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Review article

Stimuli-responsive microcarriers and their application in tissue repair: A review of magnetic and electroactive microcarrier

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ABSTRACT

Microcarrier applications have made great advances in tissue engineering in recent years, which can load cells, drugs, and bioactive factors. These microcarriers can be minimally injected into the defect to help reconstruct a good microenvironment for tissue repair. In order to achieve more ideal performance and face more complex tissue damage, an increasing amount of effort has been focused on microcarriers that can actively respond to external stimuli. These microcarriers have the functions of directional movement, targeted enrichment, material release control, and providing signals conducive to tissue repair. Given the high controllability and designability of magnetic and electroactive microcarriers, the research progress of these microcarriers is highlighted in this review. Their structure, function and applications, potential tissue repair mechanisms, and challenges are discussed. In summary, through the design with clinical translation ability, meaningful and comprehensive experimental characterization, and in-depth study and application of tissue repair mechanisms, stimuli-responsive microcarriers have great potential in tissue repair.

1. Introduction

Tissue repair and regeneration has always been a research hotspot because most tissues cannot self-return to their original level after damage. Meanwhile, different tissues have various structures, and the causes of defects are also disparate, so it is meaningful to be more targeted when designing and developing tissue engineering scaffolds [5–7]. Microcarriers are a kind of scaffolds with three-dimensional connected porous structure (i.e. large specific surface area), which were originally used for 3D cell culture in vitro [1,2] and are now seen as promising scaffolds for tissue engineering (along with three-dimensional bulk blocks and hydrogels [3,4]). Compared with other types of scaffolds, microcarriers (mainly 100–300 μm [8], on the micrometer scale) are controllable at the micro-scale, and can be modularly constructed as micro-tissues when integrating with the host [9]. They can load cells with a higher density while preventing cell death caused by inadequate transport of nutrients and metabolic wastes [10,11] and load drugs or cytokines with greater concentration while preventing early inactivation and side effects to other tissues. On the other hand, the biggest advantage is that microcarriers are allowed for minimally invasive injections to avoid open surgery, minimize complications, and relieve the pain of the patient. Besides, through targeted design, microcarriers could also influence cellular phenotype maintenance, regulate microenvironment and intercellular signaling pathways [12], which thus promote tissue repair.

Technologies for the commercial synthesis of microcarriers like emulsion-solidification, microfluidics, and spray-solidification [13–15] have already matured. By adjusting reasonable parameters of the synthesis process, microcarriers acquire distinctive shapes, sizes, structures, and surface properties, which can influence the behavior of loaded substances and subsequent tissue regeneration effects [16]. It is challenging to achieve satisfactory repair effect only by microcarriers which matrix is composed by one or two polymers. The microcarriers must be modified to attain better stability and richer function. Methods commonly used for modification include chemical ways such as graft polymerization, physical ways like electrostatic adsorption and layer-by-layer self-assembly, and biological ways such as biomineralization and RGD modification [17–21]. Effective modification endows microcarriers with matching biological properties, and more conducive to the specific adhesion, proliferation, and differentiation of loaded

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cells. Then the microcarriers can face more complex tissue damage conditions and eventually help tissue repair and functional recovery [22].

Stimuli-responsive microcarrier is a kind of modified microcarrier, which can respond quickly to external stimuli. The stimuli-responsiveness makes researchers control the in vivo behavior of microcarrier more effectively. For example, motion control and precise orientation can be achieved through external magnetic fields. These stimuli are divided into in vivo response and in vitro response according to the reaction site, or divided into physical forms (magnetic fields, electric fields, light, mechanical force, temperature, etc.) and chemical forms (pH, ROS, ions, and other components altered due to injury) according to the mechanism (Fig. 1) [23–25].

Previous studies have summarized the application of microcarriers in cell culture and tissue repair, and also the biological application of stimuli-responsive materials, but there not exists a thorough analysis on stimuli-responsive microcarriers and their potential repair mechanism. Since magnetic and electroactive microcarriers not only serve as carriers, but also have richer functions, therefore, this review will focus on the magnetic and electroactive microcarriers, and then selectively analyze their response components, repair mechanisms, and existing applications in tissue repair. Finally, taking magnetic and electroactive microcarriers as examples, further analysis of the challenge of stimuli-responsive microcarriers in design, testing, and innovation is given. This review may bring some insights into the development of stimuli-responsive microcarriers.

2. Principles of literature selection

Bone, cartilage and nerve are important tissues in the human body which are prone to damage and difficult to recover. There have been a certain number of studies on magnetic and electroactive microcarriers in the repair of these three tissues, so it is of significance to analyze and summarize. Therefore, this review focus on the application of stimuli-responsive microcarriers in the repair of bone, cartilage, and nerve. Relevant literature was screened in the two databases, *Web of Science* and *Pubmed,* by means of combined search of keywords (Fig. 2) and the initial screening was achieved according to the abstract and conclusion. A total of 4380 literatures was indexed. Secondary screening was more targeted, these principles included that the research involved must have a clear application scenario, the microcarrier size must be in the micron (10–1000 μm) or submicron (1–10 μm) scale and microcarriers should have tissue repair functions rather than simply deliver cells or drugs, or be used for tracing. Meanwhile, microcarriers involved are used alone and injectable, instead of being implanted in hydrogels or bulk scaffolds. For magnetic microcarrier, the application of magnetism was necessary. For electroactive microcarriers, the included articles should either incorporate electroactive materials or explicitly state that the studied microcarriers could facilitate the reconstruction of electrophysiological microenvironment. Finally, a total of 51 articles was included in this review.

3. Magnetic microcarriers

Magnetic microcarrier are defined as microcarriers that can move directionally and targeted fix under the stimulate of external magnetic field and load cells or drugs to achieve tissue repair. There are two ways to achieve the magnetism of microcarriers. Researchers can first prepare the microcarrier matrix by emulsification or microfluidic method, and then fix the magnetic-responsive components to the surface of microcarriers by chemical bonding, electrostatic interaction, hydrogen bonding, or physical adsorption [26,27]. Some researchers also in-situ dope or encapsulate the magnetic components in the matrix during the synthesis process of microcarriers.

Most of the microcarrier matrix are biodegradable, such as natural polymer chitosan (CS), alginate (Alg), gelatin (Gel), hyaluronic acid (HA), and artificial polymer poly (lactic-*co*-glycolic acid) (PLGA). With the degradation of the matrix, the magnetic components are gradually released. These components are usually paramagnetic magnetic nanoparticles, which are small in size. They can specifically recognize the cell membrane [28] or be endocytosed by cells, and thereby affecting the behavior of cells [29,30].

3.1. The application of magnetic microcarriers in tissue repair

Nowadays, magnetic microcarriers have been studied in the fields of cartilage, bone, and nerve, and some related studies are organized in Table 1.

3.1.1. The application of magnetic microcarriers in cartilage

Cartilage, mainly articular cartilage, is located at the interface of bones and its function is to maintain lubrication, reduce friction, and facilitate load transfer [31]. The hyaline cartilage at the joint is composed of chondrocytes and ECM, and it exhibits a strong gradient phenomenon in both structure and composition (Fig.

3A) [32]. Because of various factors such as exercise, age, cartilage morbidity is showing a trend of increasing year by year, this damage affects the quality of life, which needs to intervene. Currently, palliative, restorative, and rehabilitative [33] treatment of cartilage are used. Considering the difficulty of cartilage repair and the disadvantages of existing methods such as producing fibrocartilage that does not match the native cartilage, magnetic microcarriers have their unique advantages in cartilage repair.

Go et al. [34] in Korea created a series of magnetic microcarriers by modifying the PLGA microspheres synthesized by emulsion. Amine-functionalized MNPs were encapsulated to target MSCs which achieved chondrogenic differentiation in vitro using an electromagnetic drive system. Changing the magnetic composition to a kind of micro-clusters consisting of negatively charged magnetic nanomedicine and positively charged chitosan, the newly formed PLGA microcarriers promoted the cartilage repair after injecting into rabbit knee defects (Fig. 3B) [35]. They also used the mussel-like properties of polydopamine (PDA) to tightly adhere MNPs, TGF-β1, and cells onto PLGA microcarriers, which led to a greater expression of ECM components than directly adding growth factors to the medium [36].

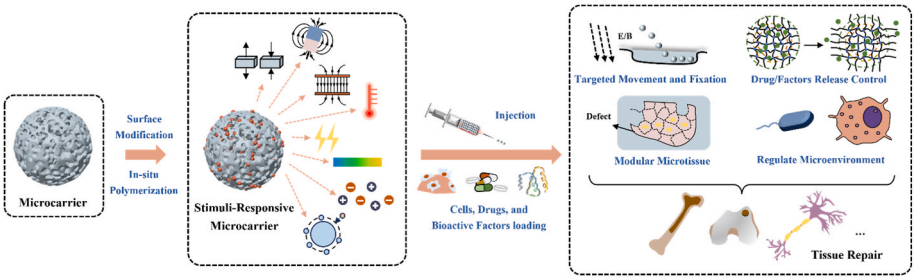

Fig. 1. The types and functions of stimuli-responsive microcarriers in tissue repair.

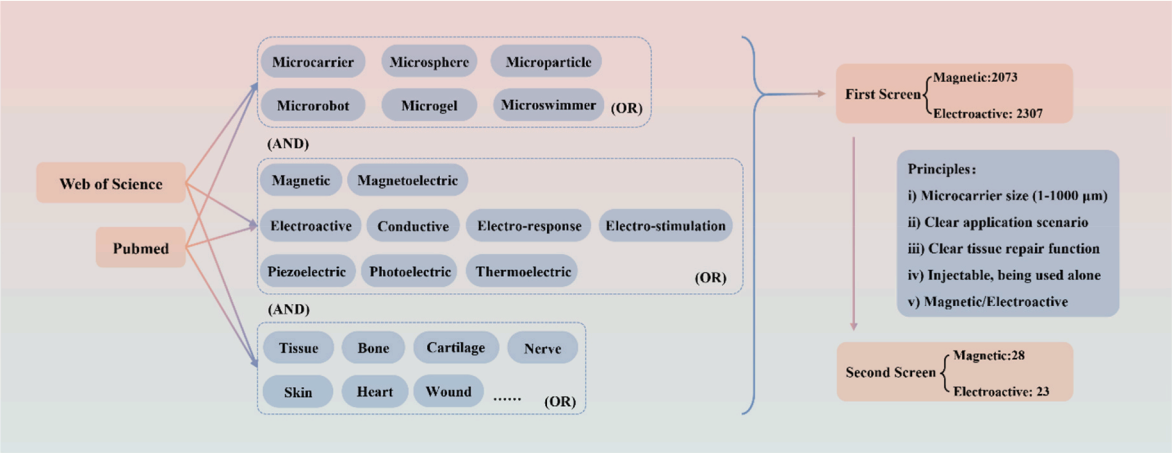

Fig. 2. Principles of literature collection and screening.

Other researchers have made microcarriers in the shape of capsules to construct a relatively stable and closed liquefied environment [20,37]. The purpose of the microcapsules was to promote the differentiation of stem cells and keep the cells safe while enabling nutrient transfer. Clara et al. formed the outer shell of the capsules by the layer-by-layer encapsulation of alginate and chitosan. In the inner part, poly-*l*-lactic acid blocks wrapped with collagen type II and TGF-β3 were used as the physical sites to support cell adhesion and trigger chondrogenic differentiation. MNPs were electrostatically deposited in the outermost layer to respond to the magnetic field (Fig. 3C). In vitro culture collagen similar to the native cartilage ECM was seen, and glycosaminoglycan content reached the chondrogenic level, indicating considerable promise for minimally invasive repair.

For osteochondral defects, Lee et al. [38] used the microfluidic method to prepare PLGA microcarriers, and obtained 250–350 μm and 750–850 μm microspheres by controlling the flow rate of the oil and water phase. The different surface area could adjust the adhesion amount of MNPs. Different microspheres have diverse movement rates in the same magnetic field: High-speed microcarriers could preferentially repair the subchondral bone to realize stratified treatment. For joint inflammation treatment, Butoescu et al. [39] embedded dexamethasone in PLGA microspheres with superparamagnetic properties to control drug release and magnetic field was used to avoid rapid loss of drugs. Besides, Li et al. [40] synthesized PLLA nanofiber-coated and drug-loaded mesoporous microspheres to mimic the structure of ECM, which may provide more possibilities for cell-based cartilage repair.

Based on the previous studies, a kind of magnetic microcarrier named CS/PDS@MS was made by Ma et al. [41]. Magnetic particles with core-shell structures were first synthesized based on the in-situ polymerization reaction of dopamine (DA) and the chelation of Fe_3O_4 with catechol. The particles were then adhered to the surface of CS microcarriers by hydrogen bonding (Fig. 3D). The microcarriers which could deform along the direction of the magnetic field can guide the migration, elongation, and growth of BMSCs, and a rapid cell expansion was achieved in vitro. Then a magnet was implanted in the muscle gap of rats. Various tests have demonstrated that the BMSCs could fix the defects and form an early cartilage matrix. Long-term treatment facilitated the regeneration of cartilage and the recovery of motor function.

3.1.2. *The application of magnetic microcarriers in bone*

Bone plays a leading role in supporting and protecting human body structure and movement. When under a magnetic field, Zhao et al. [42] created magnetic microspheres encapsulated by PLGA to guide the directional migration of the cells. After six weeks, macrophages had polarized to the M2 type, and the osteogenic-specific matrix protein expression had increased, indicating the good reconstruction effects of bone structure. Tatinan [43] added Fe^{2+}/Fe^{3+} doped hydroxyapatite to the type I collagen peptide matrix to form superparamagnetic mimetic hybrid microspheres which could release calcium and iron to support bone homeostasis and regeneration. Besides, bone repair is a kind of percutaneous implantation surgery which is prone to bacterial infection and inflammation. Gelatin microspheres with self-assembled magnetic and antibacterial nanoparticles designed by Zhou et al. [44] could targeted sterilization in the near-infrared, creating a favorable environment for bone healing. Growth factor delivery is also an important approach for the treatment of bone defects. Based on the characteristics of early angiogenesis and late osteogenesis during natural bone healing, Yang et al. [45] loaded VEGF and BMP2 respectively in the two chambers of Janus microspheres, and release them sequentially to simulate the natural repair process. Using magnetic fields to promote enrichment and localization, which obtained good results in rats (Fig. 3E). Additionally, low-dose MNPs-modified BMSC exosomes were also used as microcarriers to solve the issue of the poor stem cell survival rate. Wu et al. [46] further demonstrated that due to the synergistic effect of MNPs and magnetic field, the miR-1260a genes were greatly enriched to effectively inhibit the expression of HDAC7 and COL4A2 to enhance osteogenesis and angiogenesis (Fig. 3F).

3.1.3. *The application of magnetic microcarriers in other tissues*

Currently, only a few studies have used magnetic microcarriers for nerve repair. But magnetic microcarriers might load with cells and growth factors to promote axonal regeneration and stimulate the growth of neural synapses in the desired direction [47,48]. For example, Yuan et al. [49] synthesized a type of nerve growth factor-functionalized SPIONs-Au nanomedicine, which could be endocytosed by cells to stimulate cell differentiation and axonal growth in a dynamic magnetic field. And Ciofani et al. [50] used magnetic Alg microspheres carrying NGF to induce PC12 differentiation which opened new therapeutic options for neuronal regeneration. Magnetic microcarriers are also used in anti-tumor [51,52] and wound healing [53–55] which can specifically recognize growth factors and encapsulate drugs. However, this review focuses on tissue repair, so cancer treatment will not be elaborated.

In conclusion, magnetic microcarriers have already been used in cartilage, bone, and nerve repair. These microcarriers can be directly transported and fixed in the defect to effectively avoid cell loss and the early inactivation of drugs and growth factors. Nowadays, many improvements to the shape of the microcarriers according to the application scenarios have been made. For example, MSCs and MNPs were separated into two chambers in Janus microspheres by Thomas et al. [56] to prevent negative effects and guarantee the normal viability of cells. And a Si–Ni–Ti planar magnetic microcarrier was created by Chen et al. [57] which could more efficiently transmit a large number of cells

Table 1
Application of magnetic microcarriers in tissue repair.

No.	Tissue	Materials	Degradation Property	Synthetic Method	Modification Method	Cell/Growth Factor/Drug	MF Type	In Vivo	Ref.
1	Cartilage	PLGA	Biodegradable	W–O–W Emulsion & Template Method	Ferumoxytol & Chitosan Electrostatic interaction	TGF-β1 & MSCs	SMF	/	[36]
2		CS	Biodegradable	Antiphase suspension & Thermally induced phase separation	Fe_3O_4 NPs PDA Adhesion	BMSCs	SMF	SD rat	[41]
3		ECM	Biodegradable	Decellularization	Fe_3O_4 NPs Dip-Coating	hBMSCs	RMF	SD rat	[193]
4		SC spheroid	Biodegradable	SC Spheroid Culture	Fe_3O_4 NPs (dextran) Co-culture	Mouse MSCs	EMF	/	[194]
5		CS	Biodegradable	Freeze-drying & Femtosecond-pulsed UV laser cutting	Ferumoxytol & Col-I Electrostatic & van der Waals interactions	hADMSCs	EMF	/	[195]
6		SA	Biodegradable	Microfluidic & Calcium-mediated cross-linking	IONPs In-situ encapsulation	MSCs	EMF	/	[56]
7		SA/CS	Biodegradable	Layer-by-layer deposition	Fe_3O_4 NPs Electrostatic attraction	TGF-β3 & MSCs	/	/	[37]
8		Silicon	Non-biodegradable	Oxygen plasma treatment & Photoetching	Ni/Ti coating Magnetron Sputtering	rBMSCs	RMF	/	[57]
9		PLGA	Biodegradable	W–O–W Emulsion & Template Method	Fe_3O_4 NPs (PEI) Protein coupling	Mouse MSCs	EMF	/	[34]
10		PLGA	Biodegradable	W–O–W Emulsion & Template Method	Ferumoxytol & Chitosan Electrostatic interaction	MSCs	EMF	Rabbit	[35]
11		PLGA	Biodegradable	Double emulsion–solvent evaporation	SPIONs (PVA) In-situ encapsulation	DXM	SMF	/	[39]
12	Osteochondral	PLGA	Biodegradable	W–O–W Emulsion & Template Method	Iron (II,III) oxide PDA Adhesion NPs	/	EMF	/	[38]
13	Bone	PBLG	Biodegradable	W–O–W Emulsion & Template Method	Fe_3O_4 NPs (-NH_2) Ring opening polymerization	ADSCs	/	/	[196]
14		HAMA /GelMA	Biodegradable	Microfluidic electrospray	Fe_3O_4@SiO_2 NPs In-situ encapsulation	VEGF & BMP2	SMF	SD rat	[45]
15		Gel	Biodegradable	Cross-linking curing	Superparamagnetic CS NPs In-situ encapsulation	VEGF165 plasmids	SMF /OMF	Rabbit	[197]
16		Gel	Biodegradable	Emulsion-crosslinking	Fe_3O_4 NPs (-NH_2) Covalent linkage	IR780 NPs	SMF	SD rat	[44]
17		Carbonated HA	Biodegradable	Hydrothermal reaction	$CaCO_3$/Fe_3O_4 Carbonate through hydrothermal	hBMSCs & Gentamicin	/	/	[198]
18		Col I-like peptide	Biodegradable	Water-in-oil emulsification	Fe^{2+}/Fe^{3+} doped hydroxyapatite Heterogeneous nucleation	MC3T3-E1	/	/	[43]
19		PLA	Biodegradable	Microfluidic & Template Method	CFO@BTO/PLLA NPs Vacuum infiltration	hMG63	ACMF	/	[139]
20		Col I-based peptide	Biodegradable	Water-in-oil emulsification	Iron-doped hydroxyapatite Biomineralization	rhBMP-2	PEMF	/	[199]
21		PLGA	Biodegradable	W/O/W emulsion-solvent evaporation	SPIONs (Polysorbate-80) In-situ encapsulation	Murine BMSCs	SMF	SD rat	[42]
22		Exosome	Biodegradable	Exosome isolation and purificationpurifcation	Fe_3O_4 NPs Co-culture	/	SMF	Rat	[46]
23	Nerve	SA	Biodegradable	W–O dispersion process & Reticulation with calcium ions	Fe_3O_4 NPs In-situ encapsulation	NGF & PC12	SMF	/	[50]
24	Liver	CS	Biodegradable	Silica colloid crystal beads templates	Fe_3O_4 NPs In-situ gel doping & cross-linking	LPS & MSCs	AMF	ALF rat	[200]
25	Tumor	Gel	Biodegradable	Microfluidic & Ultraviolet crosslinking	Fe_3O_4 NPs In-situ encapsulation	PRMT5 inhibitor	RMF	/	[52]
26	Wound	AG & HA	Biodegradable	Microfluidic electrospray & Ultraviolet solidification	Fe_3O_4@SiO_2 NPs In-situ encapsulation	bFGF	/	STZ mice	[54]
27		PLGA	Biodegradable	W–O single-emulsion	DNIC:cMIL-500 (rod-like) In-situ encapsulation	NO	AMF	BALB/c	[55]
28		CS	Biodegradable	Microfluidic electrospray & NaOH solidification	Fe_3O_4@SiO_2 NPs In-situ encapsulation	Zn^{2+} & VEGF	/	Rat	[53]

Abbreviations: PLGA (poly(lactic-*co*-glycolic acid)), CS (chitosan), ECM (extracellular matrix), SC (stem cell), SA (sodium alginate), PBLG (poly(γ-benzyl-*l*-glutamate)), HAMA (hyaluronic acid methacryloyl), Gel (gelatin), GelMA (gelatin methacryloyl), AG (agarose), PEI (polyethyleneimine), PVA (polyvinyl alcohol), CFO ($CoFe_2O_4$), BFO ($BiFeO_3$), DXM (dexamethasone), LPS (lipopolysaccharide), SMF (static magnetic field), RMF (rotating magnetic field), EMF (electromagnetic field), OMF (oscillating magnetic fields), ACMF (alternating current magnetic field), PEMF (pulsed electromagnetic field), AMF (alternating magnetic field).

over long distances in a complex environment than the spherical shape. There are still many obstacles with respect to the structure and composition of magnetic microcarriers. In vivo feasibility analysis, quantitative magnetic field regulation, magnetic targeting devices design, and repair mechanisms exploration also deserve more attention.

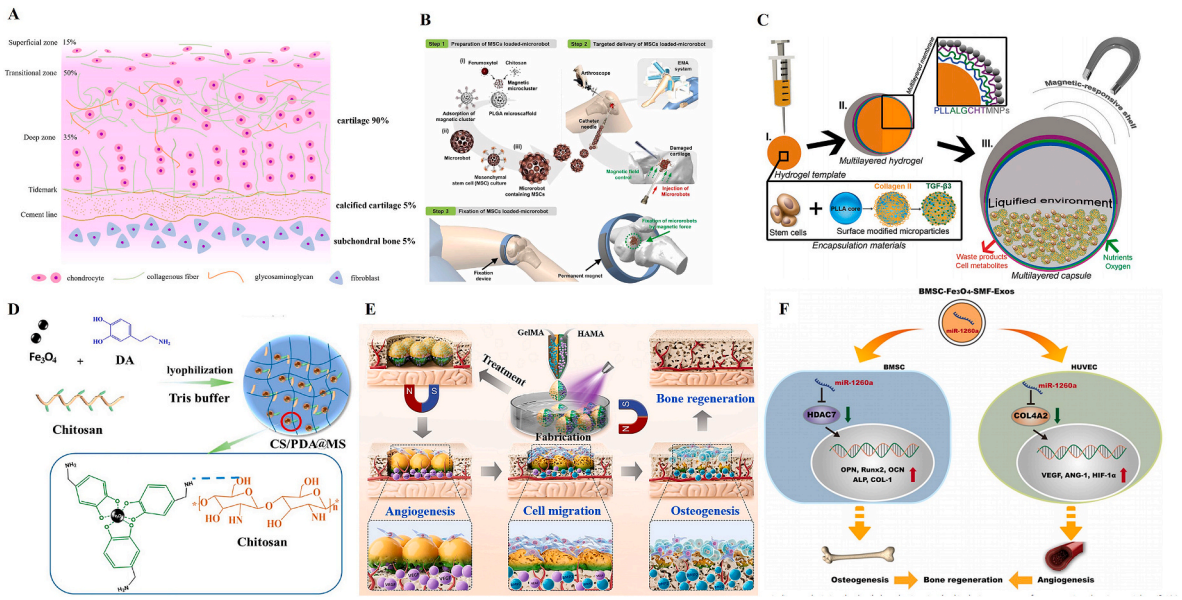

Fig. 3. The application of magnetic microcarriers in cartilage and bone tissue repair. (A) The complex structure of cartilage. (B) Knee cartilage regeneration procedures using magnetic microrobot-mediated MSC delivery system [35]. (C) The magnetic-responsive liquified capsules encapsulating stem cells and collagen II/TGF-β3 microparticles to construct closed chondromimetic environment [37]. (D) Functionalized magnetic microcarrier CS/PDA@MS for cartilage defect repair [41]. (E) Janus microcarriers with natural bone healing-mimetic sequential release ability for bone regeneration [45] (F) Magnetic BMSCs exosomes promote osteogenesis and angiogenesis by the enrichment of miR-1260a [46].

3.2. The Potential Repair Mechanism of Magnetic Microcarriers

There are various potential mechanisms for magnetic microcarriers to repair damaged tissues (Fig. 4). First, microcarriers are loaded with cells, drugs, and bioactive factors that are beneficial to tissue repair. Then, under the external magnetic field, the microcarriers can accurately reach the defect while avoiding inactivation and quick release. Finally, magnetic nanoparticles (MNPs) and magnetic field (MF) also have impact on tissue regeneration.

3.2.1. The potential influence of magnetic nanoparticles

The magnetism of most microcarriers is achieved by compound with MNPs, so the role of MNPs cannot be ignored. Typical MNPs include Fe, Ni, Co, Fe_3O_4, and Fe_2O_3 [58]. Numerous researchers have studied the safety, stability, and biocompatibility of them. The potential toxicity of Ni and Co in humans has been demonstrated [59,60], and superparamagnetic iron oxide nanoparticles (SPIONs), which are mainly Fe_3O_4, have already chosen for practical applications, such as magnetic orientation, magnetic resonance imaging, magnetic separation, and magnetic diagnosis [61–64].

When the size of the magnetic particle is below the critical one, and the temperature is between the block temperature and the Curie temperature, a single magnetic domain is formed inside, which shows superparamagnetism macroscopically. There is no hysteresis in MNPs, the coercivity and the remanent magnetization are 0. In other words, once the particles leave the external magnetic field, the magnetism of the particles vanished immediately. Meanwhile, MNPs have high saturation magnetization [65]. The metabolism of MNPs is also an important object of study, which is related to particle size, distribution, and surface properties [66]. Particles less than 10 nm can be rapidly eliminated in vivo, and the optimal size for intravenous injection is between 10 and 100 nm, which guarantees the efficient presence in specific tissues [67].

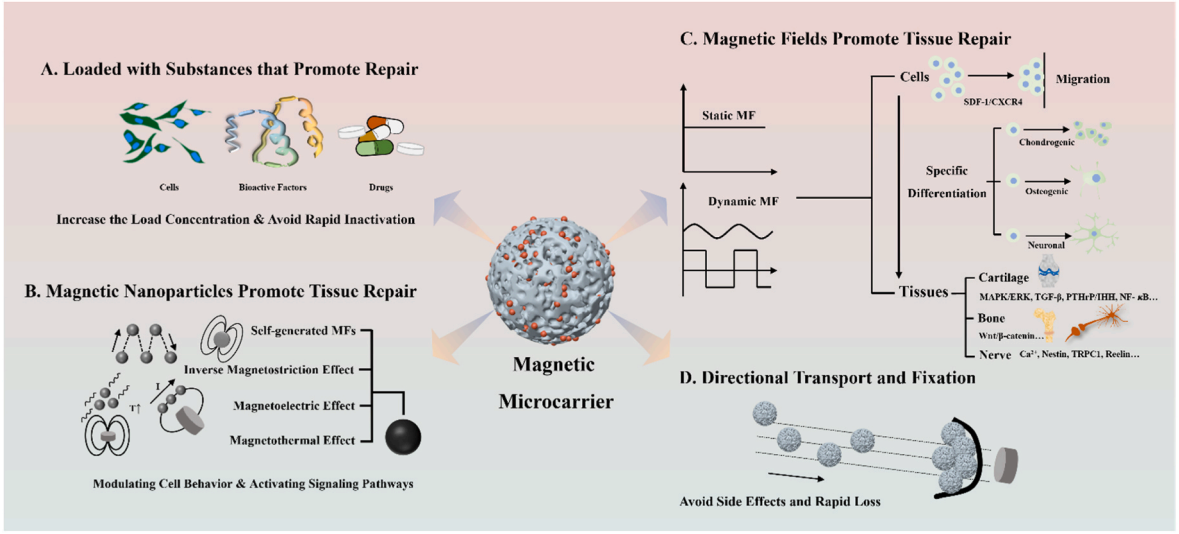

Fig. 4. The potential repair mechanism of magnetic microcarriers.

Particles larger than 200 nm will be induced to organs with high macrophage density. DMT1 and ferric reductase absorb SPIONs into the cytoplasm, and then transformed into Fe(II). These ions are then either stored as ferritin, converted to hemoglobin in the mitochondria, or moved to various organs outside the cell for storage and further oxidized to Fe(III) by ceruloplasmin [68,69]. It is worth noting that the concentration of SPIONs must be limited to an appropriate range, and some studies have shown that concentrations below 100 mg/mL may contribute to iron metabolism and storage in the human body [70]. Once iron ions overload occurs, it will lead to procedural ferroptosis [71] after cell phagocytosis, and the Fenton reaction produce excessive reactive oxygen, which will inhibit the expression of genes related to cartilage ECM synthesis [72] and the activity of osteoblasts [73], thus leading to tissue repair failure. Therefore, the size and concentration of SPIONs combined with microcarriers should be given consideration. In addition, under the combined effect of surface hydrophilicity, magnetism, and van der Waals forces [74], MNPs tend to decrease the surface energy and agglomerate, and direct exposure to the system may disturb the cells and impair cell cycle regulation [75,76], so surface modification such as covalent linkage, coupling, or click chemical is necessary [77,78]. As a result, Mahonoudi et al. [79] investigated the toxicity of PVA-coated SPIONs in mouse fibroblasts and human leukemia cells. It was demonstrated that these cells were viable at Fe concentrations ranging from 0.2 mM to 20 mM. Naosuke Kamei et al. [30] magnetized mesenchymal stem cells (MSCs) using ferucarbotran and then clinically injected them into the knee joints of five patients who had cartilage degeneration. After 48 weeks, all three patients examined had formed entirely cartilage-like tissue, and no significant side effects were observed at a follow-up 1 year later. Therefore, the magnetic microcarriers are biocompatible when they obtain the right size and concentration via appropriate composite methods, and this is a good foundation for tissue repair.

MNPs have an impact on tissue repair [80–82]. Even without an external magnetic field, SPIONs can modulate cell behavior [83], they can operate as catalase which accelerates cell growth [84] and cell cycle regulatory factors expression can also be changed by free iron ions. In bone repair, MNPs can directly interact with cell membrane and produce intrinsic magnetic field to activate signaling pathways such as MAPK and BMP in the form of mechanical stimulation through mechanosensitive ion channels to promote osteogenic differentiation [85–88]. In neural repair, some studies have proved that MNPs could direct the neurite outgrowth preferentially along the direction imposed by an external magnetic field [89], and heat emitted by MNPs can trigger the reversible discharge of TRPV1 and excite neurons in the deep brain [81]. In cartilage repair, MNPs, as a good carrier, can penetrate into the interior of the ECM, which increasing the possibility of in-situ treatment and real-time monitoring. Therefore, MNPs and the metabolized iron ions, the micro-magnetic field generated, as well as possible magneto-electricity and magnetothermal reaction, may have an impact on tissue repair.

3.2.2. The potential influence of magnetic field

Nowadays, the main function of most magnetic microcarriers is to locate and transport the loaded substances and enrich them in the defect under the induction of external magnetic field (MF). However, the MF can also play a role in regulating the behavior of cells and tissues.

The field types (static and dynamic MFs), intensity, and exposure time all affect the repair effects. It has been demonstrated that MFs can regulate ion channels and cellular pathways, generate induced bioelectric currents, and subsequently affect cell migration, proliferation, and differentiation [90,91]. For example, studies have shown that a 200 mT static magnetic field can activate Piezo 1 channels and thus mediate the SDF-1/CXCR4 signaling axis which effectively promotes the migration of endogenous stem cells to the defect [92]. Meanwhile, the magnetic gradient forces generated by the field can change the structure and ingredient of ECM and maintain the stability. MFs can also regulate inflammation, affecting macrophages polarization (from M1 to M2), neutrophils suppression, and the adenosine receptors A2A and A3 activation [93–95] (Fig. 5B).

MFs can promote cartilage repair through multiple pathways, such as MAPK/ERK [96], TGF-β [97], PTHrP/IHH [98], NF-κB [99] (Fig. 5A). After implanting the gelatin hydrogel scaffolds in the joints and applying a pulsed magnetic field, Li et al. [100] found that the p38 MARK pathway was activated, and the ERK pathway was downregulated. This led to the promotion of BMSC chondrogenic differentiation and the inhibition of hypertrophy. In bone repair, magnetic signals, such as Wnt/β-catenin, are triggered, which stimulate osteoblast differentiation and inhibit osteoclast growth (Fig. 5C) [101]. Magnetic force can also be converted into mechanical signals to rearrange the cytoskeleton. Bigham et al. [102] injected autologous bone marrow into the rabbit radial defects, and after being exposed to a MF, it had a better healing effect. And Luo et al. [103] constructed a type of microsphere loaded with the gene of superparamagnetic plasmid. The microsphere could induce magnetic micromotion in oscillating and static MFs, and the release of the plasmid effectively promoted the internal vascularization of artificial bone scaffolds. This design can be used for large osteochondral defect repair. In neural repair, magnetic fields can promote the expression of the Ca^{2+} channel [104] and the consumption of ATP [105] to increase cellular activities and the content of BDNF. Researchers also found that Nestin [106], TRPC1 [107], and Reelin [108], can be activated to influence the expression of neural differentiation genes and increase synaptic plasticity.

In conclusion, after being composed of magnetic-responsive materials, the microcarriers can be directedly transported and enriched in the damaged tissue under the magnetic field, and this effectively prevents the loss of cells and the early inactivation of drugs and bioactive factors. Meanwhile, both the suitable intensity of the magnetic field and the right concentration of the MNPs are beneficial for tissue repair.

4. Electroactive microcarriers

4.1. Structure and typical electroactive materials used in electroactive microcarriers

Electroactive microcarriers are divided into two types according to the matrix material. When the matrix polymer has intrinsic electroactivity, such as PVDF, the cells, drugs, and factors can be directly loaded. When the matrix polymer only acts as structural support, it needs to be combined with the electroactive nanoparticles or carbon-based materials by in-situ doping or surface modification. Meanwhile, by modifying ionizing groups, such as sulfonic acid and amide, the surface of microcarriers is charged, which can also be regarded as electroactive.

Electroactive materials are diverse, and common conductive materials include conductive polymers, carbon-based materials, nanoparticles of metals and their oxides, which can conduct electric current and generate electrical signals under an external field [23,109]. Electrons in conductive polymers such as polypyrrole, polyaniline, and polythiophene derivatives (such as PEDOT) can freely flow across the alternating single and double covalent bonds. Research shows that these materials are compatible [110–112]. For example, the use of sulfonated cellulose/PEDOT nanofiber composite membrane by Liu et al. [113] greatly improved the repair effects of peripheral nerves. Carbon-based materials are conductive because of a wide range of off-domain π-bond. Kunisaki et al. [114] proved that oxidation-treated CNT could induce nerve regeneration. Besides, conductive nanoparticles like Au, Ag, Pt, and ZnO can also be used based on application scenarios.

Piezoelectric materials such as polyvinylidene fluoride (PVDF) and inorganic barium titanate ($BaTiO_3$) are another type of electroactive material. The self-generated electrical characteristics of piezoelectric materials can be applied to the pressured parts of the body such as bone without the need for extra energy and electrodes. When sciatic nerve

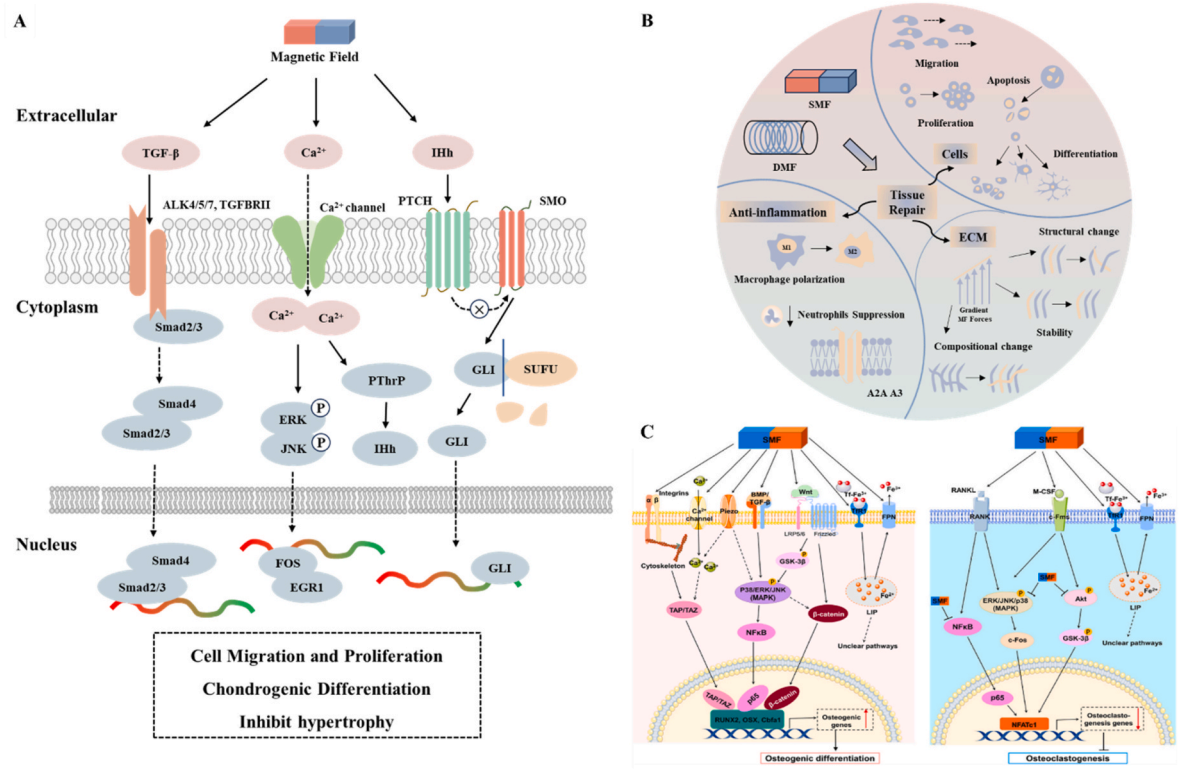

Fig. 5. The potential influence of magnetic fields on tissue repair. (A) Possible pathways involved in the effect of magnetic fields on cartilage. (B) Magnetic fields influence tissue repair. (C) Effects of magnetic fields on osteoblasts and osteoclasts [101].

axons of mice were replaced with PVDF channels, the regenerated nerves contained more myelinated axons [115]. According to the research by Feng et al. [116], tetragonal-$BaTiO_3$ nanoparticles activated by ultrasonics might eliminate *E. coli*. Compositing multiple electroactive materials is conductive to constructing the electrophysiological microenvironment. Zhang et al. [117] mixed a PVDF membrane with PDA-coated $BaTiO_3$ nanoparticles and applied it to the bone defect. The experimental results proved that the membrane could continuously maintain the electrical microenvironment, promote rapid bone regeneration and the formation of intact bone structure.

Polydopamine (PDA) has been used by many researchers because of its mussel-like properties, which is able to immobilize bioactive molecules, promote cell adhesion [118,119], and have good electroactive. Studies have shown that PDA, formed by the self-polymerization of dopamine [120], has dural electrical conductivity for both electrons and ions [121,122]. The conductivity of a bacterial cellulose/PDA film prepared by Xie et al. [123] increased with the increase of PDA content. Besides, due to the piezoelectric and pyroelectric properties of hydroxyapatite (HAP), HAP helps to respond to mechanical stress similar to bone and accelerate bone healing, which is an important component in promoting osteogenesis [124].

4.2. The application of electroactive microcarriers in tissue repair

Electroactive microcarriers have great application prospects in tissue repair due to their ability to construct electrophysiological microenvironment. However, the current research is still limited, and this section will summarize the application of electroactive microcarriers (Table 2).

4.2.1. The application of electroactive microcarriers in nerve

Nerve is an electroactive tissue, and the reconstruction of the electrophysiological microenvironment in nerve repair is one of the indicators to test the effectiveness of repair. Pinho et al. [125] synthesized a composite microcarrier of poly (vinylidene fluoride) and cobalt ferrite nanoparticles, which is capable of generating electrical signals, promoting microglial activation and inducing the release of several bioactive molecules. Arnaldi et al. [126] formed a core-shell structure of chitosan-graphite oxide nanoplatelets, and this microcarrier promoted the neuronal cell adhesion and growth, and the cells exhibited the same characteristics as in living brain tissue.

The nerve repair effects of electroactive microcarriers have been examined in animals. Wang et al. [127] prepared IGF1c mimetic peptide supramolecular hydrogel microspheres and rejected them into SD rats for the treatment of spinal cord injuries. The microspheres effectively improved motor function of rats by eliminating inflammation and promoting directed cell differentiation (Fig. 6A). CS/PDA conductive microcarriers were prepared by Ma et al. [128] using in-situ polymerization of DA. When saturated with water, The electrical conductivity of CS/PDA microcarriers could reach up to 10^{-3}S/cm. Electrical stimulation in vitro caused Schwann cells quick adhesion and growth on the microcarriers. Together with PCL conduits, the microcarriers loaded with rADSCs were implanted into the sciatic nerve defects. It was found that the microenvironment and nerve connections were significantly improved, signaling was established, the injury gap was bridged, the regeneration of nerves and the recovery of motor function were made more ideal by this electroactive microcarrier.

Besides, other shapes of microcarriers [129,130] have been developed to optimize their motor ability in liquid environments. For example, spiral-shaped microcarriers with a magneto-responsive effect can be highly controllable under low-intensity magnetic fields while utilizing the piezoelectric effect to give cells wireless electronic signals, which opening up new avenues for repairing nerves through cellular therapies.

4.2.2. The application of electroactive microcarriers in bone and cartilage

Bone is also an electroactive tissue [131–134]. Wolff's law had already stated that polarization of bone due to piezoelectric effect promotes bone growth and healing [135]. Currently, cranial bone repair has

Table 2
Application of electroactive microcarriers in tissue repair.

No.	Tissue	Materials	Degradation Property	Synthetic Method	Modification Method	Cell/Growth Factor/Drug	In Vivo	Ref.
1	Bone	PLGA	Biodegradable	Airflow shearing	Nano HAP for osteogenesis In-situ encapsulation	MC3T3-E1	Rat	[201]
2		PLGA	Biodegradable	High-voltage electrostatic	Sr-BTO NPs for restore electric microenvironment In-situ encapsulation	MC3T3-E1	Rat	[202]
3		PHBV	Non-biodegradable	S/O/W emulsion/solvent evaporation	Wollastonite for apatite layer forming In-situ encapsulation	Gentamicin	/	[203]
4		PLLA	Biodegradable	Vacuum infiltration & Template Method	CFO@BTO NPs for piezoelectric property In-situ encapsulation	MG63 cells	/	[139]
5		PLGA	Biodegradable	High-voltage electrostatic	HAP, AT for conductivity PDA adhesion	IGF-1	Rat	[138]
6		PAGTP	Biodegradable	Emulsification	AT for Electrophysiological matching In-situ chemical reaction	BMSCs	Rat	[137]
7		PAGTP	Biodegradable	Double emulsion	Ag NPs for conductivity Immersing	BMSCs	Rat	[136]
8		PVDF	Biodegradable	Electrospray technique	CFO NPs for magnetostriction In-situ encapsulation	MSCs	/	[204]
9		GelMA	Biodegradable	Microfluidic & Ultraviolet crosslinking	Black phosphorus nanosheets for conductivity In-situ encapsulation	DPSCs	Rat	[140]
10	Cartilage	HAMA	Biodegradable	Microfluidic & Ultraviolet crosslinking	PDA for adhesion Cross-linking reaction	Liposome	Rat	[141]
11	Nerve	PHBV	Non-biodegradable	O-in-W emulsion	CFO for neurite outgrowth In-situ encapsulation	hNPCs	/	[125]
12		CS	Biodegradable	Antiphase suspension & Thermally induced phase separation	PDA for endowing electroactive Immersing	rADSCs	Rat	[128]
13		Artificial mimetic peptide	Biodegradable	Piezoelectric ceramic-driven thermal electrospray	/	NSCs	Rat	[127]
14		CS	Biodegradable	Alkaline gelation & Aerodynamically assisted jetting	GO for conductivity Deposition & Assembly	h-iPSCs induced NCs	/	[126]
15		GelMA	Biodegradable	Two-photon lithography	CFO@BFO NPs for Magnetoelectric property Impregnation	SH-SY5Y cells	/	[129]
16		Spirulina	Biodegradable	/	$BaTiO_3$ NPs for piezoelectric property Two sequential dip-coating	PC 12	/	[130]
17		CNT	Non-biodegradable	Chemical vapor deposition	/	Rat neurons	/	[205]
18		PLGA	Biodegradable	Double emulsion solvent evaporation	SWCNTs for conductivity In-situ encapsulation	rADSCs	/	[206]
19	Heart	Alg	Biodegradable	Electro-spray	GO for anti-oxidizing ability In-situ encapsulation	MSCs/CMs	Rat	[207]
20	Tumor	HAP	Biodegradable	Hydrothermal reaction	PDA for photothermal conversion Immersing	DOX + Cu + F	/	[208]
21	Muscle	HA	Biodegradable	Microfluidic & Ultraviolet crosslinking	Ag NPs for conductivity Immersing & in situ metal reduction process	/	/	[209]
22	/	PVDF	Biodegradable	Flow-focusing microfluidic	CFO for electroactivity In-situ encapsulation	Rabbit chondrocyte	/	[145]
23		PVDF	Biodegradable	Electrospray	/	MC-3T3-E1 cell	/	[210]
24		PEDOT:PSS	Biodegradable	Microfluidic	PolyelectrolytePolyelecrtolyte Adsorption & Laminin Coating	L929 mouse fibroblast cells	/	[211]

Abbreviations: PAGPT (polyorganophosphazene), PVDF (polyvinylidene difluoride), PHBV (poly(hydroxybutyrate-*co*-hydroxyvalerate)), CNT (Carbon Nanotube), Alg (alginate), HAP (hydroxyapatite), HA (hyaluronic acid), PEDOT: PSS (poly(3,4-ethylenedioxythiophene):polystyrene sulfonate), GO (graphene oxide/), AT (aniline tetramer), DOX (doxorubicin).

been accomplished through the use of electroactive microcarriers. By co-polymerizing aniline tetramer (AT), ethyl glycinate, and phenyl dichlorophosphate, Huang et al. formed the polyphosphazene microspheres. The surface charge could attract the surrounding ions to accelerate mineralization [136,137]. Wang et al. [138] encapsulated electroactive AT and PDA and grafted IGF-1 on the surface of PLGA/HA microspheres. The experimental group produced denser regenerated bone tissue than the non-electroactive control group and vascularization and the formation of a medullary cavity also displayed (Fig. 6B).

A variety of electroactive nanomaterials have been composited with polymeric microcarriers for bone repair. For example, Maria et al. [139] in situ doped magneto-electric nanoparticles in the matrix of the organic ferroelectric material PLLA, which provided a favorable microenvironment, and the proliferation of osteoblasts increased by 134% compared to the control group. Sun et al. [140] utilized black phosphorus nanosheets to endow the conductivity of GelMA microspheres. The electrical signals improved the paracrine pattern of the loaded cells to promote the regeneration of bone defects.

There are fewer electroactive microcarriers for cartilage repair, but for osteochondral, such microcarriers have the potential to achieve stratification of treatment. Cartilage matrix has dense structure and high density of negative charge, so Lin et al. [141] designed positively charged nanoscale adhesive hydrogel microspheres. Under the stimulation of ROS and the guidance of electric charge, this microsphere

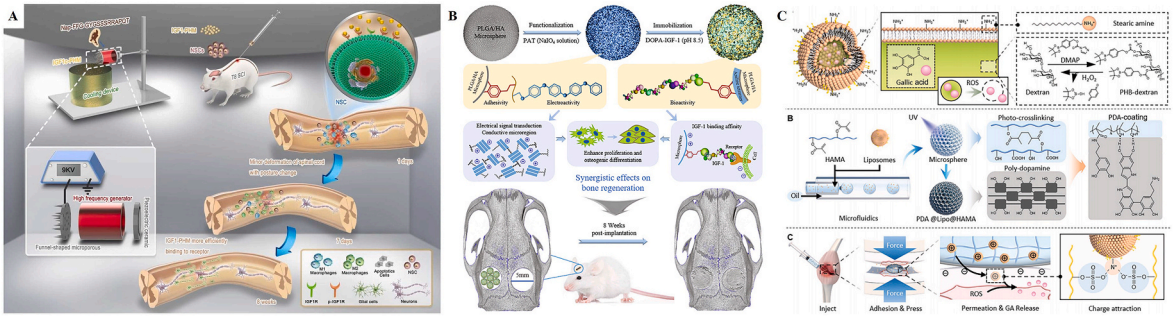

Fig. 6. The application of electroactive microcarriers in tissue repair. (A) The IGF1c mimetic peptide supramolecular hydrogel microspheres for spinal cord injuries repairing [127]. (B) Electroactive microcarriers in cranial repair [136]. (C) Positively-charged microcarriers in cartilage repair [141].

achieved efficient drug delivery (Fig. 6C).

4.3. The Potential Repair Mechanism of electroactive microcarriers

Physiological electricity is involved in the regulation of various biochemical processes in the human body. And studies have shown that electric stimulation contributes to tissue regeneration (Fig. 7) [142].

Electrical signals (ES), which is stimulated to produce by external or self-generated electric field (EF), may be the reason that electroactive microcarriers could promote tissue repair. In other words, microcarriers with surface charges can move directionally in an external EF [141], free electrons in microcarriers based on conductive materials can also move to form an electric current by the drive of an EF, and the current will be transported to the tissue. Piezoelectric materials-based microcarriers can deform in response to external stimuli, such as mechanical stress, ultrasound, and MF [143–145], resulting in charge accumulation and polarization. For example, Zhang et al. [146] prepared a magnetoelectric core-shell structure composed of Fe_3O_4 and $BaTiO_3$ to reproduce the magnetoelectric characteristics of the natural neural extracellular matrix. The photoelectric effect is also a way to generate electrical signals [147].

Various ESs can participate in tissue repair. At the molecular level, EFs can rearrange the partial charges of proteins, adjust their conformations, and regulate protein-protein interactions [148]. On the cellular level, the membrane potential affects the cell cycle and many cell behaviors. A variety of cells can migrate along the field gradient in response to physiologically intense external EFs [149]. Under electrical stimulation, cells generate a response called electrocoupling [150], which depolarizes the cell membranes or causes charged cell membrane receptors to redistribute asymmetrically to influence PI3K, ROCK, ERK1/2, and other pathways which intervene in cellular activities [151, 152], to translate into mechanical stimulation to promote cytoskeletal reorganization [153], to activate Ca^{2+}, K^+ and other ion channels [154], and to have an impact on ATP release and consumption [155]. Therefore, as shown in Fig. 8A, the appropriate form and exposure time of electrical stimulation may affect cell proliferation, differentiation, alignment, migration, and adhesion [150]. For example, Maria et al. [156] found that the ESs given during the early stage of osteogenesis induced a strong and durable effect of bone repair. Mobini et al. [157, 158] demonstrated that the cellular long-axis was rearranged in the

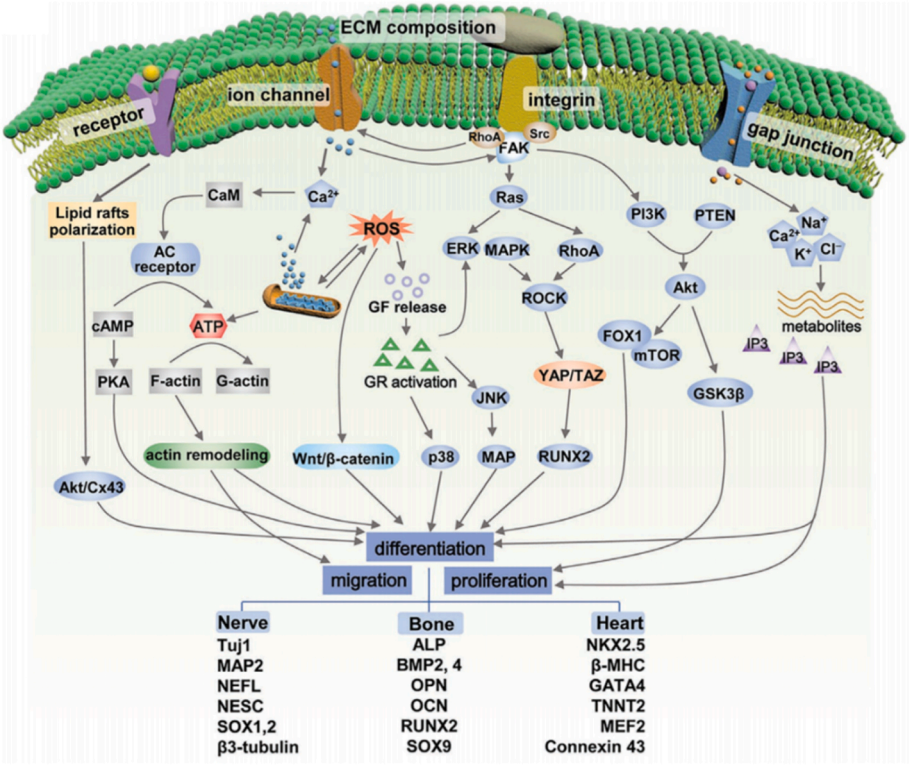

Fig. 7. Possible pathways involved in the biological response to electrostimulation [142].

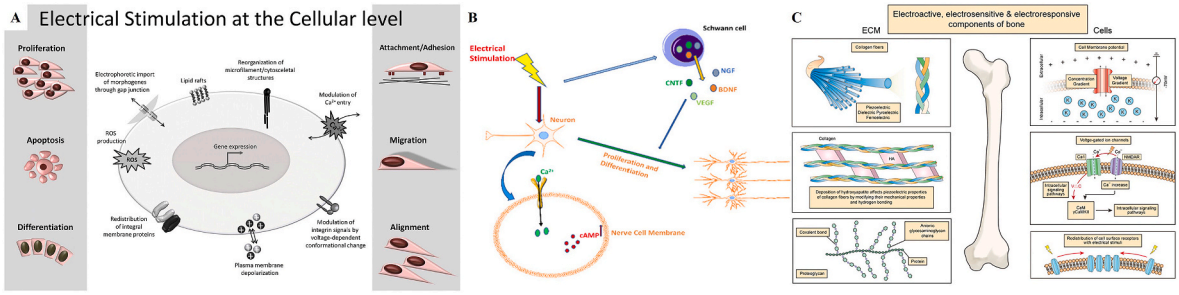

Fig. 8. Effects of electrical stimulation on cells and nerve, and the electroactive of bone. (A) Electrical stimulation influences cell proliferation, migration, differentiation, and other behaviors [150]. (B) Electrical stimulation promotes peripheral nerve injury repair [160]. (C) The reason of electroactive of bone[164].

direction perpendicular to the EF.

At the tissue level, many tissues are electroactive. Nerve impulses conduct are based on the changes of potentials [159]. When neurons are stimulated, the permeability of cell membranes changes, resulting in the variation of ion flow and membrane potential. Depolarization at the synaptic will open the Ca^{2+} channels on the presynaptic membrane and neurotransmitters are released. Then the neurotransmitters bind to receptors in the postsynaptic membrane, and thus excitatory or inhibitory postsynaptic potential are produced. Many researchers have used external electrical stimulations to repair nerve damage. Zeng et al. [160] summarized that electrical stimulation can increase the secretion level of growth factors such as BDNF and VEGF, enhancing the activity of Ca^{2+} channels in nerve cell membranes, which in turn increase cAMP level, and ultimately promoting the proliferation and differentiation of neurons (Fig. 8B) [161,162]. Moreover, this physical stimulation also expedites the axonal crossing at the site of coaptation and enhances the guidance of regenerating axons [163]. Electroactive microcarriers may play a role in nerve repair by providing electrical stimulation to neural tissue to construct a neuro-electrophysiological environment. Meanwhile, electroactivity ensures that bone functions dynamically (Fig. 8C) [164]. In the natural stage, collagen fibers (CFs) in bone are piezoelectricity, enabling spontaneously and reversibly change of orientation. When an electric stimulation or an external mechanical force is applied, CFs and HAP separate and become polarization. Studies on animals and in clinical settings have shown that the externally given ESs promote bone repair [165]. By activating calcium-calmodulin which upregulates the cytokines such as BMP and TGF-β, ESs can promote osteogenesis [166,167]. Vascularization is essential for bone repair, and electrical stimuli could enhance bone defect healing by increasing VEGF expression [168]. Furthermore, macrophage phagocytic uptake is also significantly enhanced [169]. Therefore, electroactive microcarriers can improve bone repair by multiple routes like osteogenesis, vascularization, and anti-inflammation. Although the potential of electroactive microcarriers in cartilage repair has not been fully realized, the effect of electrical stimulation on cartilage has been demonstrated. These effects include downstream pathways such as Wnt, MAPK, and JNK activation, stress and deformation induction, and chondrocyte phenotype maintenance [170–172]. Besides, charged nanoparticles can generate electric potential in cartilage when entering and exiting the ECM.

In conclusion, electroactive microcarriers, which have intrinsic electroactivity, can carry cells and bioactive molecules conducive to tissue repair. The electroactive component could deliver electrical signals to the defect, and help to reconstruct the electrophysiological microenvironment. These signals are able to regulate cell behavior, control drug release, and promote tissue regeneration. It is of interest to use electroactive microcarriers to promote tissue repair. And the specific electrical signals used of different materials needs to be analyzed concretely.

5. Other types of stimuli-responsive microcarriers and their comparison

In addition to magnetic and electroactive microcarriers, there are also a variety of stimuli-responsive microcarriers, which can deform under changes in temperature, pH, or mechanical force, etc., and realize the orderly release of loaded drugs.

A kind of microcarrier can respond to temperature changes. Materials such as hydroxypropyl cellulose and poly (*N*-isopropylacrylamide) (PNIPAM) can change the hydrophilic/hydrophobic balance of their cross-linked networks at a critical temperature. Through temperature regulation, the material structure can alter between the stretching line and the compact micelle, thus achieving drug release [10,173]. For example, Yang et al. [174] synthesized PNIPAM microcarriers laden with lubricants (HA), and when the temperature in the joint cavity rose, PNIPAM could intelligently release diclofenac sodium. Shi et al. [175] designed microcarriers with core-shell structure. *P*-phenylenediamine (PpPD) was the core while PNIPAM served as the shell. After absorbing external microwave radiation, PpPD generated a localized thermal field to heat the shell, which triggered a high-temperature phase transition to release the stored drug (Fig. 9A).

When inflammation or infection occurs at the defect, oxidation stress and metabolic dysregulation will reduce the pH around the tissue, and pH-responsive microcarriers which contain pH-sensitive groups (e.g., carboxyl, amine) can play a targeted role. The microcarriers will become hydrophilic by protonation at a low pH, and hydrophobic by deprotonation at a neutral or alkaline pH to achieve controlled drug release [176–178]. Freemont et al. [179] have hypothesized that when approaching the dissociation constant pKa, crosslinked polymer particle-containing microgels could prevent tissue degradation by filling the defect through self-expanding and this idea has been demonstrated in a model of bovine intervertebral disc degeneration (Fig. 9B).

Bone and cartilage in human body are constantly subject to force, so it is meaningful to design mechanical forces-sensitive microcarriers. It has been demonstrated that mechanical stimuli are further converted into biochemical signals via various pathways, including the extracellular matrix-integrin-cytoskeleton system or the force-sensitive ion channels, the signals are then received and responded to by cells [180,181]. And numerous microenvironmental changes can also be captured by microcarriers. For example, Zhang et al. [182] used Mg-containing microspheres which destroyed H_2O_2 and generated H_2 for •OH removal to alleviate oxidative and inflammatory responses in intervertebral disc degeneration (Fig. 9C).

Temperature-, pH-, or ROS-responsive microcarriers work by sensing the changes of the defect site, while magnetic and electroactive microcarriers can be more actively and artificially regulated, which is also the advantage of using magnetic and electroactive microcarriers.

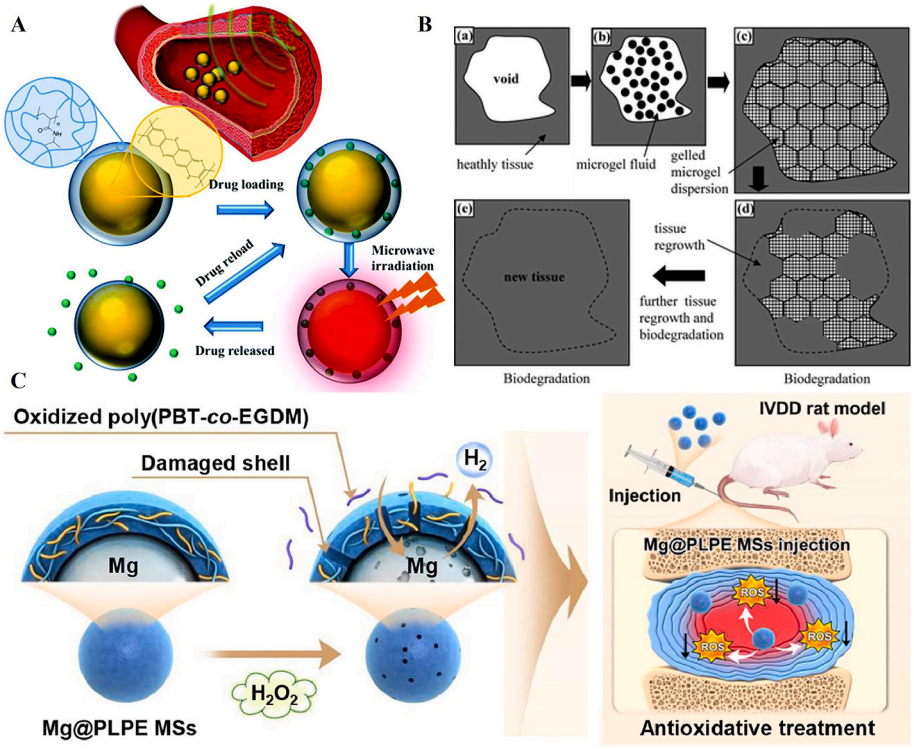

Fig. 9. Other stimuli-responsive microcarriers for tissue repair. (A) Temperature-responsive PpPD/PNIPAM microcarriers for drug loading and release [175]. (B) The pH-sensitive microgels self-swell to inhibit tissue degradation in vivo [179]. (C) ROS-responsive microspheres for the antioxidative treatment of Intervertebral disc degeneration [182].

6. Challenges in the development of stimuli-responsive microcarriers

Although stimuli-responsive microcarriers, such as magnetic and electroactive microcarriers, have made considerable progress in tissue repair, there are still several challenges to be considered and overcome.

First of all, researchers should design microcarriers according to application scenarios, because the appropriate structure and composition are the basis for realizing all functions. The compatibility and functionality of microcarriers are influenced by parameters such as material type, hydrophilicity, surface charge, pore size and porosity. Most of the current spherical microcarriers are biodegradable, allowing for the match between tissue formation and material degradation. Generally, natural polymers are more biocompatible, but the degradation rate of synthetic polymers is more easily modulated by molecular weight and chemical composition [183,184]. Meanwhile, depending on the size of the defect and the animal model, choosing microcarriers with sizes in a narrow range can effectively prevent cellular nutrient deficiency at the scaffold center. There are two basic structures of stimuli-responsive microcarriers (Fig. 10). One is to in-situ dope the response component during the synthesis process, and the other is to modify the response component through surface modification after the matrix is synthesized. Besides, microcarriers used for drug loading are usually less concerned with pore structure and more concerned with release control. In contrast, the pores and porosity of cell-loaded microcarriers need to be more focused. Substance transportation is more likely to occur in microcarriers with high porosity and large pore sizes, and cell growth is more favorable in pore sizes 1–5 times the cell diameter [185]. A certain surface charge [186] and hydrophilicity (20°–40°) [187] can improve cell seeding and adhesion.

Meanwhile, how to fully utilize the ‘stimuli’ for tissue repair is still a key for researchers. Taking magnetic microcarriers as an example, when

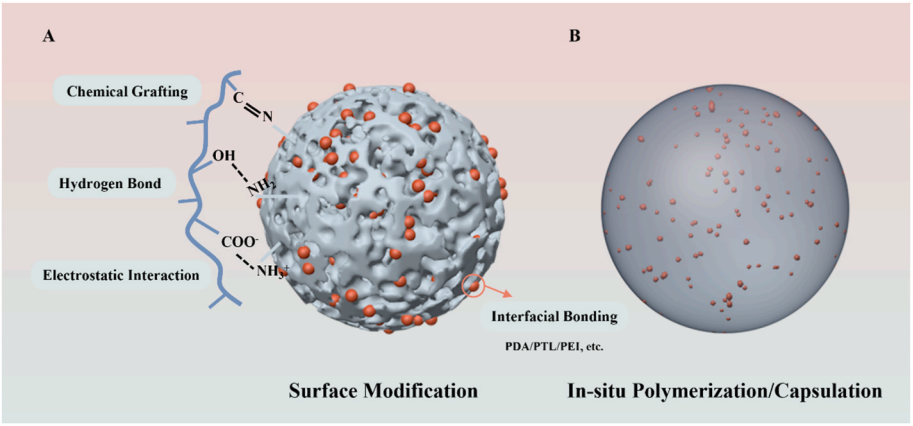

Fig. 10. The structure of stimuli-responsive microcarriers.

used for tissue repair, the main role for magnetic property is targeted delivery and enrichment of cells, drugs, and bioactive factors, to improve the utilization and avoid early inactivation. However, researchers have made less use of other advantages that magnetic microcarriers may bring to tissue repair. It should also be noted that the parameters of the external magnetic field are complex and cannot be standardized, in the process of application, the microcarriers may be generate heat or polarization, in another word, occur magneto-thermal or magneto-electric effects. How to utilize these effects to promote tissue repair without side effects on the human body is very challenging.

Although magnetic and electroactive microcarriers are capable of targeting, it is vital to endow microcarriers with 'active targeting' capabilities in certain situations, for example, sites that are complex and difficult to reach, sites where the use of external fields may produce side effects, sites that require long-term immobilization. In earlier studies, some researchers have chosen RGD peptides and antigen-antibody as the target spots. Most integrins on the cell membrane will identify RGD sequences when conveying information, and antibodies are natural molecular markers that can specifically recognize antigens [77,188]. For example, Yang et al. [29] modified RGDs on magnetized chondrocytes to create a high-density accumulation on the surface of cartilage. This concept was also applied by Woo et al. [28] to obtain shear-reversible aggregates of alginate microspheres and chondrocytes, which demonstrated good in vivo biocompatibility. Bozkurt [189] used the specific recognition of antigen-antibody to construct better-regenerated tissues in sheep joints, which had a more ordered cellular arrangement and superior quality compared to the scaffold and microfracture groups. Therefore, researchers can create microcarriers with improved targeting capabilities based on the particular tissue cells.

Nowadays, there are still many shortcomings in the research of microcarriers. First, many studies were incomplete, researchers merely proved the biocompatibility of microcarriers in vitro by co-culturing the microcarriers with cells, which made the conclusions unconvincing. Every study should have a complete experimental design, including an in vivo one. Secondly, the clinical feasibility of stimuli-responsive microcarriers is severely limited since the current supporting response equipment is less suitable. For example, for magnetic microcarriers, researchers must decide whether to wear the matching portable magnetic device outside the body [35] or implant the magnet in a suitable site in Ref. [41]. Thirdly, it is desired to mimic native tissues when designing scaffolds, some studies have shown that microcarriers with ECM composition and structure similar to those of natural tissues have greater tissue repair effects [190]. However, the directly injected microcarriers are usually arranged in a disordered state at the defect site, so researchers have to consider how to balance the orderliness of tissue structure and the disorderliness caused by injection. Possible solutions for this problem may include injecting microcarriers with different properties fractionally, combining microcarriers with hydrogel scaffolds, sintering the microcarriers into scaffolds, or specifically immobilizing them at the defect by self-crosslinking or external fields [191,192].

7. Conclusions

In this paper, the applications of magnetic microcarriers and electroactive microcarriers in bone, cartilage, and nerve were reviewed. These microcarriers have a three-dimensional connected porous structure and can deliver cells, drugs, and bioactive factors noninvasively. Under the synergistic effects of the magnetic field, magnetic nanoparticles, and loaded substances, magnetic microcarriers can directionally move and promote tissue repair. Electroactive microcarriers, through external stimulation or self-generated electric fields, can generate electric signals in vivo to promote tissue repair.

By reviewing the previous research, it must be acknowledged that stimuli-responsive microcarriers, particularly magnetic and electroactive microcarriers, have significant potential for tissue repair and regeneration. In future studies, researchers should pay more attention to the following points: First, the appropriate composition and structure of the microcarrier should be designed according to the clinical application scenario. Then, it is necessary to conduct a comprehensive and meaningful characterization of the physiochemical properties and the repair effects of the microcarriers, so that making the material design more convincing. Finally, a more in-depth study of the repair mechanism of each stimulation form at the biological level is needed, which is indispensable in solving the repair problem. Through further research, stimuli-responsive microcarriers will have a broader development space.

Ethics approval and consent to participate

This review article does not require any ethical approval or allied consent for publication.

CRediT authorship contribution statement

LiYang Zhang: Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Mengjiao Ma:** Investigation, Data curation. **Junfei Li:** Writing – review & editing, Investigation. **Kun Qiao:** Writing – review & editing. **Yajie Xie:** Writing – review & editing. **Yudong Zheng:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare the following personal relationships which may be considered as potential competing interests: Mengjiao Ma is currently employed by Beijing Wanjie Medical Device Co., Ltd., Kun Qiao and Yajie Xie are currently employed by Beijing Gerecov Technology Company Ltd.

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