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REVIEW ARTICLE

Stem cell homing-based tissue engineering using bioactive materials

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ABSTRACT: Tissue engineering focuses on repairing tissue and restoring tissue functions by employing three elements: scaffolds, cells and biochemical signals. In tissue engineering, bioactive material scaffolds have been used to cure tissue and organ defects with stem cell-based therapies being one of the best documented approaches. In the review, different biomaterials which are used in several methods to fabricate tissue engineering scaffolds were explained and show good properties (biocompatibility, biodegradability, and mechanical properties etc.) for cell migration and infiltration. Stem cell homing is a recruitment process for inducing the migration of the systemically transplanted cells, or host cells, to defect sites. The mechanisms and modes of stem cell homing-based tissue engineering can be divided into two types depending on the source of the stem cells: endogenous and exogenous. Exogenous stem cell-based bioactive scaffolds have the challenge of long-term culturing *in vitro* and for endogenous stem cells the biochemical signal homing recruitment mechanism is not clear yet. Although the stem cell homing-based bioactive scaffolds are attractive candidates for tissue defect therapies, based on *in vitro* studies and animal tests, there is still a long way before clinical application.

KEYWORDS: stem cell homing; cell migration; cell proliferation; tissue engineering; scaffold; biochemical signals

Contents

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1 Introduction

Tissue and organ defects are a common problem in clinics. There are tens of thousands of patients who die from tissue defects every year [1–2]. Autologous and allogeneic tissue/organ transplantations are the main current treatments for tissue defects in clinics [3]. However, these techniques both have their own drawbacks. Autologous transplantation has the risk of donor shortage and allogeneic transplantation has a large risk of rejection [4]. In the 1980s, tissue engineering was presented by Langer and Vacanti, and since then has experienced three decades of development [5]. Tissue engineering focuses on repairing tissue and restoring tissue functions by employing three elements, i.e., scaffolds, cells, and biochemical signals [6].

Scaffolds play roles in cell infiltration and cell migration, which are used to provide extracellular matrix (ECM) for cells [7]. Fundamentally, cells are building blocks elements for complex tissues and organs. In tissue engineering applications, cells are cultured on scaffolds to prepare a cell-based scaffold and promote its bioactivity. Then, the cell-based scaffolds are used to enable the fabrication of functional tissues or organs which can be used for reparative procedures in patients [8]. As a promising treatment for tissue defects, tissue regeneration by the localization of cells has gained increasing attention over the past few years. The basic approach is to create cell-based tissue engineering scaffold by combing a patient's own cells with a biomaterial scaffold, resulting in tissue constructs that can be implanted *in vivo* [9]. However, this approach requires an extensive cell expansion step before implantation and isolated tissue-derived primary cells are often heterogeneous and difficult to standardize. In this case, stem cells are widely used to fabricate stem cell-based tissue engineering scaffolds because they have the ability to be renewable and differentiable. The prerequisite for cell therapeutics by stem cells is stem cell homing, i.e., the stem cells must be recruited to the defect tissue site. The exogenous stem cells which are cultured on the bioactive scaffold were recruited to the defect sites by implantation.

Stem cell homing is a recruitment process for inducing the migration of the systemically transplanted cells, or host cells, to defect sites. This technique is then combined with bioactive scaffolds for application in tissue engineering. The main principle of stem cell homing is to utilize the body's own biologic resources and its reparative capability by using a biochemical signal to recruit endogenous stem cells to the defect sites [10]. In most cases of tissue engineering, biochemical signals were loaded on the bioactive scaffold materials which play an important role in cell growth, cell proliferation, and cell differentiation [11–12]. Specifically, a series of biochemical signals such as stromal-derived factor-1 (SDF-1) [13], hepatocyte growth factor (HGF) [14], and monocyte chemotactic proteins (MCPs) [15] for example were loaded to assist in the recruitment of endogenous stem cells [16]. When these bioactive scaffolds are implanted into the tissue defect sites, the biochemical signals are released and will function to improve the efficiency of cell homing to tissue defects sites and assist in preparing cells for differentiation and proliferation.

As suggested above, all of the three elements of tissue engineering (scaffolds, cells, and biochemical signals) play important roles in repairing tissue defects. Each of these components can be improved individually or in combination to improve the regeneration of tissue via stem cell homing. In this review, stem cell homing-based tissue engineering has been considered by using the bioactive materials scaffold and the biochemical signal which are able to promote stem cell homing (Fig. 1).

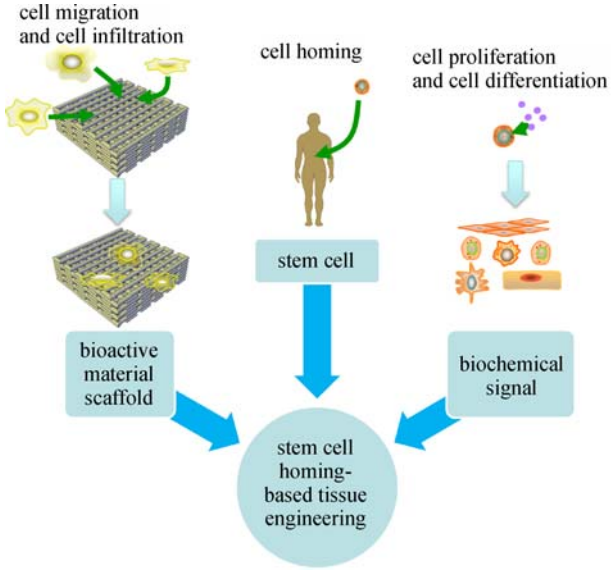

Fig. 1 The triad of stem cell homing-based tissue engineering.

2 Tissue engineering scaffolds

Previous investigations have revealed that there are some requirements for the use of tissue engineering scaffolds in clinical applications [17]. The requirements are that: 1) the scaffold must be nontoxic and have good biocompatibility; 2) the scaffold can be degradable after tissue regeneration; 3) the scaffold must require mechanical properties for its application; 4) the stiffness of the scaffold in regards to cell growth must be considered; 5) nutrients should be able to be exchanged between the inside and outside of the scaffold via its micro- or nano-structure; 6) some of the growth factors, or bioactive signals, should be provided on the scaffold [18–21]. In summary, bioactive materials and methods for preparing tissue engineering scaffold are very important.

2.1 Bioactive materials for preparing tissue engineering scaffolds

During a previous study, non-degradable materials were used to fabricate tissue engineering scaffolds for tissue regeneration in clinical applications, just like metal, bioglass, silicone, etc. [22]. However, these scaffolds cannot be absorbed by the body and long-term duration in the human body caused adverse effects which required another operation to remove it. With the development of science and technology, degradable materials, composed of synthetic and natural materials, were developed to be used in preparing tissue engineering scaffolds [23]. Some examples include polylactic acid (PLA) [24], polyglycolic acid (PGA) and polycaprolactone (PCL) [25], polyhydroxybutyrate (PHB), poly(L-lactic acid-co-ε-caprolactone) (PLCL), chitosan, collagen [26], gelatin, silk fibroin and alginate etc. Park et al. used PCL to fabricate a 3D bone tissue engineering scaffold [27]. The results indicated that PCL scaffolds show good biocompatibility. Kim et al. fabricated and characterized a new tubular, macroporous, fibrous scaffold using PLCL. The tensile strength and elastic modulus of scaffold were 3.39 and 1.22 MPa, respectively, and the scaffolds exhibited 500%–600% elongation at break. Combined, these mechanical properties are good for vascular tissue engineering applications [28]. Silk fibroin (SF) is a protein, which has good oxygen and water vapor permeability, biocompatibility, low inflammatory response, and has a low cost [29]. In one study, Yang et al. developed a novel biomimetic design of the SF-based nerve graft (SF graft) which was composed of a SF-nerve guidance conduit. The animal test results of their study show that SF grafts could promote peripheral nerve regeneration [30].

Previous experiments have shown that having both good biocompatibility and good mechanical properties are important for tissue engineering scaffolds. Usually, synthetic materials show better mechanical properties but natural materials show better biocompatibility. As a result, synthetic and natural materials were blended together fabricate a tissue engineering scaffold for tissue regeneration application. Zhang et al. fabricated a nanofibrous scaffold by blending PLCL and SF and studied the ratio between PLCL and SF. The results indicated that when the weight ratio of SF to PLCL was 25:75, the PLCL/SF blended nanofibrous scaffolds significantly promoted cell growth in comparison with PLCL nanofibrous scaffolds [31]. Prabhakaran et al. fabricated electrospun PCL, chitosan, and PCL/chitosan blended fibrous scaffolds with average fiber diameters of 630, 450, and 190 nm, respectively [32]. Their results demonstrated that the PCL/chitosan nanofiber scaffold surface alteration led to enhanced rat Schwann cell attachment and proliferation (48% increase in proliferation) on PCL/chitosan scaffolds as compared to only PCL over an 8 d culture period, all while maintaining the characteristic cellular morphology along the fibers.

Hybrid materials were also used to fabricate tissue engineering scaffolds as they show good mechanical properties, biocompatibility, and biodegradability. In addition, material modification is another approach to prepare good materials for tissue engineering. For example, Sacks et al. modified polyurethane (PU) to poly(ester urethane) urea (PEUU), and used PEUU to electrospin a soft tissue engineering scaffold which showed good mechanical properties and biodegradability [33]. Poly(ethylene glycol) (PEG) hydrogels were also investigated as potential encapsulation matrices for osteoblasts. To assess their applicability in promoting bone tissue engineering, the non-adhesive hydrogels (PEG hydrogels) were modified with adhesive Arg-Gly-Asp (RGD) peptide sequences to facilitate the adhesion, spreading, and consequently, cytoskeletal organization of rat calvarial osteoblasts. Mineral deposits were seen in all hydrogels after 4 weeks of *in vitro* culture, but a significant increase in mineralization was observed upon introduction of adhesive peptides throughout the network [34].

2.2 Methods for preparing tissue engineering scaffolds

There are many various scales present in the structure of the

ECM, and the purpose of tissue engineering scaffolds was to fabricate a similar ECM structure for cell adhesion and cell migration. The following sections focus on methods and techniques to fabricated ECM-like structure functional biomaterial scaffolds.

2.2.1 Electrospinning

Electrospinning is an attractive method to prepare nanofibrous and porous ECM-like structure scaffolds with a high specific surface area for tissue engineering [35]. The basic experimental set up for electrospinning includes a promoting pump, high-voltage power, syringes, needles, and collectors [36]. While electrospinning, an electrospinning solution is pumped through the syringe which forms a droplet on the needle tip. Then, by applying a high voltage, the droplet forms a Taylor cone and nanofibers are injected to the collector. Throughout this process, the solvent evaporates and a solid fibrous network is generated. Different types of nanofibrous scaffolds, such as films, mats, and tubes, can be obtained through the use of different collector shapes. In Jin et al.'s study, they prepared electrospun nanofiber mats with SF. The experiment results indicated that electrospun silk matrices had the ability to support bone mesenchymal stem cell (BMSC) attachment, spreading, and growth *in vitro*, as well as suggested potential further applications of these biomaterial matrices as scaffolds for tissue engineering [37]. Panseri et al. used electrospun tubes made of biodegradable polymers (a blend of poly(D, L-lactic-co-glycolic acid) (PLGA)/PCL) to regenerate a 10-mm nerve gap in a rat sciatic nerve *in vivo*. The results showed that the electrospun tubes induced the nervous regeneration and functional reconnection of the two severed sciatic nerve tracts [38].

In addition, the development of functionalized fibers by coaxial electrospinning is another aspect of electrospun fiber scaffold processing beyond the simulation of the structure of the extracellular matrix. Coaxial electrospinning allows various functional factors (i.e. growth factors) to be added within the fibers in order for them to be used as controlled release vehicles. This gives the tissue engineering scaffolds an additional level of functionality in the redevelopment of tissue constructs. In one study, nerve growth factor (NGF) was incorporated into core–shell nanofibers, where the core solution was NGF and the shell solution was PLGA, by coaxial electrospinning. Then, the scaffold was transplanted into the rat sciatic nerve defect *in vivo*. The results showed that NGF can be released from the electrospun nanofibrous scaffold while retaining its function of promoting nerve regeneration [39].

2.2.2 Thermally induced phase separation

Thermally induced phase separation (TIPS) is considered as one of the most promising approaches for preparing nanofibrous scaffolds. By quickly freezing the high temperature polymer solution to drive phase separation, nanofiber scaffolds are produced by this temperature change. The diameter of the nanofibers fabricated by this method ranges from 50 to 500 nm and the scaffold porosity is greater than 90%. Therefore, the scaffolds created by the TIPS method show good potential for applications in tissue engineering. Keshaw et al. prepared microporous collagen spheres using a TIPS technique and assessed their biocompatibility. The results from this study indicate that microporous collagen spheres produced using TIPS are biologically active and could offer a novel scaffold for tissue regeneration in poorly accessible wounds [40]. In another study, highly porous PLGA scaffolds were fabricated by the TIPS method to deliver plasmid DNA in a controlled manner. It showed that plasmid DNA released from the scaffolds fully maintained its structural integrity and showed comparable transfection efficiency to native plasmid DNA. Also, it suggested that these biodegradable polymeric scaffolds are capable of sustained DNA release and could be potentially applied for various tissue engineering applications that require a combined gene delivery strategy [41]. Ma et al. used PLA to fabricate tissue scaffolds using TIPS. They thought to utilize the differences in thermal conductivities of the mold materials and benzene as the solvent, and as a result, scaffolds with oriented, gradient microtubular structures in the axial or radial direction could be created. The porosity, tubular size, and orientation of the microtubules can be controlled by the polymer concentration, the TIPS temperature, and by utilizing materials of different thermal conductivities. This suggests that these scaffolds could be fabricated for the tissue engineering of small-diameter blood vessels by utilizing their advantageous structural features to facilitate blood-vessel regeneration [42].

2.2.3 Bio-printing

Printing is a computer-controlled, layer-by-layer scaffold fabrication technique. 3D scaffolds can be produced either by laser-based, printer-based, or nozzle-based printing; of these, the printer-based method is most suitable for printing

cells. Compared to printing, bio-printing includes the addition of cells, growth factors, or other functional elements. It has been demonstrated that 3D bio-printed scaffolds show good potential application in tissue engineering, because they are convenient, fast, and customizable. Kim et al. printed PCL/collagen fibrous scaffolds designed with core (non-fibrous structure) and shell (fibrous bundles) regions through an electrohydrodynamic technique. The experiment results demonstrated that the fibrous hybrid scaffold provided significantly greater cellular activity relative to the general electrospun fibrous mat due to the enhanced mechanical properties and controlled pore structure [43]. In one report, collagen bioink containing three different types of cells – hepatocytes (HCs), human umbilical vein endothelial cells, and human lung fibroblasts – was infused into the canals of a PCL framework to induce the formation of capillary-like networks and liver cell growth. The results demonstrated the prospect of using cell printing technology for the creation of heterotypic, cellular interactions within a structure for liver tissue engineering [44]. As well, bio-printing is also can be used as a drug delivery system for tissue engineering [45]. 3D printed scaffolds have already been used in clinical applications and continue to show important potential for tissue engineering applications.

In summary, electrospinning and the TIPS method can be used to fabricate nanofiber tissue engineering scaffolds which are not only good for cell migration but are also easy to be prepared. Also as a new technology, bio-printing shows it has advantages as well as some disadvantages, such as low print resolution and fewer types of printing material. It is predicted that with the further development of bio-printing technology, it will overcome these shortcomings and play more important role in tissue engineering in the near future.

3 Stem cell homing

Stem cells are undifferentiated cells that can differentiate into specialized cells and can divide (through mitosis) to produce more stem cells. Typically, stem cells can yield almost any cell in the human body and are capable of developing into almost any tissue [46]. With their differentiate ability, stem cells show important potential to cure a broad range of significant diseases such as myocardial infarction, multiple sclerosis, Parkinson's disease, diabetes, Huntington's disease, and also healing tissue defects [47–50]. Cell homing is a phenomenon in which cells migrate to the organ of their origin. Stem cell homing is very important for tissue regeneration and the prerequisite for stem cell therapeutics, despite its mechanisms and modes being complicated [51–52]. During this section, the specific stem cell homing mechanisms and modes will be discussed.

3.1 The prerequisite for cell therapeutics by stem cell homing

Tissue defects are a common problem in clinics, whereby tissue engineering scaffold bioactive materials have been used to restore and replace lesion tissue. These bioactive materials can restore the structural integrity of damaged tissue in clinical applications, but this is purely a structural alternative to replace all or most structural functions at the expense of sacrificing; the transplantation of bioactive materials cannot restore the physiological function of tissue defects. There could also be other issues that arise after implantation fracture and displacement such as secondary infections, foreign body reactions, and other problems in the body. Considering this, improving the biological activity of biomaterials, and promoting damaged tissue structure and function recovery is the most important aspect of tissue engineering technology.

It is well documented that stem cells are present in many adult organs and tissues, including the brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, all areas where the bone marrow is the main reservoir of many types of stem cells. Stem cells have the ability to differentiate into the cells of the defect tissue and restore the defect. Current stem cell therapies in hospital clinics are based on the rationale that exogenous stem cells or progenitor cells can differentiate into new cells with an appropriate physiological environment; hence, demonstrating the regenerative potential of the exogenous stem and progenitor cells.

The use of *ex vivo*-cultivated stem cells typically involves the harvest of suitable autologous donor tissues and transport to a manufacturing facility where the resident stem cells can be recovered and cultured to a larger population. These cells are then either transplanted back into the patient by injection, or they are seeded into a prefabricated tissue engineering scaffold and then implanted back into the patient. Alternatively, the cell-seeded scaffold may be incubated in a bioreactor or other such system to create a tissue-like construct prior to transplantation. In these types of environments, the cells are exposed to biological, chemical, or physical stimuli that

promote the formation of the appropriate tissue to be used in the repair procedure.

3.2 The mechanisms and modes of stem cell homing-based tissue engineering

Generally, "cell homing" is defined as when a cell arrests in a target organ after the cell has traveled throughout the body via the blood stream. As previously described, it is known that stem cell homing is present and plays an important role in promoting tissue regeneration for tissue engineering [53–55]. In some recent studies, stem cells and bioactive material scaffolds were used to cure tissue defects by many researchers [56].

The mechanisms and modes of stem cell homing based tissue engineering can be divided into two types based on the source of the stem cells: endogenous and exogenous (Fig. 2). For exogenous stem cells, the stem cells were isolated at first from host tissue, and then cultured and amplified *in vitro*. Then, the exogenous stem cells were seeded onto a bioactive scaffold material and this cell-based scaffold is implanted into tissue defect sites. As well, biochemical signals, such as cell growth factors, can be loaded onto the scaffold to promote cell differentiation, cell proliferation, and tissue regeneration. For endogenous stem cells, the stem cells are not seeded onto the scaffold as they come from within the host body. First, signals that regulate stem cell homing including chemokines, cytokines, and adhesion molecules are loaded onto the scaffold. Then when the scaffold is implanted into the body, the endogenous stem cells will be recruited to the scaffold because of the presence of these biochemical signals. Both of these two kinds of stem cell homing mechanisms and modes have the potential for tissue regeneration applications.

4 Biochemical signals for stem cell homing

In the initial stage, a key to tissue regeneration is the proficient recruitment of host stem cells into the defect sites [57–58]. As mentioned previously, there are two potential types of this cellular recruitment. Either exogenous stem cells are recruited by preloading them onto scaffolds where they are subsequently implanted or endogenous stem cells are recruited to the implanted scaffold, it has been preloaded with biochemical signals. For the second approach, adult stem cell populations in the body are generally too low in number to have a significant impact on accelerated tissue regeneration. Moreover, the use of these endogenous stem cells today is limited by the difficulty of ensuring that sufficient populations of stem cells are able to reach the damaged areas. Therefore, it is worthwhile to

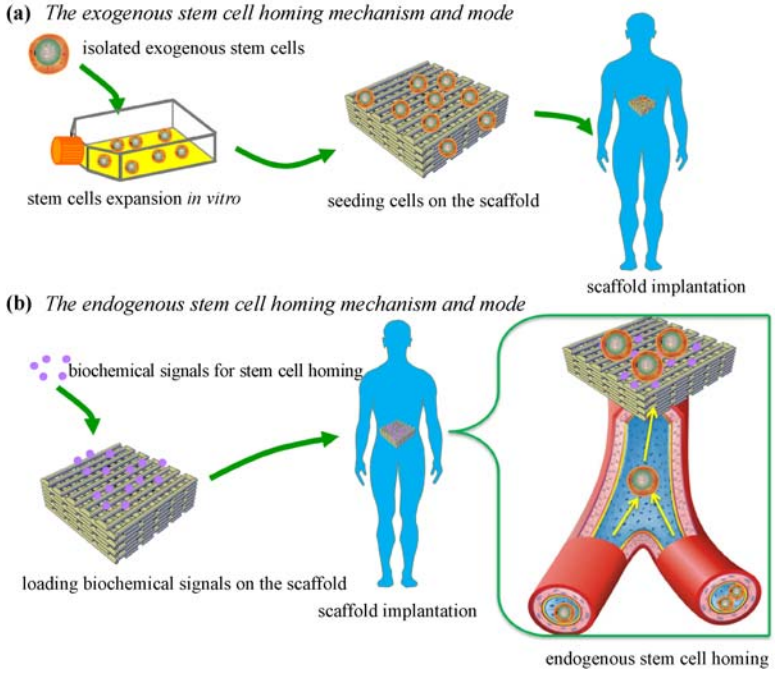

Fig. 2 Schematics of the two principal mechanisms and models of stem cell homing-based tissue engineering: **(a)** exogenous; **(b)** endogenous.

target the effective mobilization of adult stem cells into the peripheral blood system of defects tissue. During the mobilization process, also known as homing or engraftment, some biochemical signals are very important to increase stem cell migration efficiency. The application of specific biochemical signals related to stem cell homing have been previously reported in several tissue engineering experiments.

Stromal cell-derived factor 1α (SDF-1α) is a classic stem cell homing factor that has been shown to attract stem cells, both mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs), to injured tissues by the amount of the SDF-1 protein receptor, chemokine receptor type 4 (CXCR4), expression [59–60]. Normally, CXCR4 shows a low level in our peripheral blood, and low numbers of stem cells can be maintained at a balanced level. When tissue is damaged, it can mobilize stem cells into peripheral blood and cause them to migrate to the defect site by increasing CXCR4 expression [61]. Thus, SDF-1α contained within an implanted scaffold could generate a high concentration gradient of some factors and drive efficient stem cell migration into the implant. To investigate whether stem cells could be targeted to the site of biomaterial implantation and whether increasing local stem cell responses could improve the tissue response; Thevenot et al. loaded SDF-1α and MSCs onto a PLGA scaffold and implanted it. The results indicated that SDF-1α increases the engraftment of MSCs to subcutaneously implanted PLGA scaffolds [62]. In another study, Riccardo et al. prepared polylactic acid microcarriers (μCs) which acted as MSC delivery vehicles capable of modulating key chemotactic pathways. The effect of different functionalization strategies on MSC migratory behavior from the μCs was studied *in vitro* in relation to SDF-1α. Collagen and RGD peptides were either covalently grafted or physisorbed on the μC surface. While stable covalent modifications promoted better cellular adhesion and higher proliferation when compared to physisorption, the functionalization method of the μCs also affected the cells migratory behavior in response to SDF-1α (chemokine receptor type 12, CXCL12) stimulation [63]. Additionally, SDF-1α was used to enhance MSC homing to the injured hearts by promoting neovascularization. Recent evidence suggests that SDF-1α/CXCR4 specifically mediates the directional migration of BMSCs toward a myocardial infarction via activation of the PI3K/Akt signaling pathway. Targeting of these inhibitors represents an effective strategy for regenerative tissue engineering applications.

HGF is another stem cell homing biochemical signal and c-met is the receptor of HGF [64]. When HGF binds with c-met, it can direct a variety of biological effects such as anti-cell apoptosis, promote cell proliferation, and angiogenesis. HGF secretion was adjusting by micro environment, especially when the tissue was damaged and inflamed, and it could be activated monocytes and macrophages to secrete large amounts of HGF [65]. In 2004, Neuss et al. found that BMSCs could express HGF and c-met. The results of their experiments displayed that HGF shows strong, positive chemotactic attraction to BMSCs. Thus, this result indicates the stem cell homing ability of BMSCs to HGF [66]. There are other biochemical signals that play important role in directing stem cell homing, including MCPs [67] and matrix metalloproteinase-2 (MMP-2) [68].

In addition to stem cell homing factors that induce engraftment of host stem cells into desired tissues or organs for repair, some other biochemical signals are considered as important cues for efficient tissue regeneration which increase stem cell differentiation, cell proliferation, and tissue regeneration. One representative signal is transforming growth factor-β (TGF-β) which has been shown to attract cells as well as increase differentiation and proliferation [69]. During Huang et al's study, in which developed a biphasic implant made of a bioresorbable polymeric scaffold in combination with a TGF-β1-loaded fibrin glue. These scaffolds were implanted subcutaneously, intramuscularly, and subperiosteally to determine whether the implant scaffold could recruit MSCs and induce the process of cartilage formation. It was concluded that scaffolds loaded with TGF-β1 could successfully recruit MSCs and when this construct was implanted subperiosteally would induce chondrogenesis [70]. Vascular endothelial growth factor (VEGF) is a classic protein used to stimulate vasculogenesis and angiogenesis [71]. VEGF's normal functions are to create new blood vessels during embryonic development, new blood vessels after injury, muscle following exercise, and new vessels (collateral circulation) to bypass blocked vessels [72]. Elçin et al. conducted a study to determine the *in vitro* release behavior of VEGF from calcium alginate microspheres and the potency of this controlled release system in promoting localized neovascularization at the subcutaneous site in a rat model. The results indicated that the controlled system could release VEGF in order to promote vigorous angiogenesis; this has potential applicability for tissue engineering and wound healing [73]. NGF, brain-derived neurotrophic factor (BDNF), and epidermal growth

factor (EGF) have also been identified to play important roles in promoting cell growth, cell differentiation, and tissue regeneration.

5 Applications of stem cell homing-based tissue engineering using bioactive materials

Tissue engineering scaffolds when combined with stem cells are used to promote tissue regeneration for various therapeutic applications (Table 1 [74–84]). Various bioactive scaffolds have been previously implanted or injected into the defect areas. In this section, several tissue engineering scaffold and exogenous/endogenous stem cell applications which have been successfully performed in preclinical animal models and clinical applications will be discussed.

5.1 Bone

In clinics, an important consideration in the development of bone regeneration strategies is the broad diversity of problems with varying biological, mechanical, and structural challenges [85]. The required properties of a bone tissue engineering scaffold are mechanical load bearing within the tissue defects, and immune/inflammatory response is another problem. In order to provide adequate mechanical properties, some biomaterials like β-tricalcium phosphate (β-TCP), calcium phosphate cement (CPC), hydroxyapatite (HA) and several organic synthetic (or natural) biomaterials were used. Also, commonly used bioactive molecules for bone regeneration include bone morphogenic protein 2 (BMP-2), TGF-β, basic fibroblast growth factor (bFGF), and VEGF. Therefore, bioactive scaffolds and stem cells are used in the development of bone regeneration simultaneously. Kim et al. fabricated a PLA/β-TCP bone scaffold which was loaded with stem cell homing factors KLD12/KLD12-SP (KLD12 + KLD12-substance P (SP)). Then, the scaffolds were implanted into rat defect sites. The results of the gross morphology using hematoxylin and eosin and Masson's trichrome stains showed that the defect site was filled with new tissue and that endogenous MSCs were recruited to the defect site. This suggested that the PLA/β-TCP + KLD12/KLD12-SP scaffolds were able to enhance bone tissue regeneration [74]. In addition, exogenous stem cells also show good potential for application in bone tissue engineering. During a study by Zhao et al., a CPC paste was combined with hydrogel micro-beads which were encapsulating human umbilical cord mesenchymal stem cells (hUCMSCs). The hUCMSC-encapsulating composite paste was fully injectable under small injection forces. Mechanical test results indicated that the composite paste was comparable with the literature values of cancellous bone. It was clear that hUCMSCs in the injectable constructs osteodifferentiated, which yielded high alkaline phosphatase, osteocalcin, collagen type I, and osterix gene expressions. In conclusion, the injectable stem cell construct with load-bearing capability may enhance bone regeneration in minimally-invasive and other orthopedic surgeries [75]. All of these results demonstrated an ability to stimulate and induce neighboring stem cells and enhance bone tissue formation.

In clinics, almost all of the applications have been conducted for bone regeneration *in situ* using CPC and collagen bioactive materials combined with clinically

Table 1 Different applications of stem cell homing-based tissue engineering using bioactive materials

Bioactive materials		Biochemical signals	Stem cells	Experimental study	Refs.
Bone	PLA/β-TCP	KLD12/KLD12-P	MSCs (endogenous)	repair of rat calvarial defects	[74]
	CPC/hydrogel		hUCMSCs (exogenous)	culture of hUCMSCs	[75]
	Bioactive glass nanoparticles		MSCs (endogenous)	rat subcutaneous tissues	[76]
	PCL		BMSCs (endogenous)	culture of BMSCs *in vitro*	[77]
	PHB/PHBHHx		hASCs (exogenous)	subcutaneous layer implanted in nude mice	[78]
Cartilage	PCL/HA	TGF-β3	endogenous stem cells	cartilage defects in a rabbit model	[79]
	PGA/HA	autologous serum	MSCs (endogenous)	full-thickness cartilage defect in sheep	[80]
	PLLCL/poly (propylene glycol)		NCSCs (exogenous)	sciatic nerve defects in a rat model	[81]
Nerve	Silicone tube	TGF-β3	DPSCs (exogenous)	facial nerve defects in a rabbit model	[82]
	Cerebellar ECM	BDNF/NGF	NCSCs (exogenous)	subcutaneous and intracranial implantation in a rat model	[83]
Skin	Coll/PLLCL		BMSCs (exogenous)	culture of BMSCs *in vitro*	[84]

Notes: PLA, polylactic acid; β-TCP, β-tricalcium phosphate; MSCs, mesenchymal stem cells; BMSCs, bone mesenchymal stem cells; CPC, calcium phosphate cement; hUCMSCs, human umbilical cord mesenchymal stem cells; PCL, polycaprolactone; PHB/PHBHHx, polyhydroxybutyrate/poly(hydroxybutyrate-co-hydroxyhexanoate); hASCs, human adipose-derived stem cells; HA, hydroxyapatite; TGF-β3, transforming growth factor-β3; PLLCL, poly(l-lactic acid)–co-poly(3-caprolactone); NCSCs, neural crest stem cells; DPSCs, dental pulp stem cells; ECM, extracellular matrix; BDNF, brain-derived neurotrophic factor; NGF, nerve-growth factor; Coll, collagen.

approved BMP-2 [86–87]. However, bone tissue engineering scaffolds fabricated with PLA or PCL and some other bioactive materials are still not used in clinics, because the safety of the material still needs further evaluation and verification. Also, stem cell homing-based bioactive materials with exogenous/endogenous stem cells are not applied in clinics even though they are attractive candidates for stem cell-based therapies for tissue defect repair. The mechanisms responsible for stem cell homing are in need of further investigations.

5.2 Cartilage

Cartilage tissue defects and damage is a common clinical disease that can lead to severe arthritis because it difficult to heal naturally. Articular cartilage is a highly specialized tissue that reduces joint friction and protects the bone ends from the shear forces associated with high mechanical load. Among the possible explanations for the limited capabilities of current methods of cartilage repair, the lack of integration of the chondrocytes within the existing cartilage is a very important concept for cartilage regeneration. In early studies, chondrocyte-based scaffolds implanted into cartilage tissue were not good for cartilage repair because serious compatibility problems often were observed because of the poor integration between implanted and native tissue [88]. As a result, recent studies were focused on stem cells-based scaffold applications of cartilage tissue engineering. Ye and colleagues published a report that translated the potential of exogenous human adipose-derived stem cells (hASCs) and implanted them into the subcutaneous layer of nude mice. The scaffold was fabricated with PHB/poly(hydroxybutyrate-co-hydroxyhexanoate) (PHB/PHBHHx). The results of this study showed that PHB/PHBHHx scaffolds have excellent biocompatibility with hASCs and it provided a good environment for chondrogenic differentiation *in vitro*. In addition, an *in vivo* study indicated that the hASC-based scaffolds were able to produce neocartilage, which demonstrates its suitability for cartilage tissue regeneration [78]. In another report, TGF-β3 was used to recruit endogenous stem cells and to promote cartilage tissue regeneration. Lee et al. incorporated TGF-β3 into PCL/HA composite materials to fabricate cartilage tissue scaffolds, and then subsequently implanted them into a rabbit model. In this study, regeneration of new, avascular cartilage with vascularized subchondral bone tissue was evident. Therefore, this result shows that this technique can be effective in regenerating cartilage tissue by recruiting host stem cells to the site of the implants [79].

5.3 Nerve

Nerve defects are a common clinical problem, especially in trauma cases, and nerve tissue repair is a precious treatment concept in human health care as it directly impacts on the quality of our life. Neurons in the peripheral nervous system (PNS) get information from external sources, and then the information is transmitted to the central nervous system (CNS) which is composed of the brain and spinal cord. Although the PNS has a greater capacity for axonal regeneration after injury than the CNS, spontaneous peripheral nerve repair is almost always incomplete with poor functional recovery. When the length of nerve defects are less than 5 mm, the body can self-repair and restore its functions. However, if the lengths of the nerve defects are more than give mm, the body cannot repair the injuries by itself. The presence of scaffolds for tissue engineering with the appropriate stem cell technologies presents the possibility of repairing damaged nerve tissue. It was suggested that some growth factors may be able to enhance the mobilization and homing of endogenous neural crest stem cells (NCSCs). Some of these growth factors include SDF-1 and CXCR4, which are known to activate the NCSCs homing capability and promote nerve repair. In one study by Wang et al., NCSCs were derived from human induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) and studied for potential applications of NCSCs in nerve tissue engineering *in vivo*. The nanofibrous conduit scaffolds were fabricated by seeding NCSCs. Then, they were used as a bridge for transfected sciatic nerves in a rat model. Electrophysiological and histological analysis demonstrated that NCSCs transplantation promoted axonal myelination and sciatic nerve regeneration. This study demonstrates that iPSC-derived multipotent NCSCs can be directly used for tissue engineering and that this approach which combines stem cells and scaffolds has tremendous potential for regenerative medicine applications [81].

Although SDF-1 and CXCR4 activate NCSC homing after nerve injury, there is little known about the molecular mechanisms that govern NCSCs mobilization. However, some previous research suggests that NCSCs can migrate through the parenchyma along non-stereotypical routes in a directed manner and across great distances to nerve defect sites [89]. In conclusion, the homing of NCSCs represents a potential therapeutic option for nerve regeneration.

5.4 Skin

Skin is the largest organ in humans and is responsible for the protection of the body from the external environment as well as the regulation of temperature and hydration state of an individual. Studies have shown that skin has self-healing capabilities to some extent. However, when the diameter of skin wounds is too larger, it is difficult to completely heal by itself [90–91]. With regular homeostasis being compromised from skin wounds, there are many other problems that have the potential to arise such as bacterial infections, viral contaminations, and inflammatory responses. Adult skin tissues contain skin stem cells in the hematopoietic system which presents the possibility for treating human skin diseases such as alopecia, scarring, serious burns, and skin cancer. In one research study, electrospun collagen/poly(l-lacticacid)–co-poly(3-caprolactone) (Coll/PLLCL) nanofibrous scaffolds were fabricated and used to culture BMSCs cells. It was concluded that the electrospun Coll/PLLCL nanofibers could mimic the native skin extracellular matrix environment and had the potential to be promising substrates for advanced skin tissue engineering applications [84]. Also, Ma et al. derived BMSCs on biomimetic nanofiber scaffolds to fabricate a skin scaffold and studied it in a rat skin defect model. This result indicated that both nanofiber scaffolds and BMSCs contributed in the wound healing process [92].

The possibility of stem cell homing-based bioactive materials to repair tissue defects is an area of research gaining interest despite the cells exact contributions to the repair process still remaining unclear for therapeutic applications. Most of the results currently are coming from animal tests as clinical research in this area is still in the very early stages. In the specific application of exogenous stem cell homing-based bioactive scaffolds, the first problem to be solved is the source of stem cells. It is hypothesized that they are autologous but this is not known with certainty. Second, there is too much time in culturing the stem cells before implantation. In this specific situation, endogenous bioactive scaffolds do not have similar problems but the mechanism of endogenous stem cell homing is unclear. Detailed knowledge of these mechanisms will allow us to stimulate mobilization of these stem cells via biochemical signals which will not only produce more effective therapies for tissue defect patients, but also provide novel therapeutic approaches toward endogenous stem cell homing-based tissue engineering in clinical applications.

6 Conclusions

Despite the gold standard for the repair of tissue and organ defects, autologous grafts fail to achieve an entirely restoration of function after they are implanted. Tissue engineering scaffold play an important role for tissue repair, especially the combined with stem cells. In tissue engineering, the biodegradable materials and electrospinning method have been widely used, and usually the biochemical signals (such as growth factors) have been used as well. Stem cell homing is a recruitment process for the mechanisms and modes of stem cell homing-based tissue engineering can be divided into two types depending on the source of the stem cells: endogenous and exogenous. There are lots of stem cell-based tissue engineering scaffold have been applied *in vitro* and *in vivo*. However, there is still a long way before clinical application. Generally, stem cell homing-based tissue engineering scaffold needs further significant progress towards the development of ideal tissue engineering.

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