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REVIEW

Bioactive Materials That Promote the Homing of Endogenous Mesenchymal Stem Cells to Improve Wound Healing

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Abstract: Endogenous stem cell homing refers to the transport of endogenous mesenchymal stem cells (MSCs) to damaged tissue. The paradigm of using well-designed biomaterials to induce resident stem cells to home in to the injured site while coordinating their behavior and function to promote tissue regeneration is known as endogenous regenerative medicine (ERM). ERM is a promising new avenue in regenerative therapy research, and it involves the mobilizing of endogenous stem cells for homing as the principal means through which to achieve it. Comprehending how mesenchymal stem cells home in and grasp the influencing factors of mesenchymal stem cell homing is essential for the understanding and design of tissue engineering. This review summarizes the process of MSC homing, the factors influencing the homing process, analyses endogenous stem cell homing studies of interest in the field of skin tissue repair, explores the integration of endogenous homing promotion strategies with cellular therapies and details tissue engineering strategies that can be used to modulate endogenous homing of stem cells. In addition to providing more systematic theories and ideas for improved materials for endogenous tissue repair, this review provides new perspectives to explore the complex process of tissue remodeling to enhance the rational design of biomaterial scaffolds and guide tissue regeneration strategies.

Keywords: endogenous stem cell homing, in situ tissue regeneration, biomimetic design, wound healing, bioactive materials

Introduction

As the primary barrier against the external environment, the skin is vulnerable to various deleterious factors, which can result in different types of skin lesions and damage.[1] However, chronic, acute, massive, and complex wounds often struggle to heal[2] as they rely on the patient's self-repairing ability, which can bring severe physical and psychological burdens to patients.[3] Therefore, a variety of therapies have been developed to accelerate wound healing. These therapies usually involve traditional treatments with wound dressings, antibiotics, the removal of necrotic tissue, as well as the performance of skin grafts if necessary.[4] It is often performed together with emerging therapies and using biophysical modalities such as electrical stimulations[5] or shock waves.[6] In addition, it comprises tissue engineering therapies that rely on prefabricated biomaterials,[7] ex vivo expanded cells, and selected growth factors.[8]

The term homing, known as recruitment in tissue repair and regeneration contexts, typically refers to the ability of a cell to be recruited and find its way to the site of an injury.[9] In natural healing, after platelets are activated, platelet-derived factors are released to induce the homing of innate immune cells to the damaged tissues. After this, the recruited immune cells create a favorable microenvironment and secrete paracrine factors at the injury site, where both resident and circulating reparative cell populations are recruited. For example, progenitors and stem cells are subsequently involved in tissue repair and the regeneration of new tissue (Figure 1).[10,11] However, natural endogenous regenerative processes, in many cases, are often too limited for completing wound repair.[12] As such, a substantial number of stem cell

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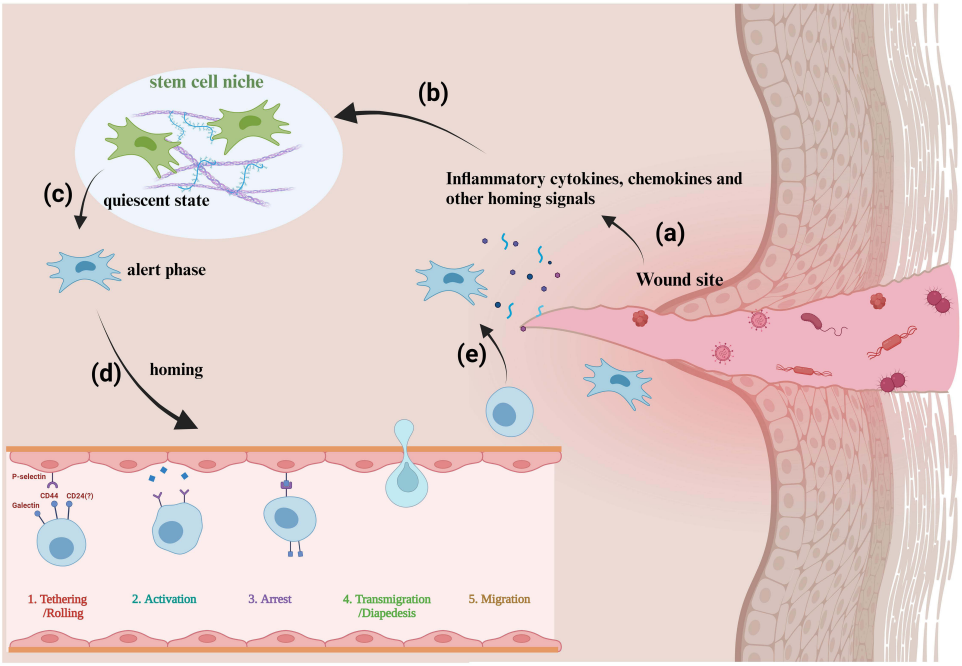

Figure 1 MSC endogenous homing promotes wound healing. (a)–(e) The wound site sends recruitment signals through inflammatory cytokines and chemokines, etc. These signaling molecules diffuse to the vicinity of the stem cell niche and are captured by the quiescent stem cells. These then change from quiescence to alertness and subsequently begin to migrate and home in, thus arriving at the wound site for paracrine secretion and differentiation. Created with BioRender.com.

therapies have thus been developed.[13] Bone marrow mesenchymal stem cells (BMSCs) are one of the most intensively studied candidates for cell therapy.[14] Despite this, however, transplanted MSCs have poor efficacy due to inhospitable wound microenvironments and low homing efficiency.[15] In addition, in vitro cell transplantation has to overcome high economic costs and significant market regulatory hurdles while requiring meticulous handling at all stages of stem cell acquisition, processing, and transplantation.[16] Consequently, it is crucial to improve homing efficiency.

Endogenous stem cell homing refers to the transport of endogenous mesenchymal stem cells (MSCs) to damaged tissues.[15] Endogenous regenerative medicine (ERM) is defined as the paradigm of using well-designed biomaterials to coax the homing of resident stem cells toward injured sites, orchestrating their behaviors and functions to promote tissue regeneration.[17,18] Endogenous regenerative medicine is a promising new avenue in regenerative therapy research, which focuses on the mobilization of endogenous stem cells for homing. By understanding the MSC homing process, we are able to modulate endogenous MSC homing by interfering with MSC-influencing factors, which promotes more resident MSCs in the stem cell niche to reach the site of injury and participate in tissue repair without the need for exogenous implantation of MSC cells. Promoting more endogenous MSCs to reach the site of injury or facilitating more targeted and increased secretion of already reached MSCs by carrying key homing factors, or carefully designing the physical properties, 3D structure and microstructure of the material is the main means to promote endogenous homing. Compared with cell transplantation, promoting the homing of endogenous MSCs to increase tissue self-repair can avoid the risk of direct application; moreover, it is safer, simpler, more practical, and more economical.[19] Indeed, the enhancement of endogenous stem cell homing can be applied not only directly, but also as an adjunctive strategy to optimise the efficacy of cellular therapies, where homing is a critical step after transplantation of cellular material. Achieving efficient and optimal cell homing at the target site is also an ongoing challenge in cell transplantation technology.[20]

Undoubtedly, ERM is a promising new avenue in regenerative therapy research, and the mobilization of endogenous stem cell homing is its mainstay. In this review, we summarize the notable research on endogenous stem cell homing in the field of skin tissue repair. We also identify the tissue engineering strategies currently available for regulating the stem cell homing process. This article outlines the progress that has been made in this study area and the obstacles that still to

be overcome. We hope to inspire more tissue engineers, biomaterials scientists, and surgical clinicians to actively engage in this field and provide practical solutions to clinical issues.

How Mesenchymal Stem Cells Homing

Homing is usually divided into systematic homing and non-system homing.[21] In systemic homing, MSCs are endogenously recruited or administered into the bloodstream, and they then must go through a multi-step process to leave the blood circulation and migrate to the damaged area. In non-systemic homing, MSCs are locally transplanted into the target tissue, and they are then directed to the site of injury by a chemokine gradient. Systemic homing can be divided into five steps: the initial tethering of selectins, chemokine-mediated activation, integrin-promoted arrest, matrix remodeler-assisted diapedesis or transmigration, and chemokine gradient-guided extravascular migration (Figure 2).[22]

Tethering

The first step, tethering and rolling, is contributed to by the selectins that are expressed by endothelial cells.[23] Only if they are already arrested or trapped could MSCs adhere to the endothelium; meanwhile, in intact vessels, MSCs would be rare under normal circulatory conditions.[24] The selectin that primarily contributes to bolting and rolling of MSC is the P selectin. The CD44 expressed by MSCs catches onto the selectins and causes the cell to start rolling along the vasculature wall.[23] The glycoprotein CD44 is expressed on the surface of many different cells, and it acts as a ligand to adhere to cells through other molecules, including hyaluronic acid.[25] Its role as a ligand for P-selectin has also been reported. Therefore, P-selectin may be a ligand for the P-selectin that are expressed by MSCs. Galectin-1 or CD24 may also serve as ligands for P-selectin on MSCs.[26,27] The selectin used by MSCs has yet to be well understood, whereby several studies have suggested that the interaction of mesenchymal stem cells with endothelial cells is mediated by P-selectin.[26] Other studies have shown that E-selectin and L-selectin are not expressed in MSC cell membranes.[28] Their interaction with the vessel wall is not apparent. One study found that, by blocking the E-selectin on endothelial cells, the adhesion of BMSCs was not reduced.[29] However, other researchers have found that the CD44 on MSCs interacts with E-selectin and L-selectin.[30] Several adhesion molecules, thus far, have been identified as being connected with MSC transendothelial migration. These include particularly late antigen-4 (VLA-4), ICAM-1,[31] VCAM-1, and P-selectin.[32] Antonín Sedlá ř et al found that the interaction between Galectin-3 and integrins mediates the cell–matrix adhesion in endothelial cells and mesenchymal stem cells.[33] Rüster et al proposed that P-selectin and α4β1-integrin/VCAM-1 play important roles in the venule recruitment to mouse mesenchymal stem cells.[29] Under the current concept of homing, tissues will need to recruit circulating mesenchymal stem cells from the bloodstream to ensure an efficient delivery to the damaged site. To this end, the surface of mesenchymal stem cells has many different adhesion molecules, and these molecules are also shared with leukocytes. These adhesion molecules include CD29 (β1-integrin), CD24, CD49a-f (α1-α6 integrin),[34] and CD44, although CD24 was not found in other studies.[35] The role and mechanism of selectin in MSC homing are not yet clear, and there is still controversy over

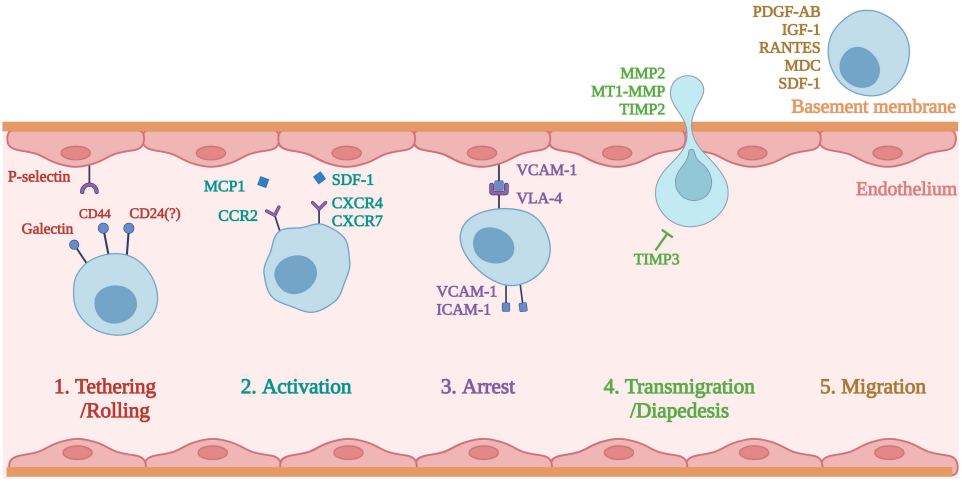

Figure 2 The process of the systematic homing of mesenchymal stem cells (MSCs). Created with BioRender.com.

whether CD24 is an adhesive molecule that plays a role in this process. In the application of tissue engineering, there are currently almost no biomaterials targeting selectins to promote endogenous homing. This may be due to the unclear mechanism and insufficient impact of selectins on homing efficiency, which makes the application or engineering of selectins not an ideal way for endogenous regenerative medicine.

Activation

The second step, activation—which is generally in response to inflammatory signals—is facilitated by chemokine receptors. In MSC trafficking, the chemokines released from endothelial cells and tissues can promote the activation of ligands that are involved in multiple homing processes, including the adhesion, chemotaxis, and migration of MSCs in target tissues. Stromal cell-derived factor (SDF)-1 expressed on endothelial cells is critical for this step.[36,37] SDF-1 is the ligand to the chemokine receptor CXCR4, and it is considered expressed by MSCs.[38–40] Indeed, it has been researched that CXCR7 is also expressed in MSCs, which similarly binds SDF-1 to promote the homing to various tissues.[41–43] No matter how the specific receptors and ligands interact, the effect of the activation step is to multiply the affinity of the integrins' extracellular domain by inducing conformational changes; furthermore, these integrins are essential for cell arrest.[44,45] Chemokines that mediate the activation step, such as monocyte chemoattractant protein-1 (MCP-1) or SDF-1, increase the affinity of integrins, thus leading to cell arrest. Integrin arrest is most likely primarily mediated by CD49d (α4β1) via its binding to VCAM-1 (CD106) on endothelial cells.[46] Certain studies have reported the expression of chemokine receptors in MSCs, including CCR1, CCR2, CCR4, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, and CXCR6; moreover, they have noted the functional roles of some of the chemokine receptors during the MSC migrating process.[44,47–49] Other studies have shown that, during the movement of MSCs from bone marrow, the SDF-1 / CXCR4 axis also plays an essential role.[50–52] The chemokines released from tissues may lead the CXCR4 receptor in the cell to move to the cell surface, which facilitates the migration of MSCs to their destinations. For example, Andong Zhao et al have shown that the SDF-1/CXCR4 signaling pathway guides systemically transplanted bone marrow mesenchymal stem cell migration toward the lesion site.[51] Although SDF-1/CXCR4 is the most well-studied chemokine–chemokine receptor axis, according to recent findings, other signaling interactions are also important mediators of stem cell homing, such as CCL27-CCR10 and CCL21-CCR7.[53–55] Chemokines are the most commonly used homing factors in endogenous regenerative medicine to bind material applied to the wound site, and by applying chemokines to provide navigational signals to MSCs in the surrounding stem cell niches to mobilise more and more distant MSCs to homing towards the damaged site.[56]

Arrest

The third step is the arrest, which is facilitated by integrins. VLA-4 (integrin a4b1) expressed by MSCs becomes activated in response to chemokines such as SDF-1. Following activation, the integrin VLA-4 binds to the VCAM-1 on endothelial cells.[15] Steingen et al reported that, instead of undergoing full diapedesis, MSCs could use the VLA-4/VCAM-1 molecule to migrate through non-activated endothelia; furthermore, they are inclined to integrate with the endothelial layer.[57] Just like the interactions of intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM)-1), the adhesion molecules on the endothelial surface interact with the integrins expressed in MSC cell membranes, which then lead to the formation of transmigration wells and docking structures. These positions are sites that are rich in VCAM-1 molecules, ICAM-1, proteins, and cytoskeleton components like α-actinin.[28] However, anti-VCAM-1 and anti-VLA-4 antibodies cannot entirely block the transendothelial migration of MSCs; As such, other integrins that are also involved in this process can be assumed.[57] MSCs have been shown to express varieties of receptors that are associated with adherence to extracellular matrix proteins and intercellular contacts, such as integrins α1~α5, αv, β1, β3, and β4, together with other adhesive molecules, ie, ICAM-1, ICAM-3, VCAM-1, and CD166.[28] Engineering integrins and their receptors are also commonly used methods to promote endogenous homing. By designing peptide segments with high affinity for integrins or integrin ligands, they promote the residence of MSCs in target tissues, thereby promoting endogenous regeneration.[58,59]

Transmigration

In the next step, diapedesis or transmigration, MSCs must trans-cellularly travel through the endothelial cell layer and, later, the basement membrane. To accomplish this, MSCs break down the endothelial basement membrane by secreting membrane matrix

metalloproteinases (MMPs).[60] Various other proteins regulate the maturation and activity of MMPs, of which, most prominently, are the tissue inhibitors of metalloproteinases (TIMPs). Inflammatory cytokines induce the expression of these remodeling enzymes, and the expressed remodeling enzymes then serve as a signal for migration into harmed tissue.[61] For instance, TNF-α and IL1β stimulate MSCs to produce matrix metalloproteinases (MMPs), as well as to trigger the activation of chemotaxis through the extracellular matrix.[62,63] Proteolytic enzymes-MMPs play an essential role in MSC migration by regulating the degradation of the extracellular matrix.[64] Different MMPs and their signaling pathways affect MSC differentiation, migration, proliferation, and angiogenesis. Migration and invasion into the damaged tissues of MSCs are facilitated by the expression of MMP-2, CXCR4, and MT1-MMP.[65,66] MMP is a key influence on cell migration, and MMP overexpression can enhance cell invasiveness. Some materials will carry bioactive factors to promote MMP overexpression to accelerate wound healing.[67]

Migration

The final step is led by chemotactic signals that are set free in response to tissue damage. MSCs must migrate to the site of injury through the interstitium. The damaged tissues release specific factors, such as chemoattractants, to promote the adhesion, migration, and homing of marrow mesenchymal stem cells in the affected areas. In response to the factors regulated under inflammation, MSCs can migrate toward inflamed tissues.[68–70] Inflammatory cytokines, such as IL-6, IL-8, IL-1β, and TNF-α, are included. Numerous growth factors, eg, the vascular endothelial-derived growth factor-A, epidermal growth factor, platelet-derived growth factor (PDGF-AB), fibroblast growth factor, transforming growth factor-β1, hepatocyte growth factor, insulin-like growth factor (IGF1).[47,70–73] Additionally, this includes, to a lesser extent, the chemokines RANTES, MDC, and SDF-1.[66,74] MSCs migrate to these signals and thus to the damaged tissue. The creation of a suitable microenvironment at the wound site by the material can attract more MSCs to the target tissue, and the combination of chemokines, inflammatory cytokines, and a variety of growth factors with well-designed materials can help more MSCs to migrate to the damaged site to participate in tissue repair.[56]

Factors Influencing the Homing Process

The use of tissue engineering to promote endogenous wound healing is an emerging direction in wound repair. To promote MSC homing through bioactive materials, we must first know what factors affect MSC homing (Figure 3). Adhesion molecules, chemokines, pro-inflammatory cytokines, growth factors, and the MMPs involved in the natural homing process are the main influencing factors of homing. The exogenous application of key homing factors can provide more attraction, as well as more stable and durable navigation clues for MSCs to guide endogenous MSCs to their destination (Table 1). Adhesion molecules are

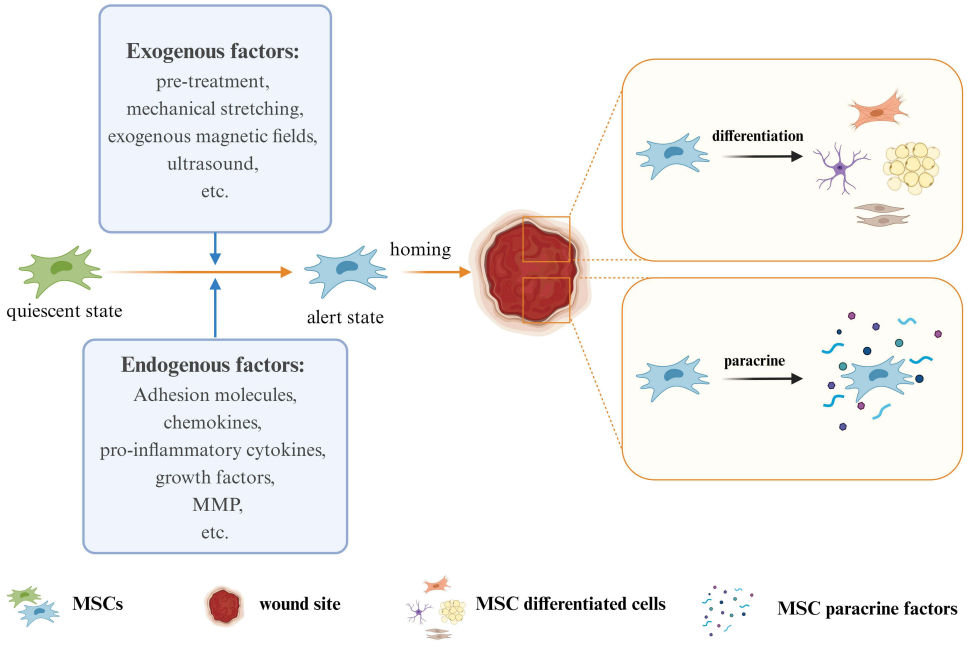

Figure 3 Factors affecting the homing of MSCs. Created with BioRender.com.

Table 1 Factors Influencing Endogenous MSC Homing

				Reference
Endogenous factors	Biochemical factors	Adhesion molecules	VCAM-1, ICAM-1, ICAM-2, P selectin, CD24, CD44, CD29 (β1-integrin), CD49a-f (α1-α6 integrin), CD51/61	[15,25–27,31,34,75]
		Chemokines	CXCR1-6, CCR1/2/4/6/8/9, MCP-1, MIP-1α, SDF-1	[65,66,74,76]
		Pro-inflammatory Cytokines	IL-3, IL-6, IL-8, IL-1β, TGF-β, TGFβ1, IGF-1, TNF-α	[47,65,70–73,77–79]
		Growth factors	VEGF, PDGF, EGF, FGF, HGF, IGF, SCF	[47,65,70–73]
		Matrix metalloproteinase (MMP)	MMP-1, MMP-2	[80,81]
		Other factors	ATP, intracellular ceramide kinases, Platelets	[81–84]
	Physical factors	Hemodynamic shear stress, cyclic tensile strain, and the diameter of blood vessels, endogenous electric fields (EFs)		[85–88]
Exogenous factors	Exogenous magnetic fields			[89]
	Ultrasounds with different parameters		Pulsed ultrasound (p-US)	[90]
			Low-intensity pulsed ultrasound (LIPUS)	[91]
			Ultrasonic microbubbles	[92]
			Ultrasound-targeted microbubble destruction (UTMD)	[93]
	Shortwave in high-frequency electrotherapy			[94]
	Exogenously applied electric field			[95]
	Mechanical Stretching			[96]

mainly involved in rolling and transendothelial migration during homing.[28] It has been confirmed that the adhesion molecules involved in homing are as follows: VCAM-1, ICAM-1, ICAM-2, P selectin, CD24, CD44, CD29 (β1-integrin), CD49a-f (α1-α6 integrin), and CD51/61. The main ones involved in the chemotactic process are chemokines and their receptors, pro-inflammatory cytokines, and growth factors.[75] Chemokines and their receptors mainly include CXCR1-6, CCR1/2/4/6/8/9, MCP-1, MIP-1α, and SDF-1. Pro-inflammatory cytokines such as IL-3, IL-6, IL-8, IL-1β, TGF-β, IGF-1, and TNF-α, as well as growth factors such as VEGF, PDGF, EGF, FGF, HGF, IGF, and SCF, are released from the site of injury to provide chemotaxis signals for MSCs to attract them to the designated location. The action of metalloproteases allows MSCs to cross the endothelial basement membrane during homing, and the MMPs that have been studied with respect to this are mainly MMP-1 and MMP-2.[65]

In addition to the influence of various homing factors, certain internal factors can also regulate the homing process. For instance, intracellular ceramide kinases regulate BM–MSC migration, while the inhibition of ceramide kinases inhibits migration.[82] Lin-Hua Jiang et al proposed that ATP-induced Ca^{2+} signaling can regulate MSC migration.[83] Histologic origin can also affect the homing ability of MSCs. MSCs (DPSCs) are isolated from the pulp exhibit top-notch osteogenic potential, as well as the highest proliferative capacity, when compared to fat and bone marrow sources.[97] Platelets have also been found to promote the adhesion ability of MSCs to homing.[84] Physical factors in the body can also affect the homing process, such as hemodynamic shear stress,[85] cyclic tensile strain,[86] and the diameter of blood vessels.[87] And endogenous electric fields (EFs) can be harnessed by MSCs for directed migration.[88]

The exogenous factors affecting homing mainly include culture conditions, various pretreatments, mechanical stretching, exogenous magnetic fields, and ultrasounds with different parameters. Culture conditions can affect the expression of cell surface markers. A 3D culture can better adapt MSCs to their cell niche environment than 2D cultures, thus enhancing their paracrine signaling activity.[89] H_2O_2 pretreatment, cytokines (such as interleukin (IL)-6 and

hepatocyte growth factor), and hypoxia conditions[98] can stimulate the expression of the chemokine receptor (CXCR) 4 receptor. In addition, collagen structure can regulate the behavior of MSCs. For instance, collagen has a more advanced collagen structure than gelatin, which can promote biological cell–matrix interaction by regulating MMP activity, thereby promoting MSC diffusion and proliferation.[99] Experiments by Xiao Liang et al show that mechanical stretching can promote MSC transdifferentiation and homing.[96] Magnetic targeting technology has been proven to improve the delivery of MSCs to targets. Using selected magnetic nanoparticles to magnetize MSCs, MSCs can be promoted via differentiation and secretion, or through improving targeting under an external static or dynamic magnetic field.[100–104] Other studies have shown that combining a magnetic field and electrospun scaffold can produce directional synergy, which can be utilized to promote the cartilage differentiation of MSCs.[105] Ultrasound is a physical signal that is often enhanced to promote homing and accelerate MSC secretion; moreover, different types of ultrasounds can play different roles. Yanni He et al recruited endogenous BM-MSCs using the sound capture force generated by pulsed ultrasound (p-US) irradiation.[90] Dongmei Ye et al found that a shortwave in high-frequency electrotherapy can upregulate the expression of HIF-1, CXCR-4, and SDF-1 in osteoblastic culture media when promoting the process of endogenous MSC chemotaxis.[94] Experiments by Rebecca M. Lorsung et al show that cavitation forces or acoustic radiation from low-intensity pulsed ultrasound (LIPUS) can shape the microenvironment that supports MSC tropism.[91]

Biomaterials for Skin Tissue Regeneration Using MSC Endogenous Homing

Promoting the homing of endogenous stem cells to accelerate repair and regeneration has been widely used in many fields, including the reconditioning of bone,[106] cartilage,[107] tendons,[108] the heart,[109] lungs,[110] the endometrium,[111] teeth,[112] and other tissues and organs. In contrast, the application in promoting skin wound healing has yet to be explored thoroughly. Mesenchymal stem cells in a static state reside in the central or surrounding stem cell niches. When injured, the MSCs transition from a quiescent state to an alert phase, which then migrate to the injured site through homing to participate in the in situ repair of tissues (Figure 1).[113,114] It is a vital part of endogenous regenerative medicine to design bioactive materials for diverse targets in different stages of homing to promote stem cell homing (Table 2). In tissue regeneration, we must advance more mesenchymal stem cells to set out from the niche, to assist more coordinated cell movement during migration, and stimulate the paracrine secretion of mesenchymal stem cells at the wound (Figure 4).[115–119] In addition, there has been evidence that in vitro-transplanted cells trigger endogenous cell recruitment in the process of inducing tissue regeneration, which indicates that endogenous homing is not only an event in ERM. Cell therapy and endogenous regeneration can also promote and assist each other.[120]

Table 2 Bioactive Materials That Modulate Different Physicochemical Factors to Promote Homing of MSCs

Function	Classification	Material Design or the Homing Factor it Carries	References
Mobilizing more MSCs from the stem cell niche	Chemokine	SDF-1 α	[56,111,121,122]
	Integrin-targeting proteins and peptides	LLP2A, Gly-Arg-Gly-Asp-Ser-Pro-Lys Peptides	[58,59,123]
	Cytokine	G-CSF	[56]
	Growth factor	Transforming growth factor beta-3 (TGFβ3)	[124]
	Other molecules	Substance P, Bone marrow homing peptide (BMHP), leptin receptor (LEPR)-binding peptide, irisin	[9,121,125–127]

(*Continued*)

Table 2 (Continued).

Function	Classification	Material Design or the Homing Factor it Carries	References
Promoting more effective migration of MSCs	Imposing signaling molecular cues that direct migration	IL-6, IL-1 β, MiR-9-5p, CSF-2 Parathyroid hormone 1–34, TNF-α, Prostaglandin E2 (PGE2), Vascular endothelial cell growth factor-C (VEGF-C)	[77,78,80,128–131]
	Increasing receptor-ligand binding during migration	Engineering integrin ligand assembly	[132]
	Increasing substrate degradability	MMP-1 MMP-2	[80,133]
	Designing the physical properties and microstructure of artificial substrates	Micropatterned Porous Fiber Scaffolds	[134]
	Applying physical clues	Electromagnetic fields (EMF), Low-intensity pulsed ultrasound (LIPUS)	[81,135]
Promoting paracrine secretion of MSCs after reaching damaged tissues	Designing the structure and physicochemical properties of materials to influence MSC secretion through cell-substrate and cell-cell interactions	Designing mechanical strength	[136]
		Applying improved 3D printing techniques	[137]
		Regulating two- or three-dimensional structures	[138]
		Adjusting the aperture of the scaffolds	[139]
		Designing 3D morphology of fiber scaffolds	[140]

Promotion of MSC Leaving

Making more stem cells leave the stem cell niche is undoubtedly an effective means through which to promote endogenous homing. In the ERM field, increasing the attraction of the destination (the wound site) to the stem cells in

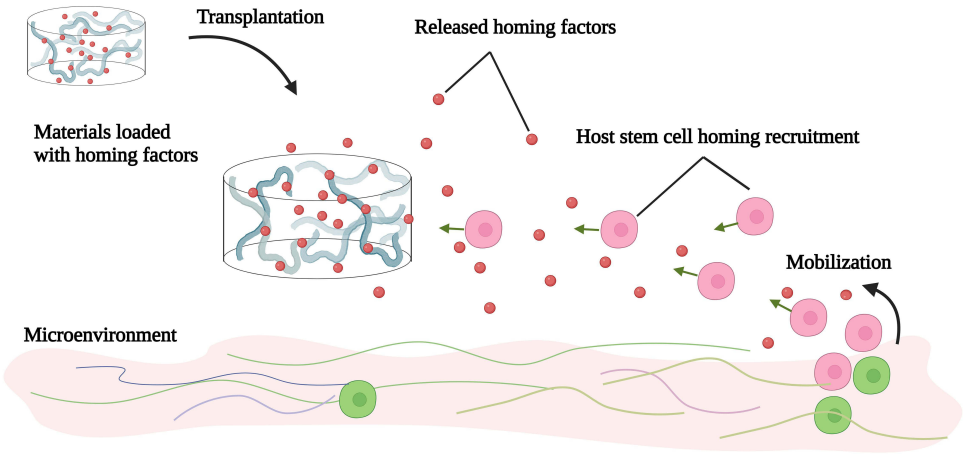

Figure 4 Bioactive materials loaded with various homing factors to promote MSC homing in order to aid skin wound repair. Created with BioRender.com.

the stem cell niche is the research focus. The essential way through which to increase the attraction of the destination is to make homing signals more visible to the stem cells, make the stem cells more sensitive to homing factors, and make the navigation clues more stable and lasting. Making stem cells more visible to homing signals depends on applying various homing factors. Using homing factors alone or combined with tissue engineering materials can make stem cells receive more homing signals, which then promotes endogenous homing.[56] When combined with cell therapy, MSCs are often pretreated with homing factors or placed in various biomaterials (such as hydrogels and sponge scaffolds) that combine homing elements or other substances that can promote homing. They are then implanted into the body as a whole. Making stem cells more sensitive to homing factors is mainly conducted in cell therapy. Through genetic engineering technology, exogenous MSCs have been gene edited to improve their homing efficiency after transplantation into a body. Making navigation clues more stable and lasting is usually carried out simultaneously by applying homing factors. Advanced slow-release technology controls the release concentration of homing factors in the optimal range.

The microenvironment is critical to cell function and activity. Different microenvironments have different effects on the biological functions of MSCs. The differentiation potential of MSCs is highly dependent on microenvironmental soluble factors, including cytokines (TNF-α and IL-6), growth factors (VEGF, TGF-β, IGF-1, and FGF), and hormones (estrogen, parathyroid hormones, and growth hormones).[141] Under normal conditions, cells live in the complex and dynamic extracellular matrix (ECM), which contains various complete microenvironment clues that determine cell behavior and function. The natural matrix has a great potential in promoting cell homing, and it does not require additional engineering to play a beneficial role.[142] Relying on the mixtures of the natural ingredients they contain, acellular matrices and acellular tissue have been directly used as biomaterial scaffolds.[143] The biomaterial components used to attract stem cells to guide in situ regeneration mostly drew inspiration from ECM components, and they mainly rely on mimicking one or a few components of the ECM. Substitutes for its applications mainly include proteins (gelatin,[144] collagen,[145] silk fibroin,[146] etc.) and polysaccharides (hyaluronic acid,[147] starch,[148] chitosan,[149] etc.). Scientists have applied one or more ECM components into hydrogels or sponge scaffolds, which are then placed into the wound to promote endogenous homing and to help skin regeneration. The bionic design that simulates the ECM, which is simultaneously combined with navigation hints for the specific aspects of the MSC homing process and small molecule drug delivery, is also a primary research direction of bionic technology and regenerative medicine. For example, in one study, horseradish peroxidase (HRP)-catalyzed sprayable gelatin hydrogels (GHs) were used as a platform to direct the carrying of two chemokines (in the process of the in situ crosslinking for endogenous cell recruitment in diabetes wounds[150]): interleukin-8 (IL-8) and macrophage inflammatory protein-3a (MIP-3a) hydrogel excipients. In diabetes wounds, MSC migration is inhibited and chemotaxis is insufficient.[151] In comparison, the local application of these two in situ hydrogels with chemokines for MSC recruitment can improve the wound's local microenvironment, as well as promote the chemotaxis process in MSC homing, thus promoting the wound healing of diabetes. van de Kamp et al loaded collagen and silk fibroin with a chemoattractant for MSCs and the hepatocyte growth factor (HGF). The experimental results showed endogenous MSCs were recruited from the local environment after subcutaneous implantation.[145] In addition to the well-known growth factors and chemokines that can be used in tissue engineering to promote homing, certain particular substances can also play a role in recruiting endogenous MSCs, such as substance P, as well as the bioceramics that can provide bioactive ions such as Ca, Mg, and Si.[152] Graphene oxide has also been employed to construct nucleo-shell microfiber array hydrogels with chemokines (SDF-1α), which can effectively recruit and stimulate the neuroid differentiation of BMSCs.[153]

We already know the basic process of MSC homing and its various homing factors. How one is to introduce the key factors involved in the homing process into tissue engineering is a problem worth exploring. To play a more stable role in damaged parts, the homing factor is combined with various materials to promote its steady and lasting release. Electrospinning technology and 3D printing technology are focused on[154] because they can not only simulate the tissue structure,[155] such as the blood vessel structure,[156] but they can also emulate the natural tissue (such as pores and microchannels) in the microstructure.[157]

It is beyond doubt that more MSC homing can be promoted by combining navigation clues that enhance endogenous homing with bioactive materials, as well as by making them release at a constant speed and for a long time. However, not all homing factors in vivo are suitable for direct application to tissue engineering. For example, although SDF-1α is one

of the most widely studied potent homing factors (as a high molecular weight protein), it is not easily processed or introduced into the support material. Additionally, SDF-1α is easily degraded by the proteolytic enzymes activated when tissues are damaged, such as matrix metalloproteinase (MMP-2) and endogenous CD26/dipeptidyl peptidase IV (DPP-IV). To solve this problem, researchers have used small molecular weight inhibitors to block and inactivate the enzyme, as well as designed anti-protease (MMP-2 and DPP-IV/CD26) cleaved SDF-1α peptides; these, in turn, have produced SDF-1 molecules that have high stability. Used alone, it can enhance endogenous cell recruitment to repair myocardia.[158] It has been shown that SDF-1α peptide can be incorporated into synthetic grafts to promote cell growth and tissue repair. For example, Muhammad Shafiq et al synthesized SDF-1α-derived peptide and heparin-tethered poly (L-lactide-co-ε-caprolactone) (PLCL) copolymer by coupling SDF-1α-derived peptide and heparin to eight-arm star-shaped PLCL copolymers, as well as by making a double-layer tubular scaffold with electrospinning technology. It was implanted subcutaneously in rats to observe its effect in the promotion of regenerating skin blood vessels. The results showed that PLCL copolymers can provide a stable local gradient of chemokines in scaffold material, which is beneficial for attracting and enriching endogenous cells. The number of blood vessels, stem cells, and α-SMA positive cells in SDF-1/ heparin grafts was found to be significantly higher than that found in the control group.[156] Zhen Xu et al designed a microgel array patch that encapsulates SDF-1, which can be customized with its concentration gradient and is capable of generating a long-lasting concentration gradient of signaling molecules that promotes MSC recruitment, thereby recruiting endogenous stem cells for the treatment of skin damage.[159] Yucong Li et al designed a bioactive microsphere (MESS) capable of endogenous stem cell recruitment and induction based on hBMSCs secretion and supramolecular hydrogel. Oxidised alginate (o-alg), tris(hydroxymethyl)aminomethane (THAM) and gelatin were the basic components of the hydrogel microspheres. And the biophysical stimulation by pulsed electromagnetic field (PEMF) was utilised to enhance the quality and bioactivity of MESS after injection into the body, constituting PEMF-enhanced MESS (PE-MESS). The hydrogel injection was implanted subcutaneously on the back of rats, and it was observed that significantly more MSCs were recruited in the MESS hydrogel compared with the other groups.In addition, after the application of the pulsed electromagnetic field, significantly more MSCs were attracted and migrated within the PE-MESS hydrogel, and a large number of MSCs were aggregated around the PE-MESS. This suggests that both engineered MESS and PEMF have desirable stem cell chemotaxis effects and that the combined application maximises the promotion of stem cell aggregation around the microspheres (Figure 5).[12]

Making cells more sensitive to homing signals depends on gene technology, which usually requires operating cells in vitro. Therefore, it is mainly used in cell therapy to improve homing after cell transplantation. Durand et al transfected BMSCs with CXCR4 mRNA, thus creating BMSCs that overexpress CXCR4. This increased the directed cell migration of the MSCs, as well as altering their cytokine secretion.[160] Shuhong Kuang used genetic engineering techniques to produce MSCs that are overexpressed by C-motif chemokine receptor 2 (CCR2), which enhances the targeted migration and immunomodulatory potential of MSCs in vitro in response to the C-C motif chemokine ligand 2 (CCL2).[161]

Promotion of More Efficient Cell Migration

Cell migration is a highly dynamic physiological process that is regulated by biochemical factors, physical factors, and is primarily driven by the cytoskeleton.[162] Its biochemical factors mainly include guide cues, bonding ligands, and matrix degradability.[163] Its physical factors mainly include the ECM's stiffness, elasticity, and viscosity, as well as the ECM's topology, pore size, etc.[164] The migration of cells in one-, two-, and three-dimensional environments have been described as different processes.[165] Broadly speaking, when migration occurs, the cytoskeleton—including the microtubules, intermediate filament, and actin microfilament—is rearranged under the control of an extensive signaling cascade; next, the cell is polarized, and then the cell migration is completed by actin that is protruding forward, adhesion to the surrounding matrix, and actin contraction.[166] Cell-to-matrix interactions and cell-to-cell interactions play a crucial role in migration. Tissue engineering technology can realize the regulation of cell migration through intervention in the ECM environment, restriction of the mechanical properties of the matrix, and a careful design of material topology. TNF-α,[78] IL-6,[77] and other inflammatory factors chemokines (such as SDF-1α,[167] matrix metalloproteinases,[168] integrin[169] and engineered integrin-ligands[132]) are the usual methods of tissue engineering that control cell migration by interfering with biochemical elements.

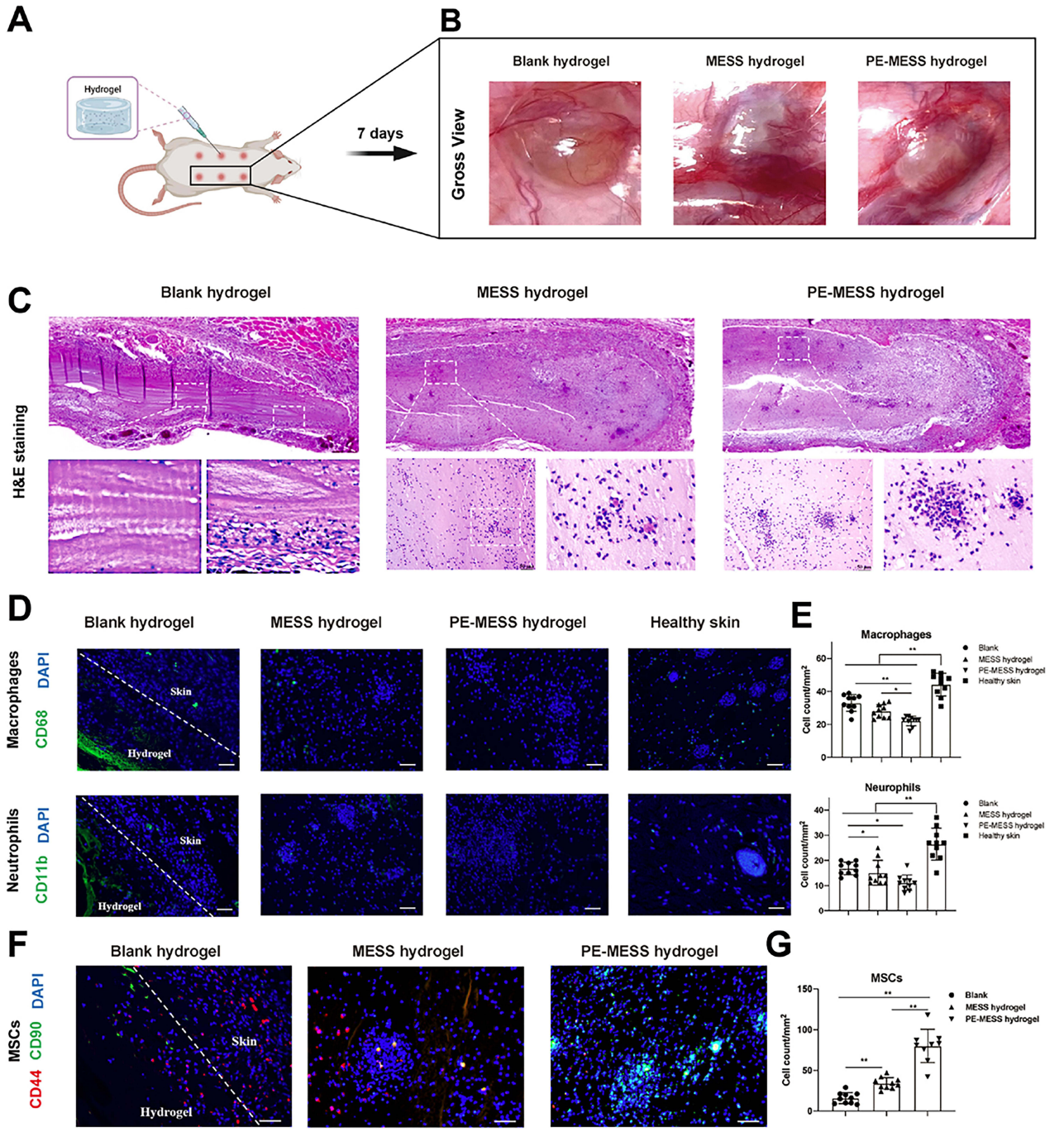

Figure 5 An oxidised alginate-tris (hydroxymethyl)aminomethane (THAM)/gelatin hydrogel as a scaffold combined with an hBMSCs-derived bioactive microsphere system as a bioactive supplement promotes endogenous MSC recruitment under pulsed electromagnetic fields (PEMF). (**A**) Hydrogel injection was implanted subcutaneously in the back of rats. (**B**) Gross condition of the hydrogel microsphere system 7 days after implantation with (**C**) H&E staining. (**D** and **E**) IF staining and semi-quantitative analysis of CD68 and CD11b. (**F** and **G**) Dual-labelled IF staining of CD44 and CD90, and semi-quantitative analysis of double-positive cells for CD44 and CD90 recruited to the hydrogel. *p < 0.05, **p < 0.01. Reprinted with permission from Li Y, Li L, Wang M, et al. O-alg-THAM/gel hydrogels functionalized with engineered microspheres based on mesenchymal stem cell secretion recruit endogenous stem cells for cartilage repair. Bioact Mater. 2023;28:255–272.[12]

In addition to regulating chemical factors, the design of the physical properties of a matrix is also a means of constructing skin substitutes that promote cell migration. An eligible wound implant should promote endogenous cell recruitment and allow cells to pass freely. Furthermore, 3D printing technology is typically used to construct ingen microstructures (such as pores and microchannels), and it is specially designed for hardness gradients.[170–173]

Electrospinning, advanced foaming techniques, and various engineering methods for hydrogel or scaffold structures can also create rich pore and microchannel networks, or it can provide dynamic and controllable mechanical properties to aid cell migration.[174–179] Electric fields were found to be able to adjust the hierarchical microstructure of materials. By adjusting the hierarchical microstructure of the silk fibroin matrix in an electric field, researchers have created an anisotropic porous scaffold that provides suitable mechanical signals for migration in skin healing.[177] Researchers have also discovered certain naturally excellent fibrin arrangements that can be used to provide more explicit physical and mechanical clues for cell migration. Kimberly Nellenbach et al found that the fibrin network of neonates had a higher fiber arrangement; through in vivo and in vitro experiments, they showed that, compared with adult fibrin scaffolds, fibrin scaffolds from neonates can enhance wound healing results.[180] Degang Yang et al introduced gradient channels in tissue engineering scaffolds.[181] With the help of 3D printing technology, the spatial connection of different nanocomposite hydrogel slurries, which change by changing the concentration of the nanomaterials, is formed in order to construct a gradual gradient nanocomposite hydrogel and to control cell migration.[182] The combination of various components can also provide smoother passages for migration or for specially tailored hardness. Hossein Ravanbakhsh et al reported a glycol chitosan hydrogel loaded with carbon nanotubes, which promoted cell recruitment and migration relative to carrier-free hydrogels.[183] Miriam Dietrich et al introduced uniaxial strains in a matrix, thus creating local anisotropic hardness by embedding microstructured photopolymerizable hydrogel strips in channel slides to guide cell migration.[184] Jiawen Li et al adjusted the lamellar spacing and micro-ridge spacing of radial sponges with the ice template method, and they found that denser lamellae and micro-ridges could promote L929 cells and HUVECs to achieve a more ordered arrangement, as well as more efficient cell migration, thus promoting wound healing (Figure 6).[185] However, cell

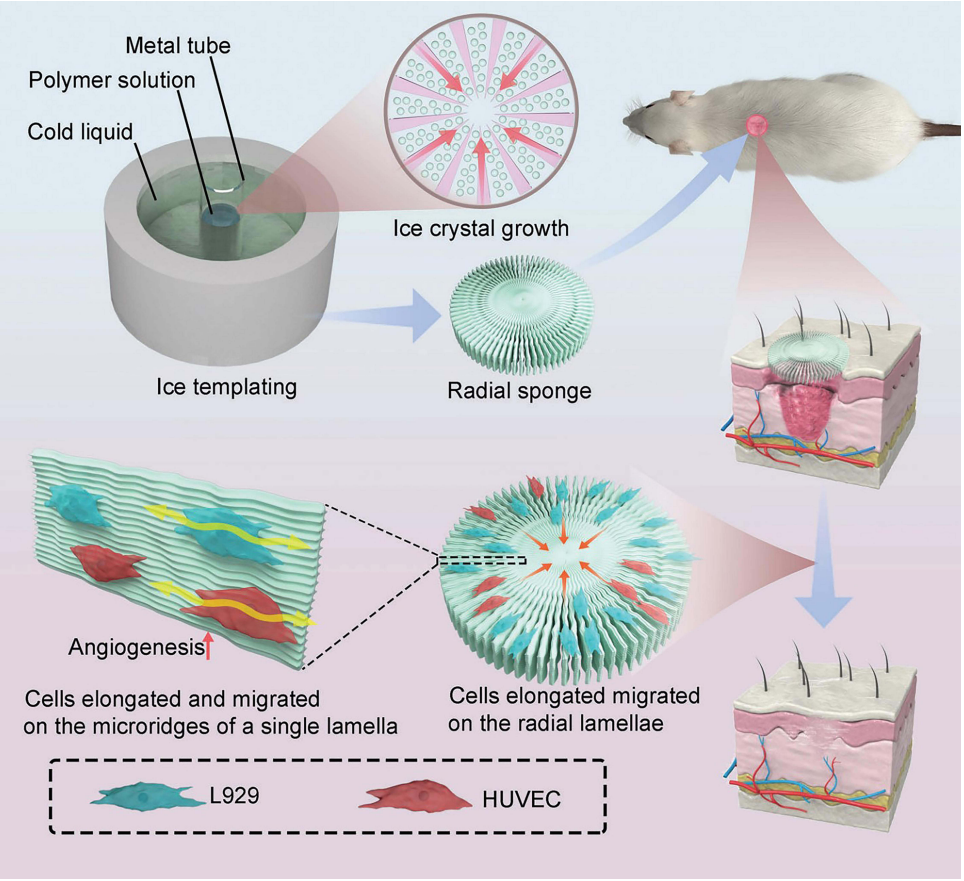

Figure 6 Radial sponges with denser lamellae and microridges that can be adjusted for lamellar spacing and microridge spacing with the ice template method, thus achieving a more ordered arrangement of cells, greater elongation, and greater migration. Reprinted with permission from Li J, Xiao L, Gao S, et al. Radial sponges facilitate wound healing by promoting cell migration and angiogenesis. Adv Healthc Mater. 2023;12(11):e2202737. © 2023 Wiley-VCH GmbH.[185]

migration in wound healing has been explored more in terms of fibroblasts, keratinocytes, and vascular endothelial cells, and little research has been done on how materials can be used to promote the harmonious migration of MSCs to improve homing efficiency. Even though the factors affecting cell migration are largely the same, migration-friendly materials for MSCs still need to be developed.

Promotion of MSC Paracrine Secretion

Studies have shown that MSCs mainly improve the proliferation and survival of target cells in a paracrine manner.[186] By enhancing the paracrine effects of each MSC that reaches the wound site, the MSC can be made to better perform their therapeutic role, thereby promoting skin wound healing. This approach has usually been combined with cellular therapy in the past. One method pretreats or co-cultures exogenous MSCs to increase their biological function after implantation. The studies by Chenyang Liu et al showed that MSCs that are pretreated with the pro-inflammatory factors IFN-γ and TNF-α exhibited a significant amplification in the secretome. This pretreated MSC supernatant of human umbilical cord-derived MSCs (UC-MSCs) is known as S-IT MSCs, and they can accelerate wound healing at the wound site by promoting macrophage migration and M2 polarization.[187] Another experiment showed that the exosomes of bone marrow-derived MSCs (BMSCs) that were pretreated by deferoxamine (DFO-Exos) activate the PI3K/AKT signaling pathway in wound repair by the miR-126-mediated downregulation of PTEN, thereby stimulating cutaneous angiogenesis in vitro.[188] Prakoeswa et al co-cultured different doses of resveratrol with MSCs, and they found that resveratrol could promote the proliferation of mesenchymal stem cells that are derived from adult and fetal tissues, as well as the secretion of wound healing-related growth factors in a dose-dependent manner.[189] In addition to applying educated MSCs individually to the treatment, cell therapy could combine with bioactive materials. Then, the complex can be implanted at the wound site to promote MSC secretion at the wound site. Meihua Gong et al developed a dopamine-methacrylate hyaluronic acid (DA-MeHA) as an effective carrier for stem cells in skin regeneration therapy. Adipose stem cells (ADSCs) from DA-MeHA hydrogels can secrete higher levels of growth factors.[190] Murphy et al reported an engineered fibrin hydrogel that was taken as a carrier of MSC spheroids; in addition, it increased the secretion of VEGF and PGE2 from MSC spheroids, enhanced the macrophage polarization at the wound site, stimulated endothelial cell proliferation, and promoted angiogenesis.[191] Jiujiang Zeng et al designed a PNIPAM-based porous hydrogel crosslinked to disulfide bonds. This porous hydrogel becomes a solution within 25 minutes of adding glutathione at 15 °C, and it gels again within 80 seconds at 33 °C. At 37 °C, the pore size is 300 μm, and the ASCs inoculated into the porous hydrogel spontaneously aggregate inside the wells to form galore spheres. This hydrogel was used to prepare stem cell spheroids that were easy to collect, and the researchers observed a marked upregulation of paracrine levels in ASC spheroids within the hydrogel.[192]

Nowadays, researchers in the field of tissue engineering have increasingly focused on the issue of the secretory function of MSCs in target tissues, and more and more well-designed tissue-engineered materials can be realized to promote the secretion of endogenous MSCs instead of complex in vitro treatments in conjunction with cellular therapies. The physical properties (eg matrix stiffness,[136] viscoelasticity, porosity, cell adhesion capacity, etc.) and microstructures (eg construction of two- or three-dimensional structures,[138] 3D-printed fibrous scaffolds to design morphology,[193] electrostatic spinning to design fiber arrangement,[140] etc.) of the materials are being designed to influence cell-matrix and cell-cell interactions and thus direct the secretion of MSCs. In addition biochemical cues provided by bioactive materials (proteins, peptides, and some small molecules) are also able to influence the secretory profile of MSCs,[194] and providing suitable physicochemical cues for MSCs at wound sites by means of tissue engineering is a promising development in the field of endogenous regenerative medicine. Aeolus Vilar et al showed that substrate stiffness modulates MSC paracrine activity and therapeutic potential, with 0.2 kPa substrate increasing IL-6 secretion in MSC, and TIMP-2, OPG, sTNFR1, and MCP-1 secretion elevated in MSC on 100 kPa substrate (Figure 7).[76] The study of Ni Su et al showed that the fibrous structure of the scaffold can regulate the paracrine function of MSCs. Compared with cells that are cultured on microplates, MSCs on electrospinning fibers produce higher levels of anti-inflammatory and proangiogenic cytokines.[195] Ruiying Huang et al prepared a polycaprolactone and bacterial cellulose scaffold using a bio-3D printing system, a fibrous scaffold with a morphology that modulates the paracrine function of Ad-MSC in skin tissue regeneration. By regulating cell-material interactions, MSC paracrine secretion was promoted thereby accelerating wound healing.[193] Meifei Lian et al developed spongy scaffolds with a layered structure and interconnected pores

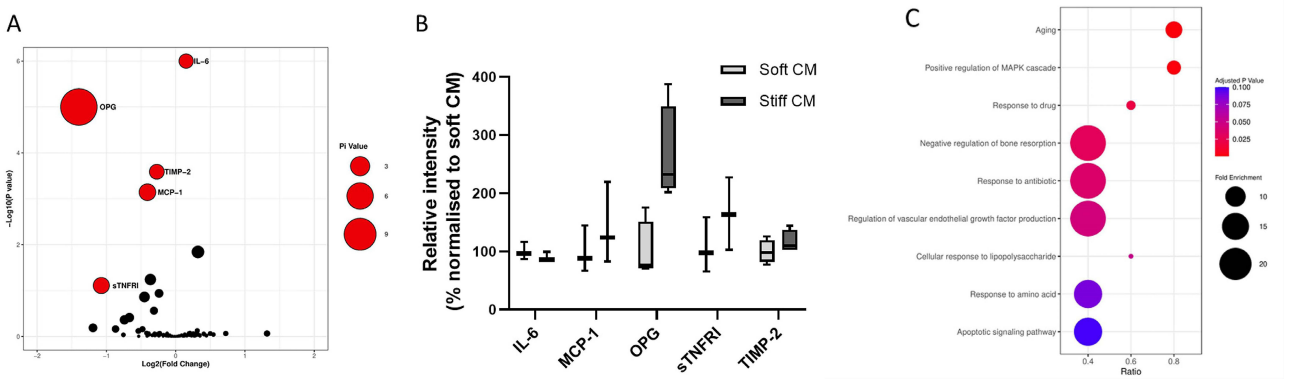

Figure 7 Secretome analysis of MSCs on soft and stiff substrates. (**A**) The pi value analysis plot identified five associated proteins: OPG, IL-6, MCP-1, TIMP-2 and sTNFR1. (**B**) The bars show the relative levels of proteins determined by Pi value analysis. (**C**) Bioinformatics analyses of the biological processes associated with these candidate proteins were performed, and the biological processes with a high proportion of differentially expressed proteins were plotted in the form of bubble plots. Reprinted with permission from A. Vilar et al, Substrate mechanical properties bias MSC paracrine activity and therapeutic potential, Acta Biomaterialia, vol. 168, pp. 144-158, © (copyright 2023).[76]

using a low-temperature deposition model (LDM) printing technique capable of facilitating cell-material interactions to promote MSC adhesion, retention, survival and inward growth. Protein function assays indicated that after using this scaffold downstream AKT, adhesion patch kinase (FAK) and yes-associated protein (YAP) signalling may paracrine the mechanotransduction pathway required for MSC paracrine secretion through which the layered porous structure stimulates MSC paracrine action (Figure 8).[137]

In addition to promoting the secretion of MSCs in target tissues, a cell-free therapy with MSC secretion products as the core has also attracted increasing attention. Exosomes are globular lipid bilayer vesicles that are secreted by MSCs with

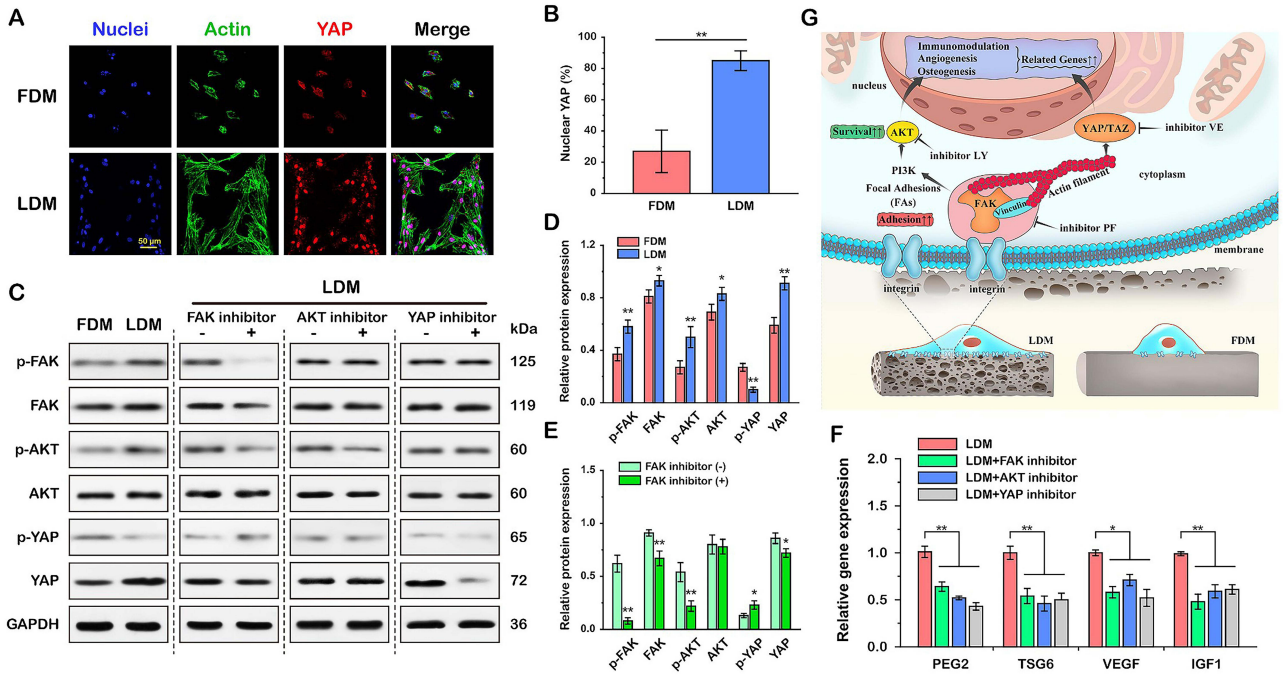

Figure 8 Molecular mechanisms by which sponge scaffolds with hierarchical structure and interconnected pores modulate paracrine secretion by mesenchymal stem cells. (**A**) Representative immunofluorescence staining images of YAP (red), F-actin (green) and nuclei (blue). (**B**) Quantitative analysis of nuclear YAP (%) of MSCs cultured for 24 h on FDM- and LDM- printed scaffolds. (**C**) Representative Western blot images and semi-quantitative analysis of FAK, AKT and YAP signaling pathway protein expression in MSCs cultured on both scaffolds (**D**) and (**E**) MSCs cultured on LDM-printed sponges containing FAK inhibitors. Activation of FAK and downstream AKT and YAP pathways was observed in MSCs cultured on LDM printed sponges. (**F**) Inhibitory effects of FAK, AKT and YAP on paracrine factor expression in MSCs cultured on LDM printed sponges were found by RT-PCR analysis. The key role of FAK and its downstream AKT and YAP signaling in the regulation of paracrine function of MSCs by LDM sponge was verified. (**G**) Schematic diagram showing the regulation of MSC paracrine function by the porous structure of LDM printed sponge through FAK and downstream AKT and YAP-dependent mechanotransduction pathways. *p < 0.05, **p < 0.01. Reprinted from Biomaterials, 274, Lian M, Sun B, Han Y, et al. A low-temperature-printed hierarchical porous sponge-like scaffold that promotes cell-material interaction and modulates paracrine activity of MSCs for vascularized bone regeneration, 120841. Copyright 2021 with permission from Elsevier.[137]

a diameter of 30–150 nanometers.[196] MSC-released exosomes can reach target cells through circulation or paracrines, and they are then internalized by recipient cells through surface molecule-mediated endocytosis, ligand–receptor interactions, membrane–recipient cell fusion, micropinocytosis, or phagocytosis.[197] Exosomes have a high skin penetration rate because they are a natural bilayer lipid sphere.[197,198] This feature allows exosomes to be administered topically at the wound site.[199]

Moreover, exosomes have a certain chemotaxis, and they can migrate to the lesion area that is a certain distance from the administration area.[200] To skin lesions, exosomes promote healing in various ways, such as regulating macrophage polarization,[201] promoting blood vessel formation,[202] enhancing reepithelialization,[203] promoting collagen deposition, and the secretion of target cell growth factors.[204] A study by Cooper et al showed that human ADMSC-derived exosomes promote the migration of human skin fibroblasts (HDFs) to accelerate skin ischemic wound healing.[205] Biomaterials offer a more flexible form for exosome applications. The combination with biomaterials can compensate for some of the shortcomings of the application of exosomes alone, such as the viability of exosomes, the release of exosomes, etc. The Pluronic F-127 hydrogel reported by Yang Zhou et al, which is injectable, biocompatible, and heat-sensitive, was used to encapsulate allogeneic human adipose mesenchymal stem cell exosomes (hADSCs-Exos). This hydrogel–exosome complex was applied topically to full-thickness skin wounds in mice; following this, the PF-127/hADSCs-Exos complex was observed to maintain the biological activity of the hADSCs-Exos when compared to hADSCs Exos alone, as well as seen to improve the efficiency of exosome delivery and optimize the performance of hADSCs-Exos.[206] Xinrong Geng et al designed a novel bone marrow mesenchymal stem cell-derived exosome (MSC-Exo) that was loaded carboxyethyl chitosan (CEC)-aldehyde carboxymethylcellulose (DCMC) hydrogel (MSC-Exos@CEC-DCMC HG) for the purpose of chronic diabetes wound healing.[207] These experiments provide a new paradigm for harnessing mesenchymal stem cell homing for the purpose of accelerating wound healing.

Conclusions and Future Perspectives

The mobilization of endogenous stem cell homing is a safe and reliable method for enhancing tissue repair, and it is currently excelling in the treatment of stress urinary incontinence,[208] repair of myocardial infarction,[209] and the repair of bone and cartilage injuries;[12,210,211] however, it has had few applications in the field of skin wound repair. In combination with tissue engineering materials, the main signaling molecule that has been applied to mobilize MSCs for endogenous homing is SDF-1; however, there are many more key molecules involved in the homing process that may be applied to the wound site in combination with biologically active materials in order to influence the efficiency of homing, such as inflammatory cytokines and growth factors. A variety of physical stimuli can also promote endogenous homing for MSCs, such as exogenous magnetic fields, ultrasound, and mechanical stretching. Moreover, combining the appropriate physical stimuli during material application may further improve the efficiency of homing. In addition to the key homing factors loaded by bioactive materials, as well as externally applied physical stimuli, the physicochemical properties of the material itself can also influence the attraction of the wound site to the MSCs in the stem cell niche. Biomaterials that adequately mimic the extracellular matrix are more capable of promoting endogenous homing, such as materials that are made from natural proteins, as well as polysaccharides that are components of the extracellular matrix. Whether the design of the topographical features of wound dressings, which modulate cell behavior and promote the migration of fibroblasts and vascular endothelial cells, can similarly promote the migration of nesting MSCs during the mobilization of endogenous wound repair is a question worth exploring. However, in any case, the design of the dressing's microscopic morphology can indeed influence the cellular motor behavior at the wound site, which can thus promote endogenous wound healing.[185]

The current mobilization of endogenous stem cells to home in and to promote tissue repair tends to be a single-process facilitation, such as through promoting more MSCs from nearby stem cell niches, facilitating faster migration, or promoting paracrine secretion that is more conducive to wound healing. These type of approaches are conducted rather than a synergistic multi-process, multi-perspective mobilization (such as the ability to increase both the homing signals given by the wound site as a guide while designing the physical properties of the material to promote the differentiation of the MSCs that reach their destination, as well as in promoting the differentiation of the MSCs that reach their destination). MSC differentiation and secretion occur at the destination. The development of mobilized materials for a multifunctional endogenous repair is a promising direction for creating more effective regenerative therapies. The mobilization of endogenous stem cells for wound repair is not subject to the regulatory constraints of stem cell

transplantation strategies, and it is able to meet the feasibility requirements for large-scale clinical translation. However, the design of scaffolding materials with spatio-temporal properties, as well as drug-carrying bioactive materials with appropriate concentration gradients (or with appropriate micromorphology and mechanical properties to modulate the behavior of stem cells at the wound site in terms of their regeneration, functional manifestation, and differentiation), is still a huge challenge.

The research findings of this review have a broad impact on the field of regenerative medicine. Firstly, it provides a more systematic theory and approach for improving materials for endogenous tissue repair, which is crucial for understanding and designing tissue engineering. Secondly, this review provides a new perspective for exploring the complex process of tissue remodeling, which is of great significance for improving the rational design of biomaterial scaffolds and guiding tissue regeneration strategies. In addition, this review also emphasizes that mobilizing endogenous stem cell homing is a safe and reliable method for enhancing tissue repair, which performs well in the treatment of stress urinary incontinence, myocardial infarction repair, bone and cartilage injury repair, and plays an increasingly important role in skin tissue repair. Compared to other tissue repair fields, there is still a lack of research on promoting endogenous MSC homing through materials for skin wound repair, which requires more attention from tissue engineers. Finally, this review proposes the development of mobilization materials for multifunctional endogenous repair, which is a promising direction for creating more effective skin regeneration therapies. Overall, the research findings of this review are of great significance for the research and application of skin tissue regeneration medicine.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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