ECM) has gained considerable attention. Biological scaffolds encompass a range of biomaterials that serve as platforms for seeding stem cells, providing them with an environment conducive to growth, similar to that of the ECM. These scaffolds facilitate the delivery and application of stem cells for tissue regeneration and wound healing. This article provides a comprehensive review of the current developments and applications of biological scaffolds for stem cells in wound healing, emphasizing their capacity to facilitate stem cell adhesion, proliferation, differentiation, and paracrine functions. Additionally, we identify the pivotal characteristics of the scaffolds that contribute to enhanced cellular activity.

Key Words: Stem-cell-based therapy; Biological scaffolds; Wound healing; Extracellular matrix mimicry; Cellular activities enhancement; Scaffold characteristics

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Core Tip: In this work, we provided a comprehensive review of the current development and application of biological scaffolds for stem cells in wound healing,

emphasizes the scaffolds' capacity to facilitate stem cell adhesion, proliferation, differentiation, and paracrine function, identifies the pivotal characteristics of scaffolds that contribute to enhanced cellular activities.

INTRODUCTION

As the body's largest organ, the skin is critically important for safeguarding the body, and any disruption in its integrity can result in acute or chronic wounds^[1]. The intricate process of wound healing involves various stages and necessitates proper coordination^[2,3]. Wound healing is a complex biological process involving four main phases: hemostasis, inflammation, proliferation, and remodeling^[2]. Hemostasis is initiated by platelet activation and the release of growth factors such as platelet-derived growth factor (PDGF), transforming growth factors (TGFs), fibroblast growth factors (FGFs), and vascular endothelial growth factor (VEGF). Inflammation is characterized by fibrin clot formation and the release of chemotactic factors that attract leukocytes, particularly neutrophils, to the wound site^[2,4]. Monocytes differentiate into macrophages (M ϕ) and secrete cytokines that are essential for the proliferative healing phase. Lymphocytes also contribute to this process by producing interleukin-2, which recruits fibroblasts^[5]. Epithelialization involves the migration and proliferation of keratinocytes, aided by EGF, keratinocyte growth factors, and TGF- α ^[6]. Angiogenesis, triggered by endothelial cell migration and tube formation, is supported by angiogenic factors such as VEGF and PDGF. Finally, in the remodeling phase, inflammatory cells depart, and fibroblasts continue to synthesize collagen^[7,8].

Numerous conventional and regenerative studies have been dedicated to achieving effective wound therapies, aiming to reduce health costs and ensure successful scar healing and long-term relief^[9,10]. In recent years, regenerative medicine and tissue engineering therapy combined with stem cells and biomaterial scaffolds have gained popularity^[11-13]. The challenges of wound healing in the field of medicine have prompted the development of new approaches that combine the use of stem cells and biomaterials^[9,14,15]. Although stem-cell-based therapy has emerged as a novel strategy,

showing significant potential in promoting skin regeneration, it also faces challenges such as poor survival and differentiation of the transplanted cells, which tissue engineering seeks to address^[9,16]. Biomaterials, which are known for their ability to control stem cell functions and enhance their regenerative potential, have garnered attention. Biological scaffolds play a crucial role in facilitating the adhesion of stem cells by providing surfaces for cell attachment, proliferation, differentiation, and paracrine functions^[17,18]. The combination of stem cells with specifically designed novel biomaterials results in different effects on the engineered skin after wounding. This review provides a comprehensive overview of the current developments and applications of biological scaffolds for stem cells and their derivatives in wound healing. It highlights the effect of scaffolds on stem cell behavior and identifies the key characteristics of scaffolds responsible for improved cell activity when used in combination with biomaterials. In addition, future research directions in skin tissue engineering focusing on further clinical applications and customized designs are discussed.

SCAFFOLD MATERIALS

Polysaccharide scaffold

Cellulose: Cellulose, a pivotal biopolymer, is an essential component of plant cell walls, fungi, and algae and is widely utilized in industries such as paper, tissue engineering, biosensors, agriculture, and water purification owing to its structural benefits^[19-21]. Unlike plant cellulose, which contains impurities such as lignin and hemicellulose, bacterial cellulose (BC) produced by strains such as *Acetobacter* and *Sarcina ventriculi* stands out in the biomedical field because of its purity, crystallinity, and superior physical properties^[22-27]. The unique nanofibril network of BC ensures high porosity and surface area, promoting exceptional liquid absorption and retention. Its biocompatibility, transparency, hydrophilicity, and non-toxicity make it ideal for medical applications, especially in tissue engineering^[26,28,29].

Cellulose-based scaffolds maintain an optimally moist environment, effectively absorb exudates, and facilitate the removal of debris, including necrotic tissue and fibrinous coatings, which are crucial aspects of wound care^[28]. Furthermore, BC-based dressings act as a barrier, effectively preventing infections by blocking the infiltration of bacteria into the wound site, thus minimizing the risk of infection^[30,31]. One study by Soliman *et al*^[32] assessed the impact of a GO-cellulose nanocomposite on skin wound healing. The GO-cellulose-treated groups displayed thick granulation tissue and intense collagen deposition. In another study, Keskin *et al*^[33] created a novel natural nanocomposite for skin tissue engineering by incorporating keratin into the BC produced by *Acetobacter xylinum*. Furthermore, cellulose materials can be functionalized or combined with other substances to enhance their properties, support soft-tissue regeneration, and reduce the risk of infection. Mao *et al*^[34] developed innovative nanocomposite hydrogels based on BC, gelatin, and selenium nanoparticles for wound-healing applications. The hydrogel exhibited superior antioxidant and anti-inflammatory capabilities and outstanding antibacterial activity. In the field of hard tissue engineering, Cao *et al*^[35] crafted a nanocomposite scaffold by reinforcing BC with chitosan (CS) and nano-hydroxyapatite (nHA), enhancing its mechanical strength, degradation rate, and water retention compared to a CS/nHA-only scaffold. An *in-vivo* experiment on rat skull defects demonstrated the ability of the scaffold to stimulate bone formation. Gu *et al*^[36] developed BC/gelatin methacryloyl (GelMA) composite hydrogels characterized by high porosity and an interconnected structure, making them ideal for cartilage tissue engineering. Furthermore, chondrocytes encapsulated in GelMA/BC hydrogels not only flourished but also retained their natural phenotype, highlighting the potential of the composite for cartilage regeneration applications.

Alginates: Alginates are naturally occurring polysaccharides derived from brown marine algae and bacteria and are widely used as wound dressings^[37]. When an alginate-containing dressing comes into contact with the wound exudate, it initiates an ion exchange process, leading to an interaction between calcium ions within the alginate

and sodium ions present in the blood or exudate. As a result, the alginate fibers undergo swelling, partial dissolution, and gel formation when a sufficient number of calcium ions are replaced by sodium ions. Their application in wound healing leverages the natural biopolymer properties of alginates to fulfill various functions in wound care^[38]. However, alginates exhibit a notable solubility in water, which may affect their stability in specific applications. Furthermore, alginates tend to swell when exposed to water, potentially constraining their practicality in certain cases^[39-41]. In a recent study, Zhang *et al*^[42] developed sodium alginate-CS oligosaccharide-zinc oxide, a novel composite hydrogel, through a spontaneous schiff base reaction. It offers a moist and antibacterial environment and displays wound healing effects. Similarly, in another study by Mndlovu *et al*^[43], a three-step approach involving partial crosslinking, freeze-drying, and pulverization was employed to fabricate a particulate, partially crosslinked, and transferulic acid-loaded CS-alginate interpolymer complex with enhanced wound-healing capabilities. This bioplatfrom can be used as a bioactive delivery system. When applied to a wound in the form of sprinkles, it undergoes *in-situ* hydrogel formation upon exposure to fluids, ultimately enhancing the wound healing process. Moreover, alginate-based hydrogel carriers, ranging from injectable to bioprinting materials, can encapsulate bioactive cells and molecules. This technology can be directly applied to damaged tissues and supports tissue repair, both *in vivo* and *in vitro*^[44].

Hyaluronic acid: Hyaluronic acid (HA), a naturally occurring glycosaminoglycan found in the skin, plays a pivotal role in wound healing. HA-based hydrogels have been extensively researched for application in wound dressing because of their inherent properties, such as biocompatibility, ability to promote fibroblast proliferation for the formation of connective tissue, and capacity to facilitate keratinocyte migration, aiding in re-epithelialization^[45]. However, the mechanical strength of HA is relatively low, which renders it unsuitable for certain applications that require high strength. Moreover, its solubility in specific solvents is limited and may be subject to restrictions based on specific conditions^[46,47]. Orellana *et al*^[48] utilized a freeze-drying technique to

create sponges comprising CS/alginate with the addition of HA, resulting in a microporous structure conducive to cell adhesion and proliferation. Bai *et al*^[49] engineered a hydrogel by combining natural macromolecules, gallic acid-grafted quaternized CS, and oxidized HA. The hydrogel displayed remarkable antioxidant properties and beneficial effects on cell migration *in vitro*. Additionally, the HA in the hydrogel exhibits pro-angiogenic effects, supporting the development of new blood vessels that are crucial for tissue repair and regeneration.

CS: CS, a cationic polysaccharide derived from chitin, is widely used owing to its remarkable therapeutic attributes, rendering it an ideal choice for wound dressings. Its advantages include antibacterial properties, hemostatic effects, analgesic attributes, biodegradability, and compatibility with blood^[50]. However, CS exhibits relatively low strength and toughness, which may render it unsuitable for applications requiring excellent mechanical properties. Additionally, its solubility in aqueous solutions is limited and is subject to specific conditions^[51,52]. Carboxymethyl-CS (CMC), a water-soluble and biocompatible CS derivative, fosters cell interactions, leading to successful cell growth, tissue regeneration, and wound healing^[53].

CS and its derivatives have garnered substantial attention owing to their roles in promoting wound healing and fostering a healing-conducive environment. Recently, Xu *et al*^[54] reported a multifunctional cryogel composed of CS, silver, and tannic acid (CS/Ag/TA). The prepared CS/Ag/TA cryogel not only exhibited consistent stability and compressibility but also demonstrated significant antibacterial and hemostatic capabilities, achieving hemostasis in less than 20 s. Additionally, Li *et al*^[55] introduced *in situ* injectable, self-healing, antibacterial, hemostatic, and biocompatible hydrogels derived from a CMC hybrid. This hydrogel showcases outstanding antibacterial properties that were primarily attributed to the inherent antibacterial characteristics of CMC. The hydrogel adhered tightly to biological tissues and exhibited excellent *in vivo* hemostatic performance. In the field of bone-tissue repair, Saravanan *et al*^[56] developed a thermosensitive CS hydrogel with graphene oxide that demonstrated biocompatibility

and metabolic activity in mesenchymal stem cells (MSCs). It enhanced osteogenic differentiation, and is a promising platform for bone regeneration. Additionally, CS serves as an effective adhesive agent for enhancing the clinical outcomes of dental restorations. Diolosà *et al*^[57] demonstrated that modified CS, when incorporated into the “etch-and-rinse” adhesive system, significantly boosts the longevity of dental restorations.

Protein scaffold

Collagen: Collagen, a crucial protein in the extracellular matrix (ECM) of connective tissues, plays a central role in wound healing. When applied to wounds, collagen dressings foster a moist environment that actively supports various aspects of the healing process^[58]. However, collagen possesses relatively modest mechanical properties, rendering it unsuitable for certain high-strength applications. It may also cause allergies. In addition, collagen exhibits limited solubility in water and requires specific solvent conditions^[59-62]. Jiang *et al*^[63] developed a collagen fibril hydrogel that significantly promoted wound healing and showed remarkable potential for aiding skin tissue regeneration. Another study by Chen *et al*^[64] compared the efficacy of a pullulan-collagen dressing with that of two commercially available wound dressings. This dressing was found to accelerate wound closure and promote tissue healing, characterized by less dense, more randomly aligned, and shorter collagen fibers. Ramanathan *et al*^[65] fabricated a highly interconnected porous dressing material incorporating a novel collagen variant (COL-SPG) for efficient wound healing. They created a three-dimensional (3D) sponge scaffold matrix that mimicked the function of the ECM and featured a highly interconnected structure with excellent biocompatibility, thus facilitating cell adhesion and attachment.

Gelatin: Gelatin, a derivative of collagen, exhibits substantial promise in wound healing owing to its ability to promote tissue regeneration and closure. In the field of tissue engineering, gelatin hydrogels and scaffolds function as templates for cell adhesion,

growth, and differentiation and can serve as carriers for growth factors, drugs, or cells^[66]. Gelatin exhibits low solubility in cold water and requires specific temperature and pH conditions for dissolution. Moreover, gelatin is a potential risk factor for allergic reactions and is susceptible to loss of structural stability at elevated temperatures, thus limiting its application in certain scenarios^[67-70]. In one study by Shan *et al*^[71], electrospun nanofibers comprising a combination of gelatin and silk fibroin were loaded with astragaloside IV. This dressing effectively increased the number of microvessels and regulated collagen deposition by controlling the drug release rate. *In vivo* experiments revealed that the dressing accelerated wound healing and inhibited scar formation by stimulating wound closure, enhancing angiogenesis, regulating newly formed collagen types, and improving collagen organization. In another study, Li *et al*^[72] employed poly (L-lactic-co-caprolactone)/gelatin/EGCG core-shell nanofiber membranes with sustained drug release capabilities using coaxial electrospinning technology. Experiments confirmed that this core-shell-structured dressing displayed excellent biocompatibility, antibacterial properties, and antioxidant abilities.

Silk fibroin: Silk fibroin, a natural protein sourced from silkworm cocoons, has immense potential for wound healing. Its unique attributes make it a promising biomaterial for tissue regeneration and wound closure. However, the extraction and processing of silk fibroin are relatively complex and require high production standards. The current high production cost of silk fibroin restricts its large-scale application^[73,74]. Previous studies have demonstrated its role in enhancing fibroblast proliferation and migration, collagen secretion, and expediting wound contraction^[75,76]. In the field of tissue engineering, silk fibroin is used to construct 3D scaffolds that mimic the natural ECM, facilitating cellular attachment and growth. Certain investigators have explored the impact of varying concentrations of silk fibroin protein on the microstructure of 3D scaffolds. Utilizing the freeze-drying technique, Zhang *et al*^[77] generated silk fibroin scaffolds with varying pore sizes, ranging from 50 to 300 micrometers. An optimized pore architecture within silk fibroin scaffolds was found to modulate the bioactivity of

bone marrow-derived MSCs (BMSCs) expressing bone morphogenetic protein 7, leading to enhanced cell proliferation and ECM production. When loaded with growth factors or bioactive molecules, these silk fibroin materials increase cellular activity and facilitate tissue repair. In a separate study, Qu *et al*^[78] fabricated porous silk fibroin microspheres loaded with bFGF and featuring interior-out channels using high-voltage electrostatic differentiation, followed by lyophilization. The encapsulated bFGF exhibited a sustained release pattern over 13 d, avoiding abrupt release. L929 cells demonstrated robust adhesion and generated a collagen-like fibrous matrix on the surface of SF microspheres.

Fibrous protein: Fibrin, a fibrous protein, plays a crucial role in the coagulation and tissue repair processes. The primary function of fibrin is the formation of blood clots. When a wound occurs, the body's clotting cascade results in the conversion of fibrinogen to fibrin, creating a mesh-like structure that entraps blood cells and platelets. This clot staunches bleeding and initiates the wound healing process^[79]. Fibrin is an attractive delivery vector owing to its structural and mechanical properties, as well as its inherent biological features. It offers several advantages: It can be injected and polymerized *in situ* and can be easily functionalized by incorporating therapeutic molecules into the fibrinogen or thrombin component in the fibrin formulation^[80]. However, the extraction and processing of fibroin involve intricate procedures that require meticulous control, imposing restrictions on its widespread application^[81,82]. Losi *et al*^[83] designed a fibrin-based scaffold incorporating poly(lactic-co-glycolic acid) (PLGA) nanoparticles loaded with VEGF and bFGF. These scaffolds, enriched with growth factors, spurred complete re-epithelialization, advanced granulation tissue maturation, and augmented collagen deposition. Alphonsa *et al*^[84] successfully integrated antimicrobial drugs (ciprofloxacin and fluconazole) with fibrin nanoparticles. In a separate endeavor distinct from drug or cell factor delivery, Mendez *et al*^[85] devised a fibrin formulation that allowed adipose-derived MSCs (ADSCs) to generate tubular structures *in vitro*. The introduction of ADSCs embedded in firm fibrin gels expedited

wound healing. Intriguingly, after five days of healing, the ADSCs remained within the fibrin gel and did not merge into the granulation tissue of healing wounds *in vivo*.

Synthetic scaffold: Synthetic polymers play a pivotal role in wound repair and tissue regeneration by providing a wide spectrum of functionalities with precisely defined and customizable chemical and mechanical properties.

Poly(vinyl alcohol) (PVA) is a biodegradable, semicrystalline synthetic polymer extensively utilized in drug delivery and tissue engineering applications, notably for its mechanical attributes. PVA hydrogels maintain a moist wound environment, making them valuable for wound dressings and controlled drug-release systems^[86]. In a particular study, El-Attar *et al*^[87] employed repetitive freeze-thawing to blend silk sericin with PVA. This hydrogel exhibited excellent hydrophilicity and swelling behavior owing to the effective blending of PVA with sericin, forming a porous structure.

Poly L-lactic acid (PLLA) and PLGA are biodegradable synthetic polymers commonly used to deliver cells to wounds^[88,89]. In a study, Kim *et al*^[88] developed an RGD-g-PLLA biosynthetic scaffold, showcasing its potential as an *in vivo* targeted delivery vehicle for endothelial progenitor cells that promotes vascular regeneration in murine dermal wound models. Another study by Chen *et al*^[90] involved the fabrication of PLGA scaffolds seeded with extracorporeal shockwave-treated BMSCs, demonstrating the ability of the scaffolds to support BMSC attachment, proliferation, and differentiation and their significant potential in tissue regeneration.

Other biodegradable synthetic polymers, such as polycaprolactone (PCL) and polyethylene glycol (PEG), have also found applications in regenerative therapies. PCL is a biodegradable scaffold material used in tissue engineering for wound healing and bone regeneration. In a related study by Unalan *et al*^[91], PCL electrospun fiber mats loaded with peppermint essential oil were created to confer antibacterial properties to the fibers for wound-healing applications. Moreover, PEG is a versatile polymer utilized in wound dressings. Kwak *et al*^[92] designed PEG hydrogels to encapsulate M2-

exos to maximize their therapeutic effects in cutaneous wound healing. These hydrogels offer adjustable degradation times by controlling crosslinking density, thus presenting a potential tool for regulating the local polarization state of Mø, which is a critical factor in tissue homeostasis and wound repair.

Types of polymer scaffolds

Hydrogel: Hydrogel scaffolds have attracted significant attention because of their tremendous potential as biomaterials for tissue engineering applications. These hydrogels are composed of structural supports made from bioactive compounds and exhibit a remarkable ability to regulate molecular-level biofunctions and provide adequate mechanical strength. Moreover, they create an ECM-like environment that enhances cellular activity^[93]. Hydrogels can be synthesized using both natural and synthetic polymers. ⁶ Naturally derived hydrogels offer several advantages over synthetic polymer scaffolds in terms of their biocompatibility, cellular interactions, and degradation. However, their limited mechanical strength restricts their range of applications. ⁶ This drawback can be overcome in synthetic polymer-based hydrogels by controlling the structure or functional groups of the polymer chains^[94]. Biocompatible hydrogels are extensively used in tissue engineering applications such as wound healing, bone regeneration, drug delivery, and cell delivery^[95]. Liu *et al*^[96] developed a hemostatic and anti-inflammatory hydrogel using ultraviolet light on a dual-cross-linked methacryloyl-substituted *Bletilla striata* polysaccharide and gelatin. This hydrogel was shown to ¹ regulate the M1/M2 phenotype of Mø, enhance the proliferation and migration of fibroblasts *in vitro*, and expedite angiogenesis. In another study conducted by Zhou *et al*^[97], ¹⁹ an injectable, biocompatible, and thermosensitive hydrogel called Pluronic F-127 hydrogel was utilized to encapsulate ADSC-derived exosomes (ADSC-exos) and was applied to a full-thickness cutaneous wound in mice. Their findings revealed that administering ADSC-exos to PF-127 improved the effectiveness of exosome delivery, preserved the bioactivity of ADSC-exos, and optimized their performance.

Fibrous scaffolds: Fibrous scaffolds are primarily fabricated using electrospinning to produce 3D constructs consisting of fibers at the microscale or nanoscale to closely mimic the architecture of natural human tissues^[98]. Electrospinning is a technique that utilizes electrostatic forces to generate continuous fibers from biocompatible materials^[99]. The orientation of fibrous scaffolds is determined based on specific application requirements, as it can influence cell adhesion, proliferation, differentiation, and paracrine functions^[100]. Fibrous scaffolds have been used in diverse areas of tissue engineering, including skin, bone, cartilage, and neural tissue engineering^[98]. Hsieh *et al*^[101] incorporated HA into electrospun PLGA/gelatin fibrous membrane scaffolds to create an environment for 3D culture and delivery of ADSCs. The resulting scaffold exhibited favorable cytocompatibility, and the ADSCs cultured on the scaffold demonstrated increased expression of genes associated with angiogenesis. In a recent study, Zhao *et al*^[102] produced 3D photocrosslinkable gelatin-based fibrous scaffolds with adjustable physical and biological properties. These fibrous scaffolds not only supported cell viability and adhesion but also facilitated cell migration and proliferation, thereby expediting the regeneration and formation of cutaneous tissues.

Porous scaffolds: Sponge scaffolds with high porosity and a uniformly interconnected pore network are created using natural or synthetic polymers through a range of techniques, such as porogen leaching, gas foaming, and freeze-drying^[103]. Furthermore, the porous structure of sponge scaffolds closely resembles the composition of the ECM, and their ability to absorb and retain water allows for the absorption of exudate from the wound bed. This creates an advantageous environment that promotes cell migration and proliferation^[104]. In a recent study by Li *et al*^[105], a fish collagen-based sponge was explored as a substitute for the dura mater after surgical resection in rabbits. A rabbit dural defect model demonstrated that the scaffolds prevented the adhesion of brain tissue, thereby reducing the risk of inflammation, promoting fibroblast growth, and enhancing tissue regeneration and healing. In another investigation by Lian *et al*^[106], a

sponge-like scaffold with hierarchical and interconnected pores was fabricated using low-temperature deposition modeling printing. These sponges improved the adhesion, retention, survival, and ingrowth of MSCs and facilitated cell-material interactions. Furthermore, the paracrine functions of the cultured MSCs on the sponges were enhanced, leading to a significant secretion of upregulated immunomodulatory, angiogenic, and osteogenic factors.

Microneedle: Microneedles, a drug delivery system under development consisting of an array of tiny needles, have attracted considerable attention because of their minimally invasive nature, user-friendly operation, capability to deliver drugs in a targeted manner, and capacity to carry diverse payloads^[107,108]. The unique structure of microneedles enables the loading of diverse substances, including drugs, nanoparticles, and cells, making them suitable for applications in wound healing and tissue regeneration^[109]. Recently, Ma *et al*^[110] introduced a novel core-shell hyaluronic HA microneedle patch integrated with ferrum MSC-derived artificial nanovesicles for wound healing. The patch demonstrated excellent efficacy in diabetic wound healing, highlighting the potential value of the proposed composite core-shell microneedle patch for clinical wound healing applications. Wu *et al*^[111] developed a novel microneedle patch loaded with stem cell spheroids (SPs) using microfluidic templating technology. By incorporating SPs into microneedles, this platform allows for the precise delivery and exchange of multiple active substances, leading to enhanced neovascularization, collagen deposition, and tissue reconstruction in diabetic wounds.

STEM CELL TYPES AND CHARACTERISTICS

ADSCs

ADSCs exhibit the ability to self-renew and differentiate into various cell types, including bone, cartilage, and fat cells^[112]. Capitalizing on their potential holds great promise for expediting the wound healing process^[113]. Additionally, cell-free derivatives of ADSCs, such as conditioned media, exosomes, and other bioactive

components, have emerged as viable alternatives to conventional ADSC-based therapies^[114]. Zhou *et al*^[115] isolated exosomes from human ADSCs and explored the combined application of ADSCs and ADSC-exo to enhance the healing of cutaneous wounds. Their findings demonstrated that the systemic administration of ADSCs and ADSC-exo effectively stimulated cell proliferation, suppressed apoptosis and inflammation, and improved skin elasticity and barrier integrity. Furthermore, Zheng *et al*^[116] revealed the protective effects of ADSC-exos against cellular oxidative damage. These exosomes enhanced cell proliferation and migration while reducing apoptosis. Subsequent investigations revealed significant enrichment of miR-378 in these exosomes. Significantly, experiments confirmed that the introduction of an miR-378 mimic could replicate the protective effects observed with ADSC-exos, whereas the application of miR-378 inhibitors to ADSCs nullified these protective properties.

BMSCs

BMSCs, sourced from bone marrow, represent the most prevalent stem cell type in the realms of cell therapy and tissue engineering^[117]. When harnessed for wound healing applications, BMSCs release growth factors and cytokines, orchestrating fundamental processes such as angiogenesis, inflammation mitigation, and collagen synthesis, which are all pivotal for effective tissue restoration^[118]. Ding *et al*^[119] preconditioned BMSC-derived exosomes with deferoxamine (DFO-exosomes). Their study revealed that DFO-exosomes employed in cell-free therapies exhibited heightened pro-angiogenic potential by triggering the PI3K/AKT signaling pathway through miR-126-mediated PTEN downregulation, thus stimulating *in vitro* angiogenesis. Gondaliya *et al*^[120] explored the combination of an ²⁷ miR-155 inhibitor and exosomes derived from BMSCs in a diabetic wound model. Their findings showed the synergistic effects of miR-155-inhibitor-loaded MSC-derived exosomes, including augmented keratinocyte migration, restoration of FGF-7 levels, and decreased inflammation. Furthermore, treatment with these exosomes ameliorated collagen deposition, angiogenesis, and re-epithelialization in diabetic wounds.

Human umbilical cord-derived MSCs

Derived from umbilical cord tissue, human umbilical cord-derived MSCs (hUC-MSCs) possess remarkable differentiation potential and can give rise to fibroblasts, endothelial cells, and immunomodulatory cells. hUC-MSCs are highly sought after because of their advantageous attributes, including low immunogenicity, immunomodulatory properties, non-invasive procurement, straightforward *in vitro* expansion, and ethical compliance^[121]. Zhang *et al*^[122] developed a PLGA-based scaffold to generate tissue sheets using hUC-MSCs. *In vitro* immunostaining revealed the formation of robust hUC-MSC sheets with a rich ECM. In a diabetic mouse model, transplantation of hUC-MSC tissue sheets significantly expedited wound healing compared with hUC-MSC injection or PLGA fibers alone. These results indicate that culturing hUC-MSCs on PLGA scaffolds is a promising approach for diabetic wound treatment. Xue *et al*^[123] engineered spherical hUC-MSCs, which were subsequently integrated into self-assembled hydrogels. This strategy significantly accelerated wound healing, resulting in a shorter healing duration.

Other MSCs

In addition to ADSCs, BMSCs, and hUC-MSCs, various other types of MSCs, such as epidermal stem cells (EPSCs), fetal dermal MSCs (FD-MSCs), and human amniotic fluid-derived stem cells, also play a significant role in wound healing and regeneration.

EPSCs, located in the basal layer of the epidermis and hair follicle bulges, are multipotent cells with diverse functions for maintaining epidermal integrity. These functions include epidermal formation, differentiation, maintenance of homeostasis, re-epithelialization, and the promotion of epidermal regeneration^[124]. Pan *et al*^[125] devised an electrospun micro/nanofiber scaffold using PCL and cellulose acetate (CA) to culture and transplant EPSCs to preserve their stemness and prevent differentiation. The results revealed that the PCL + CA micro/nanofiber scaffold effectively inhibited

EPSC differentiation by activating YAP, which in turn suppressed the Notch signaling pathway^[126].

In the field of regenerative medicine, FD-MSCs represent a novel and multipotent subset of MSCs derived from the fetal skin. FD-MSCs can counteract d-galactose-induced senescence in adult dermal fibroblasts (ADFs), primarily through their paracrine effects^[125]. Costa *et al*^[127] examined the therapeutic potential of exosomes released by FD-MSCs in the context of standard wound healing and explored their impact on ADFs. Their findings showed that FD-MSC exosomes effectively stimulated the proliferation, migration, and secretion of ADFs, accompanied by activation of the Notch signaling pathway following exosome treatment^[128].

Human amniotic fluid-derived stem cells (hAFSCs), obtained from human amniotic fluid, play a crucial role in the wound healing process. They exhibit remarkable self-renewal capabilities and are amenable to large-scale expansion^[127]. Zhang *et al*^[129] investigated the therapeutic potential of hAFSC-derived exosomes (hAFSC-exos) in full-thickness skin wounds. The results showed that hAFSC-exos expedited wound healing and promoted hair follicle, nerve, and vessel regeneration. Furthermore, the hAFSC-exos mitigated excessive myofibroblast aggregation and ECM production.

INTERACTION BETWEEN SCAFFOLDS AND MSCS

Cell behavior affected by scaffolds

Adhesion and proliferation: Stem cell therapy, when combined with various biomaterials, is a promising avenue for enhancing wound healing outcomes. This approach leverages the unique regenerative properties of stem cells as well as the structural and functional support offered by biomaterials^[130].

Biological scaffolds play a crucial role in facilitating stem cell adhesion by providing surfaces for cell attachment and spread. In a recent study, Martins *et al*^[131] characterized pectin/CS (PT/CS) membranes and discovered that their surface wettability and swelling properties significantly promoted stem cell attachment. These findings demonstrate the potential of these novel PT/CS membranes to enhance anchorage and

adhesion and support the growth of human stem cells, which makes them promising materials for tissue engineering applications. In another study, GelMA and dialdehyde-functionalized polyurethane were combined to create a double-crosslinking system, which was then loaded onto human MSCs (hMSCs). Within three days, cells within the 3D-printed hydrogel exhibited noticeable proliferation, resulting in an increased cell count. Moreover, the scaffold was nontoxic and provided a favorable environment for immediate cell growth. These results highlight the potential of 3D-printed materials as scaffolds for cartilage tissue engineering^[132].

Differentiation: Moreover, biological scaffolds can influence stem cell differentiation. Cantu *et al*^[133] conducted a study to examine the immunophenotype of Mø and the differentiation of MSCs in relation to established and experimental collagen-based biomaterials used for MSC entrapment. The results showed that MSCs cocultured with Møs exhibited reduced chondrocyte differentiation but enhanced osteoblast differentiation. Additionally, MSC differentiation into adipocytes was significantly enhanced when entrapped within a gelatin/PEG-based matrix^[133]. In another study by Ferlin *et al*^[134], scaffolds with two distinct and well-controlled pore geometries were fabricated to investigate their effects on MSC enrichment and differentiation. Their findings revealed that scaffolds with an ordered cubic pore geometry were conducive to both MSC enrichment from unprocessed bone marrow and MSC differentiation, which resulted in increased gene expression during adipogenesis and chondrogenesis processes.

Paracrine function: Furthermore, biological scaffolds have a significant effect on the paracrine functions of stem cells. They regulate the release of growth factors and cytokines, which play crucial roles in tissue repair and regeneration. Qazi *et al*^[135] investigated whether the 3D culture in different microenvironments affected the secretion pattern of MSCs. The results showed that MSCs seeded on scaffolds exhibited an enhanced secretion profile compared with MSCs encapsulated in hydrogels. These

scaffold-seeded MSCs exerted beneficial paracrine effects on various myoblast functions, including migration and proliferation. The increased paracrine effects of scaffold-seeded cells were partly attributed to N-cadherin-mediated cell-cell interactions during culture. Su *et al*^[136] fabricated electrospun scaffolds composed of random, aligned, and mesh-like fibers. The paracrine behavior of ADSCs on these scaffolds was investigated and compared to that of conventional cell cultures on microplates. Their findings revealed that ADSCs cultured on electrospun fibers produced significantly higher levels of anti-inflammatory and pro-angiogenic cytokines. This suggests that the scaffold architecture can influence the paracrine behavior of ADSCs, potentially enhancing their therapeutic effects.

Effect of characteristics of scaffolds over cell behavior: Biological materials play critical roles in the regulation of various aspects of stem cell behavior, including growth, adhesion, proliferation, and paracrine activity. The careful selection of suitable biomaterials has a significant impact on these cellular processes in stem cell applications. Furthermore, biological materials also have the ability to influence stem cell differentiation and the secretion of signaling molecules, thereby affecting their therapeutic potential in tissue regeneration and regenerative medicine^[137]. Factors such as stiffness, porosity, material alignment, and surface chemistry have been explored to gain a better understanding of the interactions between stem cells and biomaterials.

Stiffness: The mechanical properties of biomaterials, such as rigidity or stiffness, play crucial roles in regulating the interactions between stem cells and their microenvironments. Stiffness can be changed by varying the amount, concentration, percentage, and ratio^[138]. The stiffness of the HA-tyramine system, which is covalently enzymatically cross-linked *via* an oxidative coupling reaction catalyzed by horseradish peroxidase and hydrogen peroxide (H₂O₂), can be adjusted by varying the amount or concentration of H₂O₂^[139]. Several matrices become stiffer with increasing crosslinking. Sun *et al*^[140] developed 3D gelatin scaffolds with distinct stiffnesses using 1-ethyl-3-(3-

dimethylaminopropyl) carbodiimide hydrochloride (EDC)-mediated crosslinking. The mechanical strength of the scaffolds was significantly increased by the EDC treatment. Moreover, the photopolymerization parameters also affect the stiffness of the materials. Allen *et al*^[141] examined the impact of light intensity and exposure time on scaffold properties, such as shear modulus and micropore structure, and found that light intensity and polymerization time directly impact the scaffold stiffness and micropore structure, which in turn influence the cell loading capacity of the scaffold.

Stem cells can sense and respond to the stiffness of the substrate on which they are cultured, which influences their adhesion, spreading, and differentiation. Nam *et al*^[142] examined the specific effects of scaffold stiffness on the behavior of embryonic mesenchymal progenitor cells. Scaffolds with identical microstructures and surface chemistries but different mechanical properties were used. The modulus of the core-shell fibers (30.6 MPa) was more than four times that of pure PCL (7.1 MPa). The results showed that the lower-modulus PCL fibers provided a more suitable microenvironment for chondrogenesis, whereas the stiffer core-shell PES-PCL fibers supported enhanced osteogenesis^[142]. Ye *et al*^[143] used PEG hydrogels as the matrix to prevent nonspecific protein adsorption. They also allowed cell-adhesive arginine (glycine) peptides to covalently bind onto hydrogel surfaces in the form of well-defined nanoarrays to control specific cell adhesion. This approach allowed separation of the effects of matrix stiffness and surface chemistry, clearly demonstrating that matrix stiffness is a potent regulator of stem cell differentiation. Similarly, Chu *et al*^[144] fabricated four types of scaffolds with controlled stiffness and fiber size to investigate their potential to induce the differentiation of AFSCs. This study revealed that physical cues such as mechanical properties, topographical features, and geometrical factors have a profound impact on the growth and differentiation of cultured stem cells and that scaffold stiffness regulates AFSC differentiation.

Porosity: The topographical features of biomaterial surfaces play crucial roles in governing the interactions between stem cells and their microenvironments. Stem cells

are highly sensitive to surface morphology, and cues from the substrate, such as biomaterial porosity and the arrangement or alignment of biomaterials, can influence the adhesion, spreading, and activation of intracellular signaling pathways. Ultimately, these factors impact cell growth and differentiation^[145,146].

Pore sizes in biomaterials can be categorized into nanosize (nano-roughness, < 100 nm), micropore size (micro-roughness, 100 nm-100 μ m), and macropore size (macro-roughness, 100 μ m-millimeters)^[147]. Pore size affects various cellular processes. Nanopore-sized membranes have been shown to act as an interim synthetic ECM with which cells interact before forming new tissues^[148], while macropores play a crucial role in cell proliferation, differentiation, migration, and angiogenesis^[145].

Zhang *et al*^[149] developed a 3D fibrous collagen scaffold for potential pulp regeneration. The influence of the various pore sizes of these scaffolds on the proliferation and odontoblastic differentiation of human dental pulp cells (hDPCs) was investigated. Scaffolds with larger mean pore sizes of 65 and 145 μ m improved hDPC ingrowth and proliferation, with the 65- μ m scaffold group showing the highest level of odontogenic gene expression. Furthermore, Wang *et al*^[150] explored the optimal pore structure and pore size of a Ti6Al4V porous scaffold for bone defect repair and the promotion of vascularization. The results demonstrated that cell proliferation ability and viability increased gradually as the pore size of the scaffold increased. Additionally, cells exhibited a stronger ability to vascularize on scaffolds with irregular pore sizes than on those with regular pore sizes. Tytgat *et al*^[151] found that the spatial distribution of MSCs is dependent on the scaffold pore size, with larger pores leading to a more uniform spatial distribution of adipogenically differentiated cells. Wang *et al*^[152] prepared a biomimetic fibroblast-loaded artificial dermis composed of three-layer scaffolds with different pore sizes. The outer layers of the scaffolds had larger pores than the middle layers. These scaffolds significantly promoted wound healing by facilitating granulation tissue formation and wound re-epithelialization.

Orientation and alignment: Besides the pore sizes of the biomaterials, stem cells are also influenced by the spatial orientation and alignment of these biomaterials. These factors play a significant role in determining cell adhesion, spreading, and activation of intracellular signaling pathways, ultimately affecting cell growth and differentiation.

The topographic orientation of biomaterials closely resembles the structure of the ECM and can generally be categorized as random, aligned, or featuring a specific pattern arrangement^[153-156]. A recent study by Xu *et al*^[157] showed that the topographic cues of materials can directly influence cellular orientation, potentially laying the groundwork for further differentiation. Moreover, aligned scaffolds have been found to expedite bone and fiber regeneration. Similarly, Rinoldi *et al*^[158] designed a 3D system comprising stem cells and highly aligned hydrogel yarns. The aligned orientation of the fibers, combined with mechanical stimulation, led to a significantly preferred longitudinal cell orientation and enhanced the expression of collagen types I and III. Furthermore, the combination of biochemical and mechanical stimulations promotes the expression of specific tenogenic markers, indicative of efficient cell differentiation towards the tendons. In another study, electrospun scaffolds consisting of fibers arranged in random, aligned, and mesh-like patterns were fabricated, and the paracrine behavior of ADSCs on these scaffolds was compared with that of conventional microplate cell cultures. The findings revealed that ADSCs cultured on electrospun fibers produced significantly higher levels of anti-inflammatory and pro-angiogenic cytokines than those cultured on microplates. This demonstrates that the fibrous topography of scaffolds is a critical material property that modulates the paracrine function of cells^[136]. In addition, Chen *et al*^[159] pioneered the development of 3D nanofiber scaffolds with radial and vertical alignments for the transplantation of BMSCs. BMSC-laden 3D scaffolds have demonstrated the ability to stimulate granulation tissue formation, angiogenesis, and collagen deposition while also steering immune responses in a pro-regenerative direction. Andalib *et al*^[160] fabricated both uniaxially aligned and randomly distributed nanofibers from PLLA and assessed the behavior of MSCs on these nanofibers. Their findings shed light on the role of focal

adhesion kinase, a key molecular sensor in the focal adhesion complex, in governing the shape of MSC on nanofibers.

Surface modifications: To enhance biocompatibility, cell adhesion, and cell-biomaterial interactions, the surface chemistry of biomaterials must be appropriately modified^[161,162]. This can be achieved through surface functionalization or modification. Surface functionalization involves altering the atoms or molecules on a biomaterial surface using physical or chemical methods. Alternatively, bioactive molecules can be coated on the surfaces^[163]. Physical modification primarily involves the application of a biomimetic material or functional group to the surface of a biomaterial without altering its chemical characteristics. Common approaches for modifying biomaterials include coating them with collagen, integrin, fibronectin, and molecules resembling the ECM, such as CS or gelatin^[164-166]. In a recent study by Murschel *et al*^[167], a system was developed to enhance the physical adsorption of VEGF onto poly(allylamine)-functionalized polystyrene. They found that VEGF, when tagged with amphiphilic peptides, exhibited specific adsorption through coiled-coil interactions. This method effectively preserves the bioactivity of VEGF and allows its controlled release over several days. These results highlight the improved adsorption achieved by utilizing the electrostatic and hydrophobic forces on organic substrates. In a separate investigation conducted by Sadeghi *et al*^[166], a non-woven fibrous substrate made of PLGA was subjected to hydrolysis using different concentrations of NaOH. This process aimed to enhance the presence of carboxyl and hydroxyl groups on the fiber surface. To further enhance the bioactivity, the activated substrates were coated with a collagen solution. Subsequent analyses revealed a significant increase in the proliferation of HaCaT cells after the collagen coating. This suggests that proper chemical bonding and crosslinking of collagen on the substrate surface result in sufficient stability and greatly improved bioactivity.

Polydopamine (PDA), a natural bioadhesive polymer, can regulate cell behavior and influence focal adhesion behavior at the biomaterial interface^[168], as highlighted in a

recent study by Wang *et al*^[169]. This study demonstrated that PDA coating significantly enhanced the roughness, hydrophilicity, and protein absorption capacity of the film, which promoted the adhesion and migration of MSCs onto biomaterial surfaces. In another investigation conducted by Wan *et al*^[170], a PDA-mediated surface modification of decellularized intestinal scaffolds was combined with ADSC to promote intestinal wound healing. The PDA-coated scaffold effectively supported the growth and proliferation of ADSCs and enhanced their secretory activity for paracrine effects.

In the field of biomaterial modification, layer-by-layer (LBL) deposition is a prominent fabrication technique. In this technique, alternating layers with opposite charges self-assemble because of electrostatic interactions between them^[171]. da Câmara *et al*^[172] utilized the LBL deposition approach to assemble tanfloc (TN), a cationic tannin-derivative polymer, with heparin and chondroitin sulfate. The assembly of 11 layers was found to show the highest rate of cell proliferation. Furthermore, when TN was used as the terminal layer of the scaffold, the spread of ADSCs was promoted. This suggests that the surface charge and terminal layer play crucial roles in creating the microenvironmental niche that influences cellular responses.

Active ingredients: Biomaterials can replicate the ECM structure of the ECM, thereby inducing cell adhesion, proliferation, and angiogenesis, which contribute to wound healing. Furthermore, biomaterials can carry active ingredients such as drugs, peptides, and growth factors. These components can influence cell growth, migration, and secretion, thereby further enhancing their role in promoting wound healing^[173,174].

Chen *et al*^[175] designed and analyzed a unique **active drug delivery vector** that effectively addressed **the challenges of high-efficiency loading and** the simultaneous and **controlled release of Mg²⁺ and curcumin**. Their findings highlighted that Mg²⁺ released from the hydrogels bolstered the proliferation of BMSCs, whereas curcumin mitigated the damage to BMSCs from H₂O₂ exposure and reduced apoptotic cells and nuclear condensation. Elango *et al*^[176] created a PVA retinol hydrogel and discovered that the cell proliferation effect of the PVA hydrogel was significantly enhanced by

incorporating 0.1 to 0.5 wt% of retinol. They also found that retinol promotes the differentiation of MSCs into neural cells. Further research by Fadera *et al*^[177] led to the development of injectable hydrogel systems loaded with stromal cell-derived factor-1 α , which recruited ASCs and boosted ASC migration. Tao *et al*^[178] utilized hepatocyte growth factor- and 5 α -DHT-gelatin microspheres for treating human ADSCs and explored the reconstruction of sebaceous glands. They found that these gelatin microspheres stimulated ADSC migration and tube formation. In addition to drugs and cellular factors, bioactive peptides can significantly ¹⁵ enhance stem cell adhesion, proliferation, and targeted differentiation. These peptides can be immobilized on culture plates or attached to scaffolds, such as hydrogels or synthetic matrices^[174]. Jose *et al*^[179] investigated the ability of glycine-histidine-lysine (GHK) to boost the secretion of pro-angiogenic factors from human MSC in culture and when covalently linked to alginate hydrogels. They observed ¹⁴ a dose-dependent increase in the VEGF concentration in the media conditioned with GHK-treated MSC, which amplified endothelial cell proliferation, migration, and tubule formation. These findings indicate that the pro-angiogenic potential of MSC can be significantly augmented by presenting GHK with a biodegradable carrier. Gallagher *et al*^[180] conducted a systematic review of the impact of the arginine-glycine-aspartate (RGD) peptide on hMSCs in a HA hydrogel under standard and ischemic culture conditions. They found that under standard culture conditions, RGD notably increased the spread of hMSC and the release of VEGF and monocyte chemoattractant factor-1.

CONCLUSION

To tackle the complex challenges of wound repair, stem cell-based therapy has emerged as a promising strategy aimed at enhancing wound healing and promoting skin regeneration. However, the use of stem cells in this context presents several challenges. Recently, the critical role of combining stem cells and biomaterials in the wound healing process has been recognized. Both natural and synthetic biomaterials can be deliberately crafted for the purpose of treating wounds, considering their physical and

chemical properties. The structural ² properties of a well-designed biomaterial or scaffold can create a protective and sometimes stimulatory environment for stem cells, imitating the natural ECM and controlling different aspects of stem cell behavior such as adhesion, proliferation, differentiation, and paracrine activities.

Incorporating stem cells into organized biomaterials improves their ability to repair impaired ² skin tissue and enhance crucial wound-healing factors, such as epithelialization, granulation tissue formation, vascularization, and angiogenesis. The use of biomaterials can help overcome the barriers associated with stem cell-based therapies. This comprehensive review examines the development and application of biological scaffolds for stem cells and their derivatives, emphasizing their roles in supporting stem cell adhesion, proliferation, differentiation, and paracrine functions. It also highlights the effect of scaffolds on stem cell behavior and identifies the key characteristics of scaffolds responsible for improved cell activity when combined with biomaterials.

Despite yielding promising outcomes in non-clinical studies, the availability of biomaterials tailored for stem cell-based treatments in clinical settings is limited. Consequently, additional clinical trials employing biomaterials are required to clarify the influence of biomaterial characteristics on the healing, restoration, and regeneration of tissues in human subjects. Moreover, there is a growing need for customized biomaterial designs to meet various patient requirements, which entails adjusting the physical, chemical, and structural properties of materials to align with specific medical needs. This personalized approach ensures that the biomaterial optimally interacts with the patient's distinctive physiological environment, thereby fostering efficient tissue repair and regeneration. By considering factors such as biocompatibility, degradation rates, mechanical strength, and the capacity to support cell growth and differentiation, tailored biomaterials can effectively meet a wide range of patient needs, including wound healing, tissue regeneration, and organ repair.

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