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Review article

Applications of biomaterials for immunosuppression in tissue repair and regeneration

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ABSTRACT

The immune system plays an essential role in tissue repair and regeneration. Regardless of innate or adaptive immune responses, immunosuppressive strategies such as macrophage polarization and regulatory T (Treg) cell induction can be used to modulate the immune system to promote tissue repair and regeneration. Biomaterials can improve the production of anti-inflammatory macrophages and Treg cells by providing physiochemical cues or delivering therapeutics such as cytokines, small molecules, microRNA, growth factors, or stem cells in the damaged tissues. Herein, we present an overview of immunosuppressive modulation by biomaterials in tissue regeneration and highlight the mechanisms of macrophage polarization and Treg cell induction. Overall, we foresee that future biomaterials for regenerative strategies will entail more interactions between biomaterials and the immune cells, and more mechanisms of immunosuppression related to T cell subsets remain to be discovered and applied to develop novel biomaterials for tissue repair and regeneration.

Statement of Significance

Immunosuppression plays a key role in tissue repair and regeneration, and biomaterials can interact with the immune system through their biological properties and by providing physiochemical cues. Here, we summarize the studies on biomaterials that have been used for immunosuppression to facilitate tissue regeneration. In the first part of this review, we demonstrate the crucial role of macrophage polarization and induction of T regulatory (Treg) cells in immunosuppression. In the second part, distinct approaches used by biomaterials to induce immunosuppression are introduced, which show excellent performance in terms of promoting tissue regeneration.

1. Introduction

The main function of the immune system is to defend the body against pathogens; it also plays key roles in tissue development, homeostasis, and tissue regeneration [1,2]. The immune system can determine the outcome of a healing process, which normally ranges from complete regeneration that is identical to the undamaged tissue to incomplete regeneration such as fibrosis and scarring. The relationships between the immune system and tissue healing are complex because the immune responses can exert either beneficial or inhibitory effects on tissue repair and regeneration [3,4]. Normally, an inflammatory response is the initial response of the immune system to tissue injury [5,6]. However, long-time inflammation can inhibit the wound-healing process and delay the restoration of normal tissue architecture, thus making controlled inflammation necessary for improving the

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healing process [2,7]. Therefore, immunosuppression strategies can be used to modulate components of the immune system to control undesired inflammatory responses and facilitate tissue repair and regeneration [8].

Immunosuppressive factors such as cytokines, microRNAs, small molecules, growth factors, and stem cells have been used as regenerative strategies [9–13]. These factors act through binding to receptors such as Toll-like receptors (TLR) and T cell receptors (TCR) [14] and then polarizing macrophages or inducing regulatory T (Treg) cell in the healing process [15,16]. Given that systemic approaches to applying immunosuppressive factors may result in severe off-target toxicity and low efficacy, biomaterials can serve as carriers for targeted delivery of immunosuppressive agents and control their release [1,17]. Moreover, biomaterials can also provide physical support to recruit immune cells and modulate them by tailoring their physiochemical properties for tissue remodeling [18].

This brief review focuses on the applications of biomaterials for immunosuppression in tissue repair and regeneration. We highlight immunosuppression-mediated mechanisms including macrophage polarization and Treg cell induction, which correlate with the innate and adaptive immune responses, respectively. We then propose future avenues in this field, including engineering biomaterials to target certain immune cell populations in a particular tissue or organ and the combination of typical biomaterials and delivery system platforms for seeking an immune-centric approach to enhance tissue regeneration.

2. The role of immune system in tissue repair and regeneration

2.1. Innate immune response and macrophage polarization

Innate and adaptive immune systems are two main parts of the human immune system. The innate immune system can be triggered by infections or injury. The activation process involves components of the immune system which includes the complement system and patrolling cells such as macrophages, neutrophils, and dendritic cells (DCs) [19–22]. Pattern recognition receptors (PRRs) expressed on patrolling cells can bind to danger signals such as damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). PAMPs are related to simple molecules or regular patterns of molecular structures shared by pathogens, while DAMPs are related to the intracellular molecules released by damaged extracellular matrix (ECM) and necrotic or stressed cells [23,24]. Both DAMPs and PAMPs contribute to inflammation and inflammatory diseases [25,26]. After danger signals are recognized by PRRs, inflammation is triggered by activating the transcription factors NF-κB or interferon (IFN) regulatory factors [27]. Activated patrolling cells secrete more chemokines such as C-C motif ligand (CCL)-2 to recruit more neutrophils and circulating monocytes to the site, which release cytokines such as tumor necrosis factor-α (TNF-α), IL-1β, and IL-6 to induce inflammatory responses [28]. Recruited circulating monocytes rapidly differentiate into inflammatory macrophages at the injury within three days [29]. Both neutrophils and inflammatory macrophages provide the first defense of innate immunity by phagocytizing invading pathogens, apoptotic cells, and cellular debris and efficiently destroying them with degradative enzymes [30,31]. In addition, innate immune cells such as neutrophils, macrophages, and DCs play key roles in tissue repair and regeneration. Neutrophils produce vascular endothelial growth factor (VEGF)-α and IL-17 to recruit more inflammatory cells, enhance angiogenesis, and activate the proliferation of epithelial cells, fibroblasts, and keratinocytes [32,33]. Activated DCs modulate the proliferation and differentiation of myoblasts in the skeletal muscle [34]. Furthermore, DCs can release extracellular vesicles to promote mesenchymal stem cell (MSC) recruitment for bone repair and regeneration [35]. The effects of macrophages in tissue repair and regeneration will be introduced in detail in the following text.

Intensive investigation for several decades has revealed that apart from being scavenger cells, macrophages contribute to tissue repair and regeneration in much more complex roles [15,31]. At the damage site, resident and recruited macrophages proliferate and switch into distinct subtypes with different functions. They can be roughly classified into pro-inflammatory “M1” macrophages and anti-inflammatory “M2” macrophages. Macrophages are highly plastic, and their phenotype is determined by tissue microenvironments. M1 macrophages are induced by danger signals such as DAMPs, PAMPs, and cytokines such as TNF-α and IFN-γ [36], while M2 macrophages are generated by exposure to signals such as hormones, immune complexes, or cytokines such as IL-4, IL-10, IL-13, or IL-33. Accordingly, the functions of these two phenotypes are significantly different. M1 macrophages participate in phagocytosis and angiogenesis, and they secrete cytokines such as IL-1β, IL-6, and TNF-α to recruit additional inflammatory cells [37]. The long-term presence of M1 macrophages triggers chronic inflammation that can exacerbate tissue injury and inhibit the healing process [38–40]. Mosser et al. [41] suggested a new grouping of macrophage populations based on three different homeostatic activities: host defense, wound healing, and immune regulation. Macrophages are classified into classically activated macrophages, wound-healing macrophages, and regulatory macrophages. Similar to M2 macrophages, wound-healing macrophages arise in response to IL-4, while regulatory macrophages are generated in response to various stimuli, including immune complexes, prostaglandins, G-protein-coupled receptor ligands, glucocorticoids, apoptotic cells, or IL-10 [42,43]. M2 macrophages can also be classified into four subtypes-M2a, M2b, M2c, and M2d [44]. These subtypes can lead to the suppression of inflammatory responses through different pathways [45]. For instance, M2a macrophages upregulate the expression of arginase, CD206, and MHC II molecules and secretion of IL-10 and TGF-β [46]. M2b macrophages produce both anti- and pro-inflammatory cytokines and promote Th2-type immune response [47]. M2c macrophages secrete high amounts of anti-inflammatory cytokines IL-10 and TGF-β and reduce M1 macrophage-initiated immune responses [48]. M2d macrophages are a novel M2 subset and referred to as tumor-associated macrophages (TAMs) that play a detrimental protumor role in promoting tumor metastasis and progression [49,50]. The profibrotic effects of M2 macrophages can stimulate ECM assembly and remodeling which is necessary for the wound healing process, but fibrosis can destroy normal tissue architecture and lead to fibrotic diseases [51–53]. Given that the inflammatory microenvironment of a damaged site hinders the wound healing process, immunosuppression is indispensable to switch macrophages from pro-inflammatory M1 to anti-inflammatory M2 phenotype, which may inhibit inflammation, enhance tissue repair, and drive tissue regeneration. However, because of the pro-tumoral and profibrotic properties of M2 macrophages, the processes of macrophage polarization need to be carefully controlled.

2.2. Adaptive immune response and Treg cell induction

The adaptive immune response is initiated by antigen presenting cells (APCs) such as macrophages, DCs, and B cells after the activation of the innate immune system [54]. After recognizing tissue damage, immature DCs residing in peripheral tissues take up antigens and migrate to draining lymph nodes as mature nonphagocytic DCs. Mature DCs process antigens into short peptides (signal 1) and present them on the major histocompatibility complex (MHC) molecules to form peptide-MHC complexes, which can be recognized by specific TCRs on T cells. Mature DCs also

display co-stimulatory ligands CD80/CD86 (signal 2) that can bind to receptor CD28 and synergize with signal 1 to initiate priming of naïve T cells [55–58]. Then, naïve T cells are activated and become effector T cells, which can be classified into $CD4^+$ T cells including helper T (Th)1, Th2, Th17 cells, Treg cells, and cytotoxic $CD8^+$ T cells. T cell subtypes play different roles in the tissue repair and regeneration [59–62]. Cytotoxic T cells are responsible for delaying fracture healing in bone regeneration. Reinke et al. [60] demonstrated that endogenous facture regeneration was enhanced after the depletion of cytotoxic T cells, while the regenerative process was impaired by the transfer of cytotoxic T cells in a mouse model. It was suggested that TNF-α and INF-γ mainly produced by cytotoxic T cells inhibited osteogenic differentiation and the survival of MSCs, which was important for bone formation [63]. The effects of Th cells are distinct according to their subtypes. Th1 and Th17 cells produce cytokines and immune complexes [64], which promote the generation of M1 macrophages and result in more pro-inflammatory cytokines and further tissue damage. On the other hand, Th2 cells secrete cytokines such as IL-4, IL-5, and IL-13 that regulate the activities of M2 macrophages for suppressing Th1 and Th17-driven inflammation [65,66]. The contribution of Th2 cells to tissue repair and regeneration depends on M2 macrophages, and excessive activation of Th2 cells may result in allergy and pathological fibrosis [31].

Treg cells are a crucial part of regulatory mechanisms in the immune system, and they maintain immune homeostasis by suppressing autoreactive and hyperactive immune responses [67]. Because of expressing the transcription factor forkhead box protein P3 (Foxp3), Treg cells are often identified as $CD4^+Foxp3^+$ T cells. Research studies have proved that Treg cells are crucial for orchestrating tissue repair and regeneration in various tissues such as skin [68], bone [69], lung [70], and cardiac muscle [71]. Treg cells generally reside in lymphoid organs, but they can be recruited to injured sites, where they facilitate inflammation resolution by multiple mechanisms of suppression to directly and indirectly regulate tissue healing [72,73]. In the indirect way, Treg cells can produce arginase and anti-inflammatory cytokines such as IL-10 and TGF-β to suppress conventional T cells [74–76]. The anti-inflammatory microenvironment provided by the secreted factors can drive the local immune response from inflammation to tissue healing process such as the modulation of neutrophils [77], regulation of Th2 cells [78,79], and polarization of M2 macrophage [80,81]. Moreover, Treg cells can directly facilitate tissue regeneration by activating tissue-specific stem cells and progenitor cells [82–84]. Treg cells in skin preferentially localize to hair follicles, and the high expression of Jagged 1 by Treg cells is closely related to the proliferation and differentiation of hair follicle stem cells [68]. Similarly, *in vitro* induced Treg cells can effectively enhance the expansion of muscle satellite cells and inhibit their myogenic differentiation [82]. Given the important role of Treg cells in tissue regeneration, the induction of Treg cells and macrophage polarization can be used for immunosuppression to facilitate tissue repair and regeneration.

3. Biomaterials for immunosuppression in tissue repair and regeneration

The immune system participates in tissue repair and regeneration through both innate and adaptive immune responses. Therefore, it is possible to regulate immune components for tissue repair and regeneration through immunosuppression such as M2 macrophage polarization and Treg cell induction. Biomaterials have provided an ideal platform for immunosuppression in tissue healing processes. They can improve biocompatibility and alleviate foreign body reaction through optimizing physiochemical properties and delivering immunosuppressive factors [85–88]. An extensive array of biomaterials has been investigated for immunosuppression, including ceramics, decellularized ECM, collagen, elastin, alginate and hyaluronic acid (HA). Regardless of the types of biomaterial, delicate design and engineering are required for their applications in immunosuppression and tissue regeneration [89–91]. As shown in Fig. 1, the strategies of immunosuppression modulation through biomaterials in regenerative medicine can be roughly categorized into biomaterial-based, stem cell-based, and molecular signaling-based strategies [92]. Scaffolds can provide physical support to transplanted cells or host cells in the biomaterial-based strategy [93]; stem cells can rapidly proliferate and differentiate to compensate the lost tissue cells in the cell-based strategy [94]; growth factors such as insulin-like growth factor (IGF)-1 and VEGF can promote angiogenesis and tissue remodeling in the molecular signaling-based strategy [95,96]. Additionally, these three strategies can also be combined through scaffolds to co-deliver transplanted stem cells and growth factors [97,98]. Furthermore, the therapeutic effects can be further improved if biomaterials can modulate immune components and suppress undesired immune responses. The immunosuppression provided by biomaterials has significant effects on tissue repair and regeneration, and such applications of biomaterials are discussed in the following part.

3.1. Biomaterials for macrophage polarization

The pro-inflammatory function of M1 macrophages is required for triggering the healing process in a damaged site, but the resolution of inflammation is important for the healing process because prolonged inflammation can exacerbate tissue damage and inhibit tissue repair [99–102]. Furthermore, anti-inflammatory M2 phenotype has been shown to indicate constructive tissue remodeling [103,104]. Therefore, it is a promising strategy to polarize macrophage phenotype to improve tissue repair and regeneration.

3.1.1. Polarization to M2 macrophages via physiochemical biomaterials properties

Macrophages are present in a complex microenvironment with many physical and chemical signals that may influence their phenotype polarization. In the past few decades, it has been proved that ECM stiffness, architecture, and composition can regulate macrophage phenotypes [105–107]. For instance, Wu et al. [105] reported a family of thermoresponsive nanohybrid elastomer scaffolds with different stiffness softening effects. They found that stiffer substrates led to severe foreign body reaction, while softer substrates promoted M2 macrophage polarization. Yang et al. [106] fabricated hydroxyapatite (HA) bioceramics with different microscale circular patterns and nanotopographies. They found that the nanoneedle-structured HA surface could induce the M2 polarization of macrophages. Furthermore, the micro/nano hierarchical structures with the micropattern sizes of 36 μm could more significantly enhance M2 polarization of macrophages than HA bioceramics with sizes of 4 μm and 12 μm. Pinto et al. [107] compared the effect of normal and tumor ECM on macrophage polarization and found that macrophages in tumor matrices differentiated toward an anti-inflammatory M2-like phenotype. When biomaterials are implanted in the damaged tissues, macrophages are among the first immune cells to contact them. Thus, physiochemical cues of implanted biomaterials can directly change the tissue microenvironment for modulating phenotypes and functions of macrophages. After implantation of biomaterials, the initial presence of M1 macrophages triggers a necessary inflammation process, but prolonged inflammation may result in chronic inflammatory events and inhibit tissue regeneration. Therefore, appropriate physiochemical cues of biomaterials can be employed to drive macrophage polarization from M1 to M2 phenotype in regenerative strategies [108–110]. Therefore, appropriate physiochemical cues of

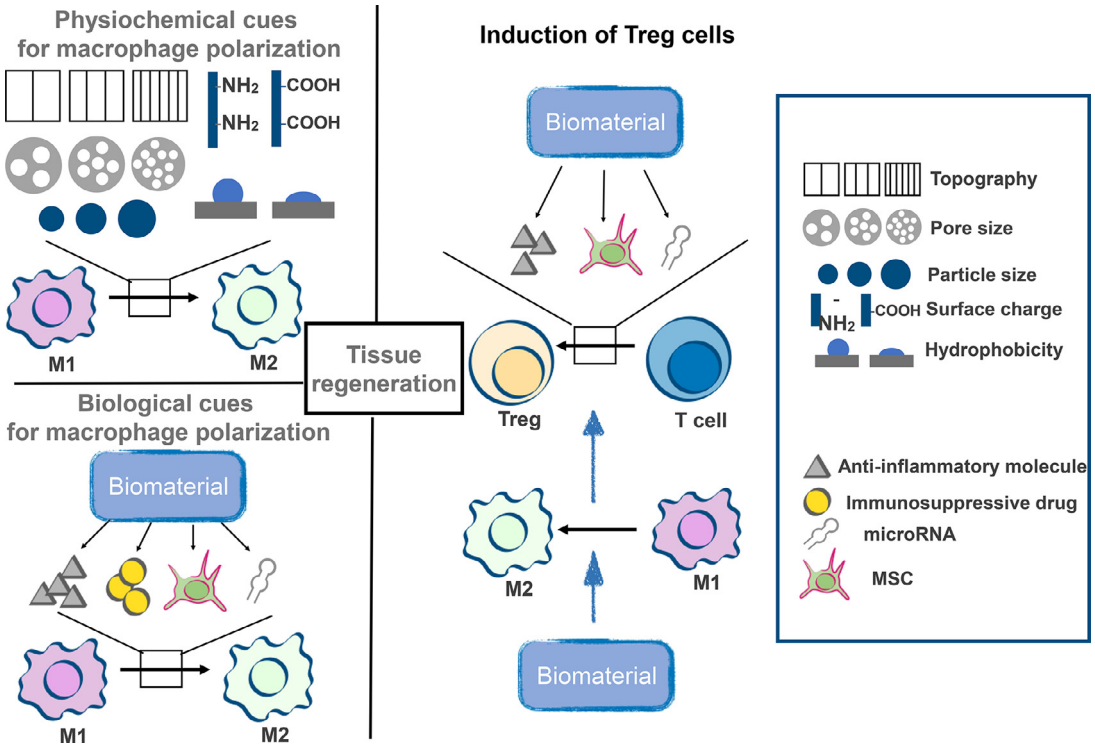

Fig. 1. A schematic illustration of biomaterials for immunosuppression through macrophage polarization and induction of Treg cells in tissue regeneration. Physiochemical cues of biomaterials, such as topography, pore size, particle size, surface charge, and hydrophobicity, can polarize macrophages from M1 to M2 phenotype. Biological cues such as anti-inflammatory molecules, MSCs, and microRNA can participate in macrophage polarization and induction of Treg cells. The process of macrophage polarization also affects the induction of Treg cells.

biomaterials can be used to induce macrophage polarization in regenerative strategies.

Physical properties such as topography, pore size, substrate stiffness, and particle size have been implicated in modulating the macrophage responses [111]. Different sizes of the microstructure on a surface can exhibit various performance on macrophages. For instance, Mcwhorter et al. [108] showed that mouse bone marrow-derived macrophages (BMDMs) could be elongated and differentiated toward M2 phenotype by 20 μm wide lines on a polydimethylsiloxane (PDMS) surface *in vitro*. However, if the width of lines was changed to 50 μm, BMDMs showed no difference from the control group without patterns. Moreover, Chen et al. [109] designed nanoporous anodic alumina with different pore sizes to examine modulatory effects of the nanopore structure and pore size on macrophage responses. They found that 50 nm nanoporous structure could effectively polarize macrophages to M2 phenotype, leading to anti-inflammatory reactions. Micro- and nano-scale fibers that are widely applied in tissue engineering can modulate macrophages through fiber arrangement or diameters. Jia et al. [110] compared the effects of aligned and random poly(L-lactic acid-co-ε-caprolactone) nanofibers on the development of macrophage phenotypes (Fig. 2A and B). Aligned nanofibers significantly induced macrophage elongation along the nanofibers and their polarization to M2 macrophages, while random nanofibers induced M1 macrophages (Fig. 2C and D). Interestingly, aligned nanofibers drastically promoted Schwann cell infiltration and axonal regrowth than random nanofibers *in vivo* (Fig. 2E and F). Furthermore, Garg et al. [112] found that mouse BMDMs were polarized from M1 to M2 phenotype when polydioxanone (PDO) fiber diameter increased from 0.35 μm to 2.8 μm and the intra pore size increased from 1 μm to 15 μm. Moreover, substrate stiffness can also affect macrophage polarization. Sridharan et al. [113] demonstrated that stiff polyacrylamide gels (323 kPa) primed macrophages toward M1 phenotype, while softer gels (11 and 88 kPa) induced M2 macrophages. In addition, surface roughness is also an important parameter of biomaterials. Rough surfaces in bone facing implants can improve the performance of osteoblasts and MSCs [114]. Compared to the flat surface, a rough surface is preferred by macrophages to adhere, which can induce secretion of inflammatory cytokines [115].

Surface charge, hydrophilicity, and hydrophobicity also play key roles in regulating macrophage phenotypes and functions [116,117]. For example, Fush et al. [116] studied the effects of surface charge on human macrophages by using carboxyl-(COOH) and amino-(NH_2) functionalized polystyrene nanoparticles (PSNPs). M2 polarization was strongly inhibited by both cationic and anionic PSNPs, but the expression of M1 macrophage markers was not significantly affected. Moreover, hydrophilicity and hydrophobicity also play an important role in macrophage polarization. Rostam et al. [117] cultured human monocytes for 6 days on untreated hydrophobic polystyrene and O_2 plasma-etched hydrophilic polystyrene surfaces. Their data showed that monocytes on the hydrophilic surface were switched to M1 phenotype with enhanced expression of pro-inflammatory transcription factors STAT1 and IRF5. In contrast, monocytes on the hydrophobic surface were polarized to M2 macrophages with high secretion of anti-inflammatory cytokines IL-10 and CCL18. Similarly, McBane et al. [118] demonstrated that a biomaterial surface coated with degradable polar hydrophobic ionic polyurethane (D-PHI) could drive human monocytes to become M2 macrophages. This was proved by the decreasing amount of pro-inflammatory cytokines TNF-α, IL-1β, and HMGB1 and the increasing amount of anti-inflammatory cytokine IL-10, which was not observed in control groups coated with tissue culture polystyrene.

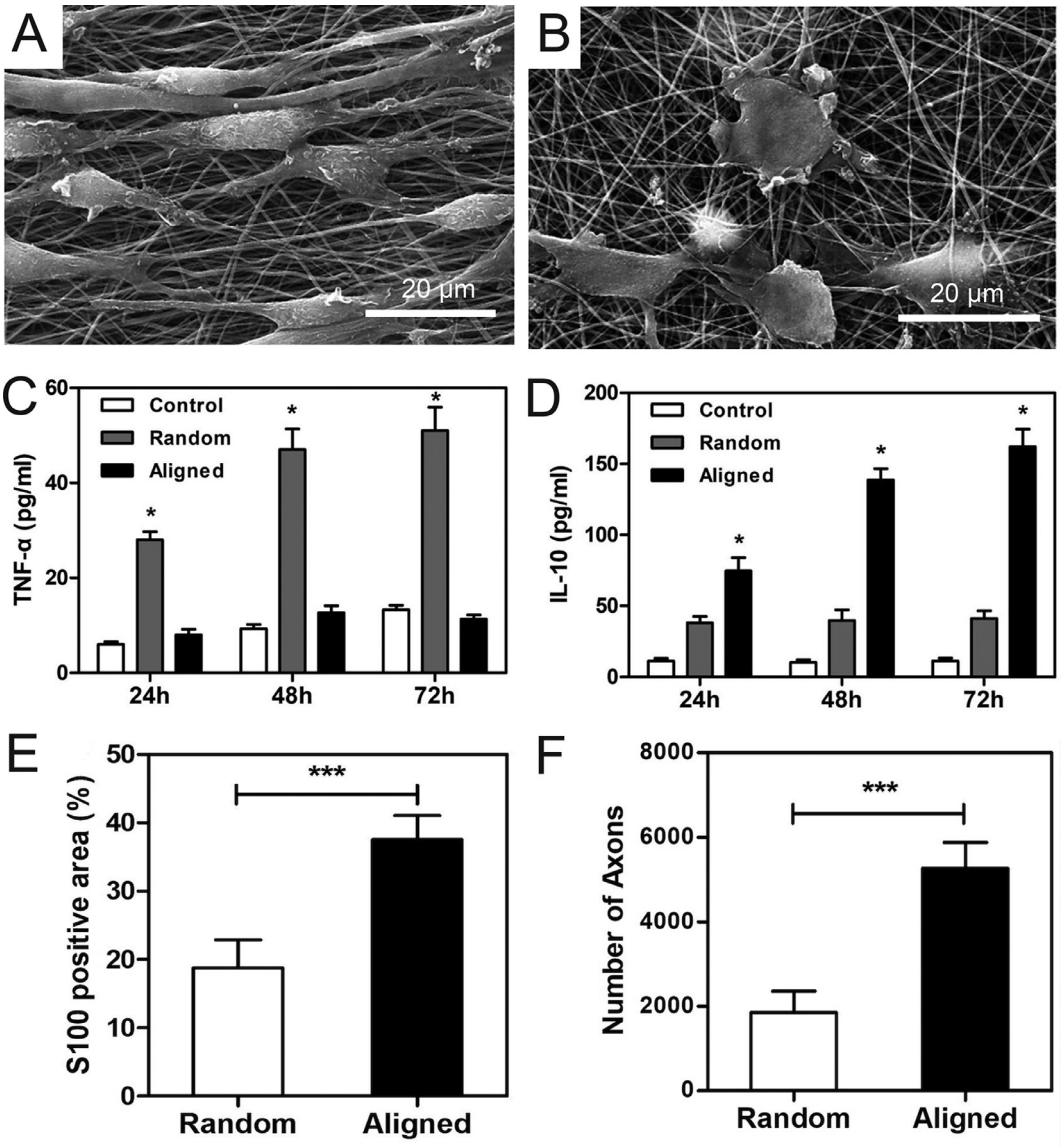

Fig. 2. Elongated macrophages are shown on aligned nanofibers (A) compared with random nanofibers (B) under SEM imaging. (C-D) Quantification of TNF-α (mainly from M1 macrophages) and IL-10 (mainly from M2 macrophages) secreted by macrophages cultured on different nanofiber scaffolds or culture plates by ELISA assay. (E-F) Statistical analysis of S-100 (Schwann cells) positive areas and axon numbers between the random and aligned nerve guidance conduit groups for assessing nerve regeneration *in vivo*. Error bars represent standard deviation, * indicates $p < 0.05$ and *** indicates $p < 0.001$[110].

Biomaterials that use ECM components or mimic ECM structures can create a microenvironment that benefits immunomodulation and tissue repair. Biomaterials composed of decellularized ECM have shown notable success in eliciting an anti-inflammatory (M2-like) host response and promoting constructive and functional tissue remodeling [119,120]. Decellularized ECM scaffolds derived from xenogeneic tissues are well tolerated by the host without showing hyperacute or delayed rejection [121]. Furthermore, the degradation of ECM scaffolds can release bioactive factors such as chemoattractant [122], growth factors [123], and extracellular vesicles [124] to promote M2 macrophage polarization and recruit endogenous stem cells for tissue regeneration. Sicari et al. [125] found that the degradation products of ECM such as solubilized small intestinal submucosa promoted M2 macrophage phenotype and enhanced the migration and myogenesis of skeletal muscle progenitor cells. In addition, the functions of ECM can be affected by multiple factors, including the use of chemical crosslinking [104], the source tissue of ECM [126] and the supplementary use of anti-inflammatory drugs [127]. Recently, Fan et al. [128] reported a red blood cell membrane-derived macroporous hydrogel that mimics ECM structure, which exhibited high performance on M2-like phenotype polarization (Fig. 3A). The microporous scaffolds were formed through chemical crosslinking of vesicles derived from red blood cell membranes (RBCMs) (Fig. 3B). In the *in vivo* experiment, RBCM scaffolds showed significantly higher infiltration of macrophages than DCs and neutrophils (Fig. 3C–E). High percentages of these macrophages had M2 phenotype as confirmed by gene expression and surface markers (Fig. 3F–G). As a major constitute of human ECM, HA is also a compelling biomaterial. The effects of HA on macrophage polarization depend on the molecular weight of the polymer chains [129]. High-molecular-weight HA is indispensable for maintaining homeostasis by facilitating anti-inflammatory responses [130]. In contrast, low-molecular-weight HA induces M1 macrophages as proved by increased expression of pro-inflammatory genes NO and TNF-α [129]. In addition, molecular weights also influence the effects of keratin biomaterials on augmenting M2 phenotype *in vitro* [131]. Both high-molecular-weight keratin (KOS^H) and keratin peptide

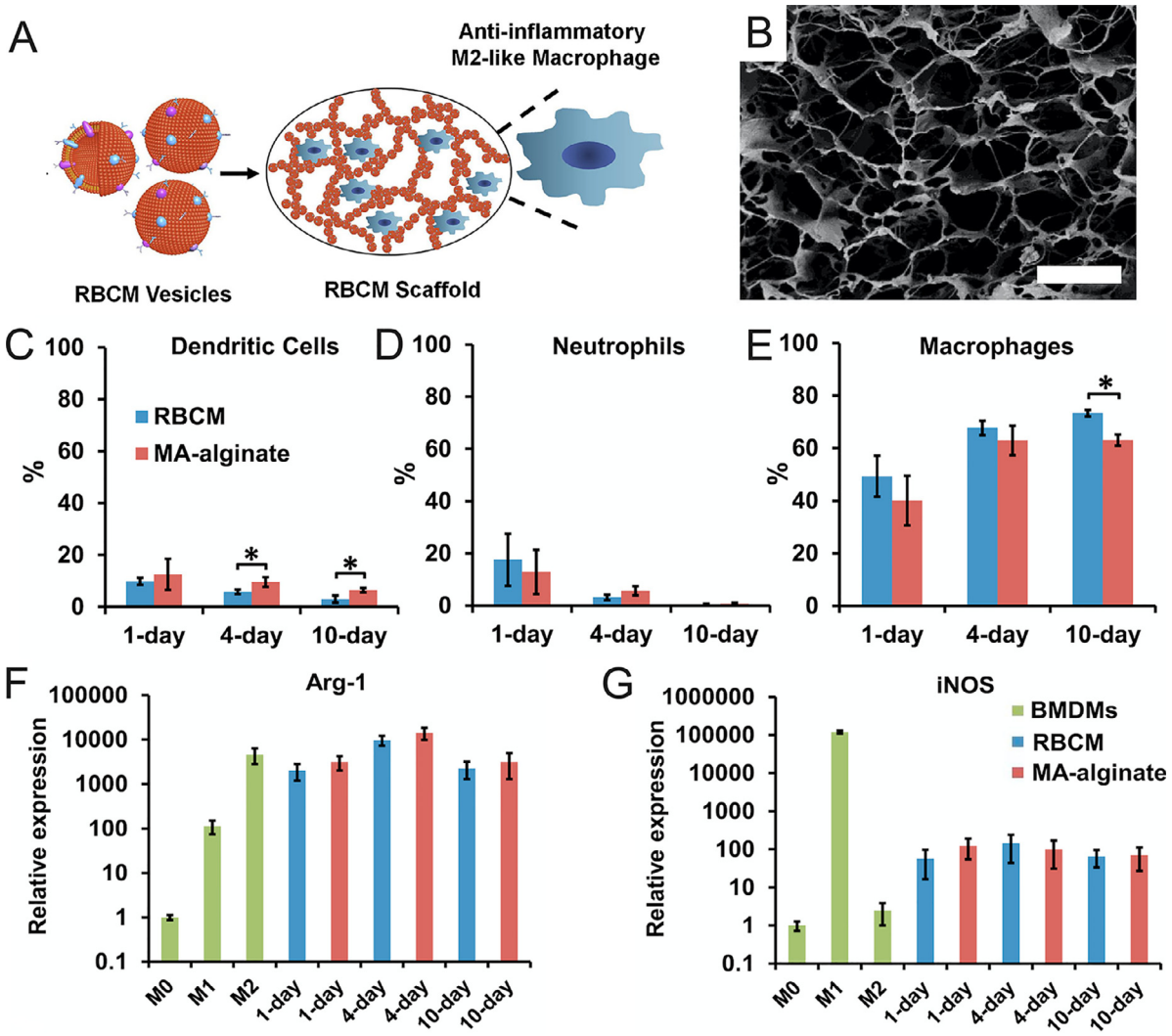

Fig. 3. (A) A schematic illustration of macroporous red blood cell membrane (RBCM)-derived scaffold. (B) RBCM scaffolds under SEM imaging. Scale bar = 100 μm. (C–E) Percentages of dendritic cells, neutrophils, and macrophages in RBCM and MA-alginate scaffolds after scaffold injection *in vivo*. (F–G) qPCR analysis of Arg-1 (M2 macrophage marker) and iNOS (M1 macrophage marker) expression in cells from RBCM and MA-alginate scaffolds and M0, M1, and M2 BMDMs. Error bars represent standard deviation, and * indicates $p < 0.05$ [128].

(KOS^P) coatings show potentials to drive macrophage polarization to anti-inflammation, but KOS^P exhibits more effectiveness than KOS^H.

Bioceramics can release bioactive ions to modulate macrophage phenotypes and regulate stem cells to enhance tissue regeneration [132–134]. For example, Huang et al. [3] demonstrated that silicate bioceramics–akermanite (AKT) and nagelschmidtite (NAGEL) could release silicon (Si), magnesium (Mg), and calcium (Ca) ions to inhibit inflammatory cytokine secretion by macrophages as compared to tricalcium phosphate (TCP) bioceramics *in vitro* and *in vivo*. Furthermore, Zhou et al. [135] showed that mesoporous bioactive glass incorporated with ionic Cu^{2+} could induce VEGF secretion of BMSCs and triggered the production of regenerative M2 macrophages, leading to enhanced angiogenesis and immune responses. Dong et al. [136] found that bioactive glass ion extracts could polarize M2 macrophages and enhance paracrine effects between macrophages and repairing cells. In addition, Shi et al. [137] reported that europium-doped mesoporous silica nanospheres could stimulate pro-inflammatory responses of macrophages to activate osteogenesis. Similarly, copper-doped mesoporous silica nanospheres could also initiate proper pro-inflammatory responses for inducing osteogenesis [138].

The combination of physiochemical properties can synergize to direct the differentiation of macrophages to the pro-healing M2 phenotype. For example, Chen et al. [139] adjusted the surface chemistry and scale of nanotopography simultaneously to modulate the osteoimmune environment. The biomaterial with carboxyl acid-tailored and 68 nm nanoparticle-coated surface showed promising performance in terms of increasing M2 macrophages and triggering the osteogenic differentiation of MSCs. Bachhuka et al. [140] fabricated nanoporous surfaces with controlled pore size and different surface charges. The data showed that the biomaterial with nanopores of 200 nm and carboxyl functionality significantly downregulated pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α and upregulated anti-inflammatory cytokines such as arginase, IL-1 receptor antagonist, and IL-10.

3.1.2. Polarization to M2 macrophages through the delivery of biological cues

Anti-inflammatory cytokines such as IL-4 and IL-10 have been frequently studied for regenerative strategies in recent years because of their capability to polarize M2 macrophages [46,103,141]. IL-10 can cause a complete regeneration in fetal mice models, and IL-10-deficient fetal mice show scar formation [10,142,143]. As a

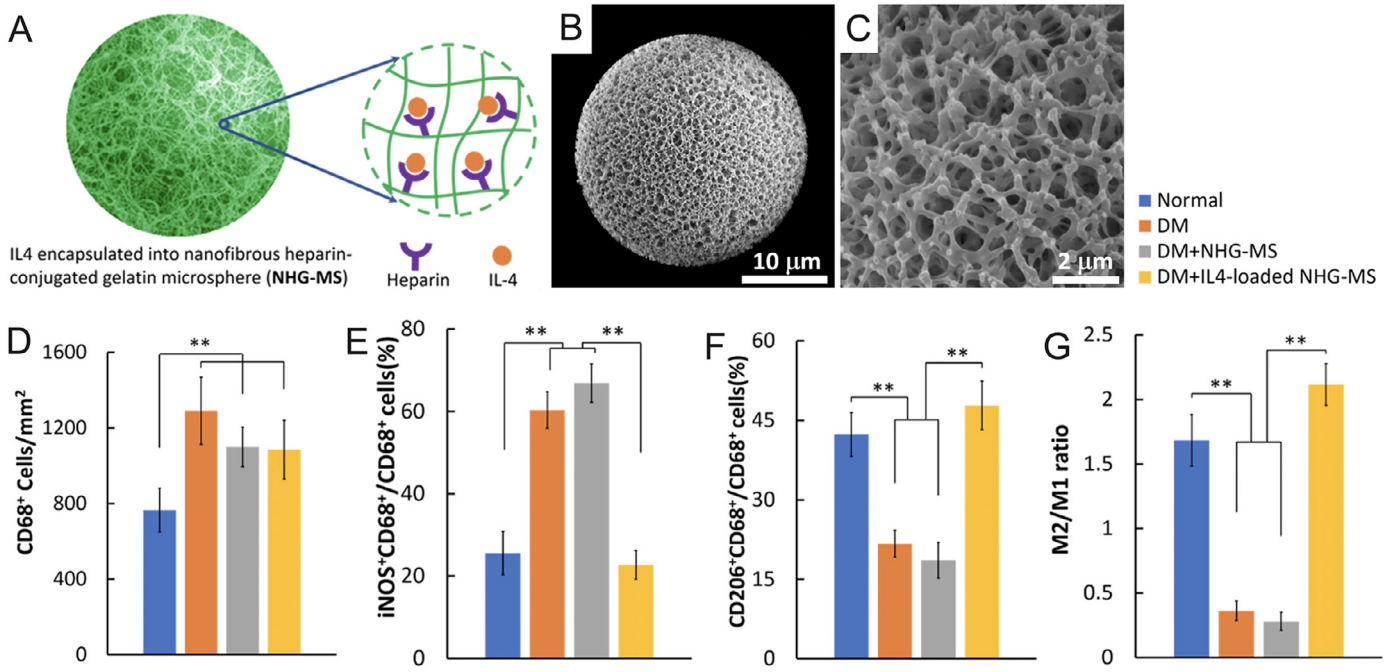

Fig. 4. (A) A schematic illustration of NHG-MS modified by heparin and loaded with IL-4. (B-C) NHG-MS with the highly porous nanofibrous architecture under SEM measurement. (D–G) Immunohistochemical assessment of macrophage phenotypes through quantitative analysis of iNOS (M1 macrophage marker), CD68 (pan-macrophage marker), and CD206 (M2 macrophage marker). (D) CD68 showed significantly higher expression in the three DM groups than in the normal control group. (E–G) Fewer M1 macrophages and more M2 macrophages observed in the control and IL4-loaded NHG-MS DM groups. Error bars represent standard deviation, and ** indicates $p < 0.01$ [145].

regenerative strategy, IL-4 is usually delivered to the injured site as proteins [144]. For instance, Hu et al. [145] developed nanofibrous heparin-modified gelatin microspheres (NHG-MS) for delivering IL-4 to provide a healing microenvironment in diabetes mellitus (DM). IL-4 was incorporated in the microsphere and could bind to heparin for stabilization (Fig. 4A). The microspheres effectively increased the number of M2 macrophages, which enhanced the bone repair and regeneration process under the DM condition (Fig. 4D–G). Bonito et al. [146] designed heparin/IL-4-functionalized supramolecular elastomers to modulate macrophage phenotypes and protein secretion. The supramolecular approach was successfully translated to a three-dimensional (3D) electrospun scaffold to prolong the bioactivity of IL-4 under conditions mimicking hemodynamic microenvironments.

Compared to IL-4 delivered as proteins, IL-10 is mostly delivered to the target through plasmid DNA or virus vectors. For example, Bridges et al. [147] designed a PLG scaffold with IL-10 viral vectors for localized and sustained IL-10 expression to resolve inflammation. Leukocytes such as macrophages, DCs, and neutrophils were modulated by the scaffold in their numbers and relative proportions. The scaffold showed high performance in terms of increasing IL-10 secretion by macrophages and decreasing IFN-γ expression in DCs, macrophages, and $CD4^+$ T cells. Holladay et al. [148] designed an IL-10 plasmid-loaded collagen scaffold for enhancing stem cell transplantation in myocardial infarction. Increased stem cell retention and the recovery of cardiac functions in animal models positively correlated with the induction of IL-10. Compared to the scaffold control, the scaffold with IL-10 plasmids modulated the immune response by downregulating $CD80^+$ macrophages (M1) while upregulating $CD163^+$ macrophages (M2). Furthermore, Jain et al. [149] fabricated IL-10 plasmid-loaded alginate nanoparticles for treating rheumatoid arthritis (RA). The IL-10 plasmid was encapsulated into alginate nanoparticles, and tuftsin peptide was modified on the surface of nanocarrier for targeting macrophages. This method significantly decreased the expression of systemic and joint tissue pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α and attenuated the inflammation and joint destruction.

Biomaterials can also sequentially release different immunomodulators to stimulate M1 macrophages at first and rapidly polarize them to M2 macrophages, which can maximize their regenerative activity and minimize their side effects [150,151]. In a natural tissue healing process, the injured site witnesses the sequential activities of pro-inflammation and anti-inflammation, which are respectively dominated by M1 and M2 macrophages [152–154]. Neovascularization is closely related to macrophage polarization, and it has been proved that M1 phenotype can initiate angiogenesis and M2 phenotype can enhance vessel maturation [155]. Thus, it is possible to induce an effective regenerative microenvironment by modulating numerous immune signals involved in macrophage polarization simultaneously or sequentially. Chen et al. [156] designed a titania nanotube system with double hydrogel layers to modulate the release of IFN-γ and IL-4. In this system, pro-inflammatory cytokine IFN-γ could be totally released in 3 days for triggering M1 macrophages. The release of anti-inflammatory cytokine IL-4 was sustained even after 4 days; thus, it could switch macrophages to the M2 phenotype. The results proved that macrophage phenotype switch correlated with the sequential release of these two cytokines and that vascularization in the site was enhanced more than that achieved using IFN-γ or IL-4 alone. Similarly, Spiller et al. [144] developed decellularized bone scaffolds for sequentially releasing IFN-γ and IL-4. In this scaffold, IFN-γ was physically adsorbed on the scaffold so that it could be quickly released. IL-4 was attached through biotin-streptavidin binding, and its release lasted a few days longer.

MSCs are widely used in cell-based tissue engineering due to their powerful regenerative potential [157,158]. Interactions between MSCs and macrophages can determine the initiation of tissue regenerative processes and the formation of scar tissue [159].

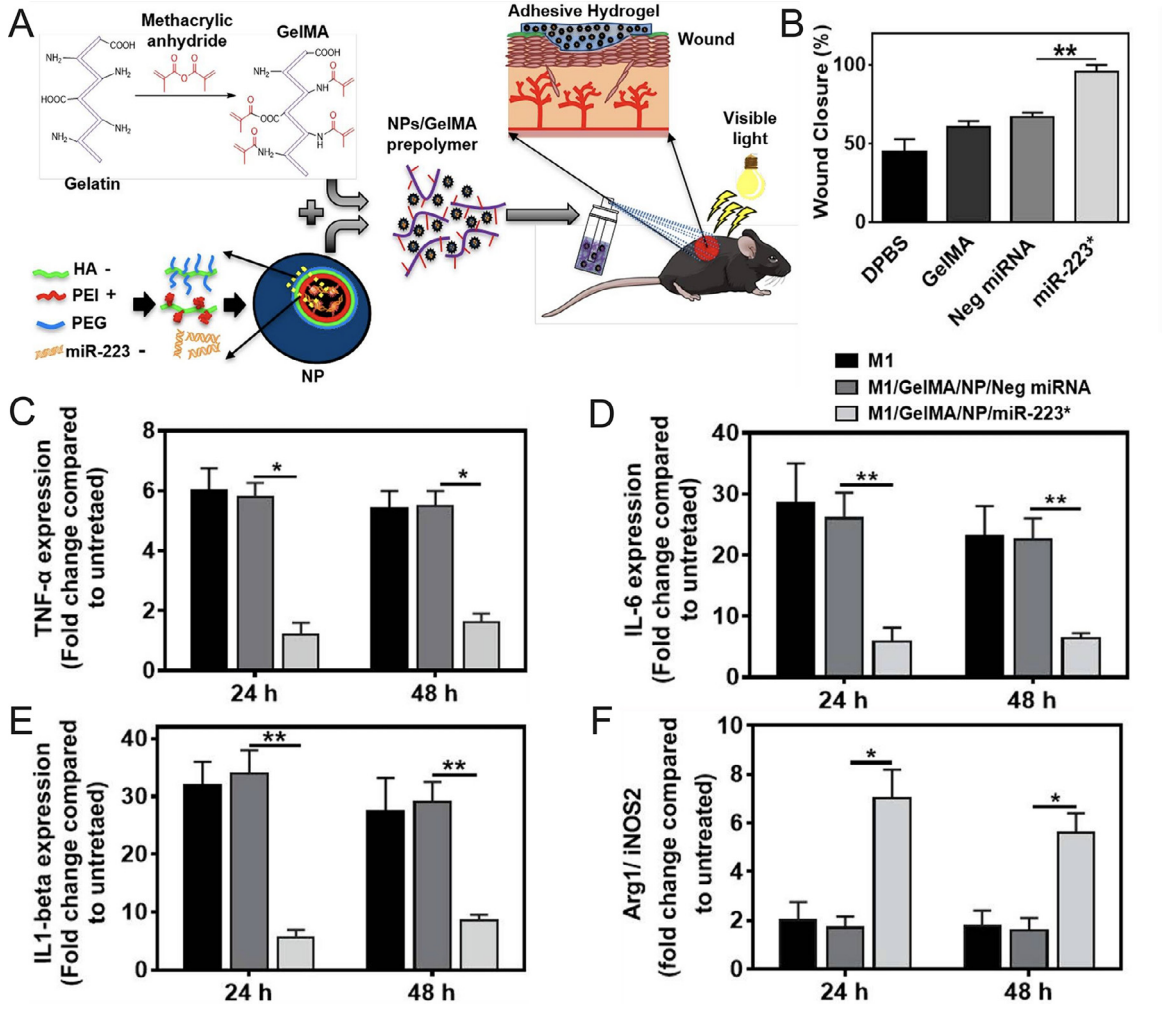

Fig. 5. (A) A schematic illustration of the process for developing nanoparticle/miR-223*-laden GelMA hydrogels and the use of these adhesive hydrogels for wound healing. (B) A quantitative evaluation of wound areas after treating wounds with DPBS, GelMA, Neg miRNA, or miR-223* for 12 days. (C–F) miRNA transfection and macrophage polarization studies in J774A.1 macrophages *in vitro*. M1 represents cells that received LPS+IFN-γ treatment for 16 h before incubation with either groups. Neg miRNA represents negative control miRNA and miR-223* represents miR-223 5p mimic. (C–E) Decreased expression of proinflammatory cytokines (TNF-α, IL-6, and IL-1β mRNA) was observed upon 24 and 48 h post-incubation with GelMA/NP/Neg miRNA and GelMA/NP/miR-223* hydrogels. (F) A significantly higher ratio of Arg-1 (M2 macrophage marker)/iNOS-2 (M1 macrophage marker) gene expression was observed in the M1/GelMA/NP/miR-223* group. Error bars represent standard deviation; * indicates $p < 0.05$ and ** indicates $p < 0.01$ [169].

Macrophages are necessary for recruiting and regulating the differentiation of MSCs during tissue regeneration [160,161]. In return, MSCs also regulate the functions of macrophages. The beneficial effect of MSCs can potentially be enhanced by infiltrating more macrophages in the defect site. Seebach et al. [162] reported that fibrin implants embedded with MSCs could rapidly attract M1 macrophages and endothelial progenitor cells to improve vascularization and bone regeneration. MSCs can also be used for macrophage polarization. In a co-culture model, MSCs dramatically enhanced the expression of anti-inflammatory cytokine IL-10 and suppressed the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 by macrophages [163,164]. Furthermore, Qiu et al. [165] showed that MSCs and decellularized ECM could synergistically drive macrophages toward the M2 phenotype to promote skeletal muscle tissue regeneration.

Apart from anti-inflammatory cytokines and MSCs, many other factors could be used to polarize M2 macrophages, such as pro-resolution mediators, microRNAs (miRNAs), and immunosuppressive drugs. Pro-resolution mediators such as resolvins and lipoxins can shift the polarization balance toward M2 macrophages [166,167]. For instance, Shi et al. [168] developed a polycaprolactone vascular graft loaded with Aspirin-Triggered Resolvin D1 (AT-RvD1), which significantly promoted macrophage polarization into M2 macrophages *in vitro* and *in vivo* and enhanced smooth muscle regeneration in rats. miRNAs can control the translation and degradation of messenger RNAs; thus, the modulation of miRNAs is essential to regulate macrophage polarization. Although miRNA-based regenerative strategies are rare, studies have shown that miRNAs such as miR-124, miR-125a-3p, miR-223, let-7c, miR-132, and miR-146a could switch M1 to M2 macrophages and contribute to tissue healing [169–172]. Saleh et al. [169] developed adhesive gelatin methacryloyl (GelMA)-based hydrogels by incorporating miR-223 5p mimic (miR-223*)-laden HA nanoparticles (Fig. 5A). The adhesive hydrogels could efficiently reduce the expression of proinflammatory cytokines and induce macrophage polarization to M2 phenotype *in vitro* (Fig. 5C–F). In the *in vivo* experiment, the percentage of wound closure for the miR-223* treatment group was significantly higher than that for Neg miRNA-, GelMA-, or phosphate-buffered saline (DPBS)-treated wounds (Fig. 5B). The adhesive hydrogels triggered the resolution of the inflammation

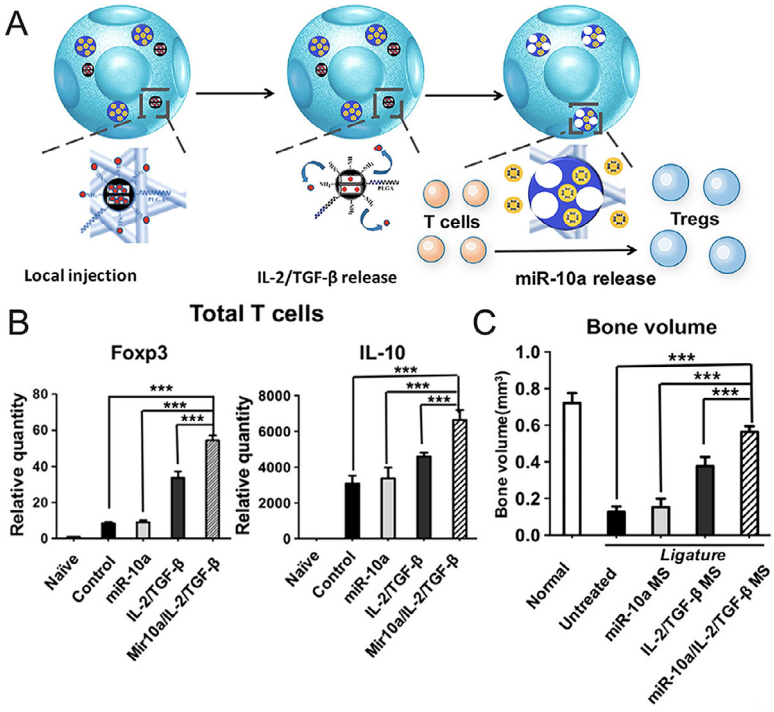

Fig. 6. (A) A schematic illustration of multifunctionalized PLLA NF-SMS with IL-2/TGF-β-loaded MSN and miR-10a-loaded PLGA MS. (B) The highest gene expression levels of anti-inflammatory cytokine IL-10 and Foxp3 in total T cells were observed in the miR-10a/IL-2/TGF-β group. (C) The bone volume changes in a mouse periodontal disease model showed that PLLA NF-SMS rescued bone resorption. Error bars represent standard deviation, and *** indicates $p < 0.001$ [11].

and enhanced the formation of new and vascularized skin tissue to accelerate the tissue regeneration rate. The immunosuppressive drug glucocorticoid is highly potent in anti-inflammation. Dexamethasone (Dex) is a type of glucocorticoids and has been shown to shape macrophage phenotypes for tissue repair and regeneration [173]. For example, Jiang et al. [12] developed a PDMS-based 3D microporous scaffold platform for locally delivering the immunosuppressive drug Dex in a diabetic mouse model. The studies showed a dose-dependent impact of Dex on M2 macrophage polarization. The elevated M2 macrophage levels suppressed the inflammatory pathways and maintained the bioactivity of islets. Given the similar effects of immunosuppressive drugs on anti-inflammatory cytokines, it is reasonable to co-deliver Dex and IL-4 to promote macrophage switch from M1 to M2 phenotype. Kumar et al. [174] designed an injectable silk hydrogel loaded with IL-4 and Dex for treating type 1 diabetes (T1D). The mild gelation of the hydrogel provided a protective 3D support for transplanted islets without compromising their functions. The hydrogel showed high performance in terms of islet viability, insulin secretion, and endothelial cell maintenance.

3.2. Biomaterials for Treg cell induction

Treg cells play a pivotal role in the healing process, and Treg cell induction can be an effective approach for tissue repair and regeneration [59,175]. Treg cells are in the downstream of immune responses; thus, their development and maintenance are regulated by macrophages, tolerogenic dendritic cells, and other immune cells [176–178]. For instance, Li et al. [179] demonstrated that RelB gene-silenced DCs could selectively promote Treg generation. Treg cells can also be induced by the delivery of cytokines, growth factors, and MSCs through biomaterials [69,154,180]. The induced Treg cells can also contribute to the resolution of inflammation and switch macrophages from M1 to M2 phenotype [16,181].

Both IL-2 and TGF-β play an important role in the induction and regulation of Treg cells. TGF-β needs IL-2 to enhance Foxp3 transcription factor expression in $CD4^+CD25^+$ Treg cells [182,183]. In contrast, IL-2- and IL-2R-deficient mice develop extensive lymphadenopathy and systemic autoimmunity [184]. Thus, the co-delivery of IL-2 and TGF-β can induce Treg cells. For example, McHugh et al. [180] developed biodegradable PLGA nanoparticles loaded with IL-2 and TGF-β to induce Treg cells *in vitro* and expanded their population *in vivo*. Induced Treg cells were stable; thus, they could exert longer immunosuppressive effects in the inflammatory microenvironment. To manipulate Treg cells *in situ*, Liu et al. [11] designed a combined delivery vehicle including poly(L-lactic acid) (PLLA) nanofibrous spongy microspheres (NF-SMS), PLLA/polyethylene glycol (PEG) co-functionalized mesoporous silica nanoparticles (MSN), and poly(lactic acid-co-glycolic acid) microspheres (PLGA MS) (Fig. 6A). In this system, IL-2/TGF-β-loaded MSN and miR-10a-loaded PLGA MS locally recruited T cells and induced their differentiation into Treg cells. PLLA NF-SMS as a scaffold helped Treg cells to adhere and proliferate (Fig. 6B). In addition, the multifunctionalized NF-SMS system enriched Treg cells *in vivo*, which suppressed the exacerbation of host immune response in mouse periodontal disease models and rescued periodontal bone loss (Fig. 6C).

Cytokine IL-33 acts as an endogenous danger signal, which attracts Treg cells to accumulate in an injured tissue [185,186]. Although the role of IL-33 in tissue regeneration has not yet been elucidated, IL-33 can induce the proliferation of Treg cells in different tissues within a few days [187–189]. For example, Liu et al. [154] developed a PLGA scaffold for the local delivery of IL-33 to facilitate allogeneic islet transplantation. IL-33 exhibited beneficial immunosuppressive effects in the animal model by upregulating Treg cells and reducing cytotoxic $CD8^+$ T cells, resulting in a prolonged graft survival and delayed islet engraftment. The rationale was that IL–33 induced the proliferation of IL-33R (ST2)-expressing Treg cells and these cells produced the

epidermal growth factor–like molecule amphiregulin to mediate tissue repair [190–192]. Furthermore, IL-33 is a promising pathway for skeletal muscle regeneration as a recent study reported that supplementation with IL-33 enhanced Treg cells for aging skeletal muscle regeneration in a mouse model [193].

The MSC-based strategy is one of the essential regenerative strategies. MSCs can produce soluble factors to inhibit T cell responses and induce Treg cells [194]. For instance, Cosenza et al. [195] reported that microparticles and exosomes derived from MSCs could inhibit T cell proliferation and reduce the percentages of $CD4^+$ and $CD8^+$ T cell subsets. In contrast, the number and percentage of Treg cell populations were elevated. Liu et al. [69] developed a hydroxyapatite/tricalcium phosphate (TCP-HA) bone scaffold with bone marrow MSCs to enhance bone regeneration. Bone marrow MSCs could induce T cell apoptosis, which resulted in the upregulation of Treg cells. The scaffold significantly improved the number of Treg cells and reduced IFN-γ and TNF-α levels in the implanted site.

In addition, *ex vivo* cultured Treg cells have been delivered directly into the injured site. For example, Roballo et al. [8] developed a degradable poly(ethylene glycol) norbornene (PEGNB) hydrogel for delivering Treg cells to prolong the survival of peripheral nerve allografts. The hydrogel sustained the release of Treg cells over two weeks. The released Treg cells effectively infiltrated the graft and blocked the host immune response. The performance of tissue regeneration in the recipient rats was comparable to that of allograft control.

4. Conclusion and future perspectives

Many current advances in biomaterials have been used for immunosuppression through macrophage polarization or Treg cell induction. The outcomes demonstrated their high performance in facilitating tissue repair and regeneration. The immunomodulators and immune cells mentioned above are only a fraction of the complex immune system. In light of the deep interactions between the immune system and the tissue healing process, it is promising to use immunosuppression by biomaterials to treat tissue damages; this area, however, requires further investigations on the mechanisms of immune responses and tissue regeneration.

To enhance the regenerative effects of biomaterials for immunosuppression, several challenges remain to be solved. First, the detailed understanding of biomaterial-immune cell interactions is lacking; thus, it is challenging to develop effective immunomodulatory biomaterials. Second, macrophages have been frequently studied during the past decades, and they play a crucial role in the tissue healing process. However, it is indicated that the induction routes and regulated processes of macrophage polarization are complex network systems rather than simple pathways. In addition, M2 macrophages have four subtype, namely M2a, M2b, M2c, and M2d, which are activated by different cytokines and can express different immunomodulatory signals. These different mechanisms can directly affect the regenerative effects of biomaterials. Third, the regenerative strategies provided by biomaterials need to follow the natural healing process. The aim of macrophage polarization is to control immune responses to enhance tissue regeneration rather than to simply polarize M1 to M2 phenotype. Although large numbers of M1 macrophages can delay tissue repair, they are necessary to induce angiogenesis. In contrast, M2 macrophages are necessary for inflammation resolution and tissue remodeling, but excessive levels of M2 macrophages may lead to pathological fibrosis. Therefore, sequential delivery of cytokines is a feasible approach for the temporospatial control of macrophage polarization to enhance tissue regeneration, which can be easily realized by delicate designs of biomaterials. Finally, compared to the large amount of studies on macrophages, research studies on T cell subsets for tissue regeneration are limited. Evidence has shown that T cell subsets such as $CD8^+$ T and Th1 cells have anti-regenerative properties and other cell subsets such as Th2, $\gamma\delta$T, and Treg cells have pro-regenerative properties. Thus, biomaterials can be used to modulate T cell activities to enhance regeneration. However, current applications of Th cell switch and inhibition of cytotoxic T cells for the healing process are scarce, which may be due to unclear mechanisms of T cells. Even for the induction of Treg cells, it is mainly used to induce immune tolerance for treating autoimmune disorders, where the effects of Treg cells are often unexpectedly altered by conventional T cells.

Presently, because of our limited knowledge of the immune system, the regenerative effects of biomaterials for immunosuppression are restricted. The evolution of biomaterials can provide an opportunity to sprint, and this opportunity can be facilitated by new discoveries in immunology.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

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