Biomaterials Translational

Engineering immune-responsive biomaterials for skin regeneration

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Key Words:
biomaterials; immune cells; immunoresponse; skin regeneration

From the Contents

ABSTRACT

The progress of biomaterials and tissue engineering has led to significant advances in wound healing, but the clinical therapy to regenerate perfect skin remains a great challenge. The implantation of biomaterial scaffolds to heal wounds inevitably leads to a host immune response. Many recent studies revealed that the immune system plays a significant role in both the healing process and the outcome. Immunomodulation or immuno-engineering has thus become a promising approach to develop pro-regenerative scaffolds for perfect skin regeneration. In this paper, we will review recent advancements in immunomodulating biomaterials in the field of skin repair and regeneration, and discuss strategies to modulate the immune response by tailoring the chemical, physical and biological properties of the biomaterials. Understanding the important role of immune responses and manipulating the inherent properties of biomaterials to regulate the immune reaction are approaches to overcome the current bottleneck of skin repair and regeneration.

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Introduction

Skin is the largest organ in the human body, and it has a very complex multi-layered structure. The skin and its appendages perform a wide range of vital functions that support and maintain human health.[1, 2] As the outermost layer, it protects the body from the invasion of harmful substances, as well as regulating the evaporation of body fluids and body temperature. As such, cutaneous wounds can lead to disability or even death. Minor superficial wounds can heal naturally. However, deep cutaneous wounds often result in non-functioning scar formation or chronic skin ulceration with extensive loss of skin appendages. Each year, more than 11 million people suffer from burn injuries worldwide, which causes a heavy psychological and economic burden.[3-6] Skin grafting is the typical procedure to treat large areas of skin trauma.[7] Autologous skin grafting is considered the gold standard to treat skin trauma. However, the available skin area of an autologous source could be very limited and the resulting trauma at the donor site causes the patient great pain. Wound healing could be achieved using a regenerative and/or repair process.[8] Although traditional skin substitutes can promote wound healing via a repair process, they often lead to dermal dysfunction and skin scarring.[9, 10] The quest to develop advanced products to achieve regeneration of the skin and its appendages remains the holy grail of both scientific research and industry.

The skin consists of multiple layers, including the epidermis, dermis, subcutaneous tissue, as well as skin appendages. The skin appendages are indispensable in that they play diverse roles in maintaining body functions, such as temperature regulation, sweat metabolism and oil secretion.[6, 10] Biomaterials are commonly developed into a three-dimensional matrix to reconstruct an *in vivo* microenvironment that promotes wound healing.[11-13] Such a matrix can promote cell infiltration and release growth factors and proteins to produce a dynamically-organized

extracellular matrix (ECM). Christman et al.[13] reiterated that an appropriately designed biomaterial scaffold can mimic the original healthy ECM so as to create a new microenvironment that will promote new tissue formation. Designing and manipulating the topological structure, surface chemistry, mechanical properties, as well as degradation rate of the biomaterials will enable efficient regeneration.

Once a biomaterial scaffold is transplanted into the body, it will inevitably induce innate immune responses, which in turn affect tissue repair and regeneration. Wound healing proceeds via three overlapping stages, comprising inflammation, proliferation and remodeling.[14-16] There is a strong interplay between the biomaterials and immune cells during the inflammation stage. When the immune system detects any foreign material invasion, it initiates a great deal of inflammatory responses.[17, 18] The characteristics of immune responses can greatly shape the way that wounds heal, and may change a fibrotic healing process into a regenerative one. Many studies revealed that innate inflammatory cells fight off invading microbes, remove debris, as well as supporting the repair process by releasing a range of growth factors during cutaneous wound healing.[19] A robust immunoresponse always leads to abnormal tissue formation. That being the case, researchers have been trying to suppress the excessive immunoresponse by improving the biocompatibility of biomaterials. Recent studies showed that the immunoresponse could play a positive role in promoting tissue regeneration.[20, 21] The traditional tissue-engineered scaffolds, which do not take the immunoresponse into consideration, achieve limited success in wound healing and skin regeneration.[22] The term "regenerative immunology" was recently coined to underline the importance of immune regulation in tissue engineering and regenerative medicine.[21] Therefore, designing immunomodulatory biomaterials can help us achieve the maximum therapeutic effects.

In this review, we will discuss the interplay between immune response and biomaterial scaffolds, particularly their application in skin regeneration. We will focus on the host immune response caused by injury and implanted biomaterials. Meanwhile, we will discuss the impact of physical and chemical properties of biomaterials on immune response to promote tissue repair and regeneration, and highlight new research directions that utilize the inherent properties of materials to control immune function and promote tissue-engineered skin regeneration. Most of the articles cited in this review were searched in the PubMed database using the following key words: immune cells; or immunoresponse; or macrophages, or T cells, and skin regeneration, and biomaterials. We screened these articles by browsing the title and abstract. In addition, we also searched the articles about the skin appendage's regeneration, such as: hair follicle, or sweat gland, and immune cells.

Immune Reaction to Biomaterial Implants

Biomaterial implantation is always accompanied by injury. The proteins, lipids and ions in the plasma are quickly deposited onto the implant surface. Meanwhile, platelets activate clotting to prevent excessive blood loss and release chemokines to stimulate cell migration.[23] The immune system immediately initiates an inflammatory response (**Figure 1**). Neutrophils arrive first at the wound beds and the implant surface to clear bacteria and fungi by engulfing and/or releasing enzymes and reactive oxygen species.[12] Moreover, they release mediators such as interleukin (IL)-1β, IL-6 and tumour necrosis factor-α (TNF α) to amplify the inflammatory response.[24]

Monocytes in the circulation are subsequently recruited to the wound site and rapidly differentiate into macrophages.[25, 26] Macrophages can mediate phagocytosis of debris, and secrete and release enzymes, cytokines and growth factors that promote cell migration and proliferation, as well as tissue reorganization.[27-29] Macrophages are important inflammatory cells that have a

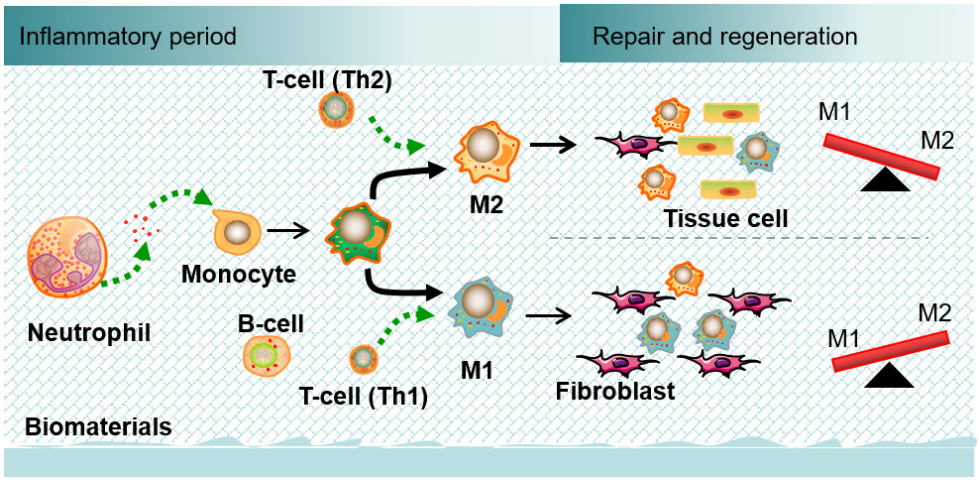

Figure 1. Temporal sequence of immune reactions to biomaterials. The main cells participate in the biomaterial–tissue microenvironment from the initial inflammatory response to tissue repair and regeneration. Biomaterials shape the immune environment by targeting neutrophils, lymphocytes (T-helper cells and B cells) and macrophages.

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great impact on wound repair and regenerative processes.[30] Under different physiologic and pathophysiologic conditions, macrophages undergo two major different phenotypic polarizations: M1 (pro-inflammatory) phenotype and M2 (anti-inflammatory) phenotype. M1 phenotype macrophages mainly clear apoptotic cells and secrete pro-inflammatory cytokines, such as IL-1 and IL-6. M2 macrophages secrete pro-regenerative growth factors (e.g. vascular endothelial growth factor, platelet-derived growth factor, epidermal growth factor). Those biomaterials that induce M2 phenotype polarization would thus promote tissue regeneration. During the later inflammatory phase, T lymphocytes, particularly helper T cells, are either directly or indirectly activated, resulting in both beneficial and detrimental effects on tissue healing and regeneration. The subsets of helper T cells (Th1 and Th2) polarize the macrophages into different phenotypes.[12, 31] Th1 cells promote M1 macrophage transformation, while Th2 cells induce the M2 macrophage phenotype. In addition, B cells produce antibodies that have a positive impact on immune response and inflammation.[32] Lymphocytes can also be deposited onto biomaterial surfaces and influence macrophage adhesion.[33, 34] Meanwhile, implants will be biodegraded or isolated by fibrotic encapsulation.

Harnessing the Immune Response Promotes Skin Regeneration

The regeneration of skin appendages (e.g. hair follicles, sebaceous glands) contributes to dermal regeneration. Recent studies showed that immune regulation impacts the regeneration of skin appendages.[35-37] There are various immune cells such as T cells, dermal dendritic cells, and macrophages in the skin immune system. These cells secrete chemokines and cytokines to modulate the immune response and further influence skin regeneration.

Hair and hair follicle regeneration

Hair follicles undergo periodical regeneration, during which they can prevent bacterial infection and inhibit scar formation.[38] Immune cells, especially macrophages, regulate hair follicle stem cells, which further facilitate skin regeneration (**Figure 2**). A murine model that allows conditional reduction of macrophages during the sequential wound healing process was employed to examine the specific role of macrophages during each stage.[31] The depletion of macrophages at different phases resulted in adverse consequences, including the reduction of vascularization and epithelialization in the early phase, increased bleeding in the mid-stage, and a slight impact on the late stage. Rahmani et al.[39] explored the function of macrophages in hair follicle regeneration. They demonstrated that wound-induced hair growth relied on $CD11b^+F4/80^+$ macrophages from 7–11 days after injury. Transforming growth factor (TGF)-β1 played an indirect role in wound-induced hair growth via macrophage chemotaxis.[39]

To elucidate the contribution of M2 macrophages to wound-induced hair growth, Kasuya et al.[40] created a full-thickness skin defect model using C57BL/6 (B6) mice and confirmed that the regenerated hair follicles were accompanied by $CD206^+$

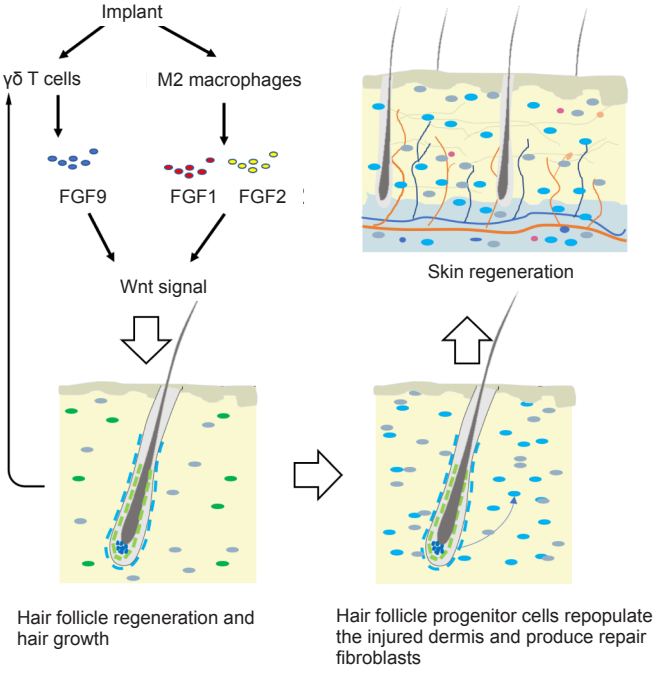

Figure 2. The effect of immune cells on hair growth, hair follicle regeneration, and skin regeneration. M2 macrophages secrete FGF2 and IGF1 that play roles in hair follicle neogenesis. The γδ T cells express FGF9, which activates Wnt signalling and further induces hair follicle regeneration and hair growth. Hair follicle progenitor cells repopulate the injured dermis, and produce repair fibroblasts. FGF: fibroblast growth factor; IGF1: insulin-like growth factor 1.

M2 macrophages. M2 macrophages promoted wound-induced hair growth by releasing such growth factors as insulin-like growth factor 1 (IGF1) and fibroblast growth factor (FGF)2. They demonstrated that the injection of IGF1 and FGF2 following injury promoted hair follicle growth in the later stage of wound healing.

T cells play significant roles in the inflammation and remodelling stages.[35, 37, 40, 41] T cells are essential to create a pro-regenerative immune environment,[21] as evidenced by the impaired wound healing without them.[42] Dermal γd T cells secrete FGF9 to support hair follicle regeneration, while inhibiting FGF9 thwarts hair follicle neogenesis.[41] FGF9 expression stimulates Wnt expression and further activates Wnt signalling, which is one of the most important signalling pathways in wound-induced hair neogenesis (**Figure 2**).[43] The regenerated fibroblasts then express FGF9 and amplify Wnt activity in return. However, adult humans are short of resident dermal γd T cells to generate enough FGF9, which might account for their inability to regenerate hair after injury.[41] As a result, FGF or Wnt pathway activators provide new insights into treatments for alopecia, and may be further developed into bioactive compounds for hair follicle regeneration.[44] Shin et al.[45] developed a new strategy to introduce T cells to three-dimensional skin scaffolds, and investigated T cell responses. They revealed that the epidermis provides a directional cue for T cell activation, migration and infiltration into the skin. The skin appendages secrete growth factors and cytokines, which in return promote wound healing. Hair follicles generate endogenous stem cells to promote skin regeneration.[46] In addition, there are distinct differences in wound healing responses between hairy and hairless body parts. A recent study showed that hair follicle mesenchymal progenitor cells contribute only modestly to wound healing. In contrast, the extracellular progenitor cells of the hair follicle produce a large number of reparative fibroblasts, mediating the regeneration of the new dermal centre of the wound and the formation of surrounding scars. In wound-activated fibroblasts, reparative fibroblasts have a potential but modifiable regenerative capability.[47]

Vascularization and nerve regeneration

The vasculature in the dermis facilitates exchange of oxygen, nutrients and wastes. Different phenotypes of macrophage have distinct effects on endothelial cell behaviour.[48] M1 macrophages induce endothelial cells to up-regulate genes correlated with angiogenesis, M2 subtype (e.g., M2a, M2c and M2f) macrophages induce endothelial cells to up-regulate genes that promote pericyte cell differentiation *in vitro*. In the meantime, macrophages are indispensable in vessel remodelling. Kreimendahl et al.[28] prepared skin scaffold that encompassed fibrin, endothelial cells and macrophages to stimulate vascularization for tissue regeneration. They revealed that the macrophages regulated the number and arrangement of keratinocytes to form an epithelial cell layer in the injured skin. They also demonstrated that macrophages accelerated skin vascularization and regeneration. The regeneration of nerves along the arteries and veins could help restore the sensory nerves involved in pain, temperature, and touch perceptions. Meanwhile, hair follicles, Schwann cells and their secretions (e.g., laminin) together contribute significantly to nerve regeneration,[49] and thereby restore sensation.

Design of Immunomodulating Biomaterials for Skin Regeneration

The immune system has both pro-regenerative and anti-regenerative effects on tissue regeneration. Tuning the immune response is becoming an attractive approach to the design of biomaterials for tissue engineering and regenerative medicine. Other than stem cells and growth factors, we typically create a microenvironment by manipulating scaffolds; increasingly, studies have indicated that immunomodulating scaffolds have greater potential to construct a pro-regenerative microenvironment. Engineering biomaterials with a pro-regenerative microenvironment that allows autologous cells to infiltrate, differentiate and proliferate will promote tissue regeneration. In this section, we will discuss different approaches to tailor biomaterial properties to harness the immune response for tissue repair and regeneration (**Figure 3**).

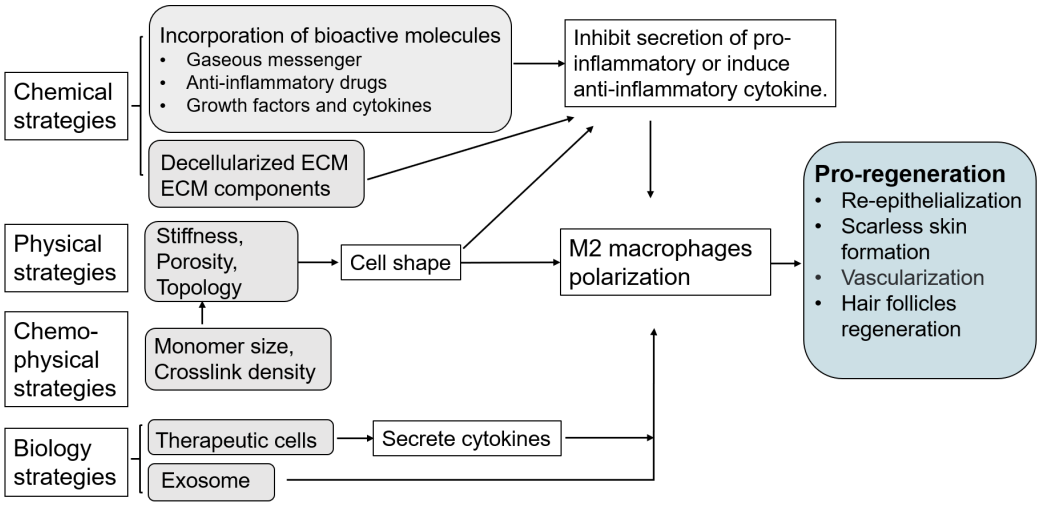

Figure 3. Strategies to engineer immunomodulatory biomaterials for skin regeneration. ECM: extracellular matrix.

Chemical strategies to engineer immunomodulatory biomaterials

The integration of functional biomaterials, surface modifications, and bioactive molecules can modulate protein adsorption and cell behaviour, thus impacting the biological behaviour of immune factors.

Incorporation of bioactive molecules

Bioactive molecules, including growth factors and cytokines, promote cell proliferation and differentiation, and regulate wound inflammation via the immune response.

As a gaseous messenger, hydrogen sulphide (H_2S) is useful in biological and clinical applications due to its anti-inflammatory effect.[50, 51] Wu et al.[52] fabricated a biomimetic hyaluronic acid (HA) hydrogel *in situ* with pH-controllable H_2S donor-JK1. The HA-JK1 hydrogel presented consistent release of H_2S. Under this condition, macrophages were polarized and transformed into the M2 phenotype *in vitro*. The hybrid hydrogel enhanced re-epithelialization, cell proliferation, collagen deposition, angiogenesis, and further accelerated the wound regeneration process. In addition, the *in vivo* results also showed that the HA-JK1 hydrogel promoted M2 macrophage polarization, which was in accord with the *in vitro* results. Taken together, these data suggest that the HA-JK1 hydrogel could induce expression of the M2 macrophage phenotype via the release of H_2S, and thus promote wound regeneration.

Anti-inflammatory agents such as heparin and dexamethasone have also been coated onto biomaterials to reduce inflammation and fibrous capsule formation.[53-56] Pharmacokinetics and an effective concentration of the drugs ought to be taken into consideration for long-term drug-eluting implants to decrease the tissue response *in vivo*. To prolong drug release, the drugs were always embedded into nanoparticles. Kim and Martin[57] prepared dexamethasone-loaded poly(lactic-co-glycolic acid) nanoparticles and embedded them in alginate hydrogel matrices to form a double-release system. Though neural probe implantation can help patients with movement disorders, the implantation procedure is always accompanied by injuries and inflammation. Dexamethasone is an anti-inflammatory drug, which has been proven to decrease the tissue reaction to implants. Probes coated with nitrocellulose-dexamethasone effectively reduced the inflammatory response *in vivo* via sustained release of the anti-inflammatory drug.[55]

Chemokines and their receptors at inflammatory sites directly regulate cell infiltration into implants.[58] Growth factors and cytokines can modulate the phenotypic transformation of immune cells. Therefore, these bioactive molecules could be incorporated onto a biomaterial to regulate the immune response. Hydrogels have been widely used to immobilize and release cytokines so as to modulate the local immune response and thus promote regeneration.[59] Dendritic cells are the bridge between innate and adaptative immune systems and are essential for initiating and directing an adaptive immune response.[36] Encapsulating immunosuppressive cytokines (e.g., TGF-β1 and IL-10) into polyethylene glycol hydrogels inhibits the maturation of dendritic cells.[60] The proteins were biologically active and suppressed the maturation of dendritic cells, and further alleviated the adaptive immune response. TGF-β1 is important for tissue repair but induces scar formation. Another isoform of TGF-β (TGF-β3) accelerates regeneration and prevents scar formation. Injection of TGF-β3 into incisional wounds reduces post-operative scarring.[61] These studies suggested that incorporation of anti-inflammatory agents into implants could prevent undesirable side effects.

Immunoengineering decellularized ECM

A key goal of tissue engineering is to construct a scaffold with chemical and physical properties similar to the natural ECM. Mimicking or using natural ECM components is thus a promising approach to create a pro-regenerative microenvironment. Decellularized ECM, derived from donor tissue by removing the cellular components, possesses immune-modulating properties, and its properties largely depend on its composition and structure. Any residue of cellular components results in an acute inflammatory reaction and leads to different M1/M2 phenotypic polarization.[62-64] A more aggressive decellularization process promotes the M2 phenotypic polarization.[62] Keane et al.[63] implanted porcine small intestine (SIS)-derived scaffolds to repair the body wall in a rat model, and compared the macrophage phenotypes around the implantation site. They found that the processing methods affected the phenotypic polarization of macrophages. Compared with carbodiimide-crosslinked porcine SIS, SIS without cross-linking induced M2 macrophages and promoted positive tissue remodelling, while carbodiimide-crosslinked porcine SIS scaffolds induced M1 phenotype macrophages and led to chronic inflammation.[65]

ECM components such as sulphated glycosaminoglycans, HA, and chondroitin sulphate in the native tissue are capable of coordinating growth factors and cytokines and modulating the function of dermal fibroblasts.[66] Immunomodulating scaffolds prepared from collagen I and sulphated HA inhibit secretion of the pro-inflammatory cytokines IL-1b, IL-8, IL-12 and TNF-α, but induce the anti-inflammatory cytokine IL-10, thus facilitating the polarization of M2 macrophages.[67] Polypropylene mesh coated with hydrogel, which was prepared from dermis and urinary bladder ECM, reduced the M1 response, and induced M2 polarization *in vivo*.[68] Of the microRNAs isolated from the ECM of dermis, twenty-two expessed the same miRNAs as those in other tissue ECMs. These ECM microRNAs play important roles in tissue regeneration by regulating macrophage polarization.[69]

Physical strategies to engineer immunomodulatory biomaterials

Although the chemical structures of biomaterials are similar, the physical characteristics of scaffolds, such as topological structure, surface roughness and mechanical strength, affect the immune cell response quite differently.

Mechanical stress affects cell behaviours in many ways, and the stiffness of the biomaterials directs macrophage polarization.[70,71] A relatively soft substrate reduces secretion of M1-related

cytokines and promotes expression of M2-related cytokines.[71] Macrophages seeded onto gels with appropriate stiffness showed anti-inflammatory properties.[71,72] Macrophages seeded onto thicker-fibre scaffolds, which were electrospun into skin-equivalent structures, tended to polarize into the M2 phenotype and secrete the anti-inflammatory factors arginase-1, found in inflammatory zone 1, and matrix metalloproteinase-2 (**Figure 4A**). In contrast, macrophages seeded on thin-fibre scaffolds exhibited the M1 phenotype and expressed pro-inflammatory factors, such as IL-6, TNF-α, monocyte chemoattractant protein-1 and melanocyte stimulating macrophage inflammatory protein-1α. After implantation, the macroporous grafts mediated M2 macrophage polarization and further promoted vascular regeneration.[73] The increase in both electrospun fibre diameter and porosity promoted M2 macrophage polarization. It is worth noting that the pore size of the scaffold played a more critical role than fibre diameter in promoting expression of M2 markers.[27]

Engineering topographical features is an important tool in the design of biomaterial scaffolds, and manipulating topography in scaffolds can also regulate the macrophage reaction to biomaterials.[74] McWhorter et al.[75] reported that micro- and/or nano-topographical structure could shape macrophage cells, which correlated with different phenotypes. Compared with M1 macrophage, the M2 phenotype exhibited an elongated shape. Macrophages cultured on a two-dimensional micropatterned scaffold were dramatically elongated, secreted anti-inflammatory cytokines (IL-4 and IL-13), and expressed M2 phenotype makers (**Figure 4B**). Clearly, the topography can shape and further regulate macrophage polarization. In our recent studies, we developed vascular grafts with three-dimensional oriented microfibers or microchannels and evaluated their regulatory effect both *in vitro* and *in vivo*.[76-78] Our results showed that the structure of oriented fibres or microchannels induced more macrophages to the M2 phenotype compared to random electrospun fibres, and promoted tissue regeneration.

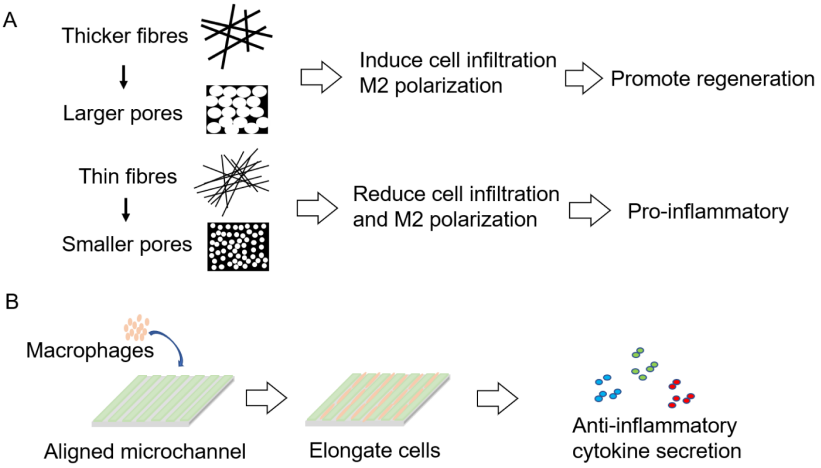

Figure 4. Physical strategies to engineer immunomodulatory biomaterial. (A) Schematic illustration showing that scaffolds with thicker fibres and larger pores promote the transformation of macrophages to the M2 phenotype. (B) Schematic illustration showing that microchannels cause cells to elongate, further facilitating M2 polarization.

Integrating chemi-physical properties into biomaterials

Three-dimensional scaffolds that mimic and maintain physiological functions can polarize macrophages to the M2 phenotype. Hydrogels, the pore size and porosity of which can be tuned by adjusting the crosslinking density, have been extensively investigated for wound healing (**Figure 5A**).[2, 79-82] We designed a series of immunomodulating hydrogel scaffolds and evaluated their biocompatibilities *in vitro* and *in vivo*.[80] Dextran-isocyanatoethyl methacrylate-ethylamine (DexIEME) showed great biocompatibility and regulated macrophage polarization. DexIEME promoted M2 macrophage phenotype transformation and provided a pro-regenerative microenvironment (**Figure 5B**). We first verified that DexIEME hydrogel was able to regenerate perfect skin on the existing scars (**Figure 5C**). Additionally, our preclinical studies further demonstrated that a deep porcine wound treated with the DexIEME hydrogel regenerated complete skin (**Figure 5D**).

Immunomodulation by therapeutic cells and their secreted factors

Recently, biomaterial scaffolds that deliver mesenchymal stem cells (MSCs) or adipose-derived stem cells (ASCs) were utilized to reduce scar formation during wound healing.[83-86] Hydrogels were used as semipermeable membranes to prevent the donor cells from direct contact with host immune cells, while allowing small molecules (e.g., reactive oxygen species, and nitric oxide) to infiltrate.[87]

MSCs secrete a broad spectrum of cytokines and chemokines that can modulate T-cell biology and promote angiogenesis, thereby facilitating a regenerative microenvironment.[88-91] MSCs encapsulated within polyethylene glycol or gelatine hydrogels were used to treat wounds in mice.[84,92] MSCs released prostaglandin E2, which induced macrophages to release anti-inflammatory factors (IL-4 and IL-10) while inhibiting the expression of proinflammatory factors (TNF-α, IL-2, IL-6, and

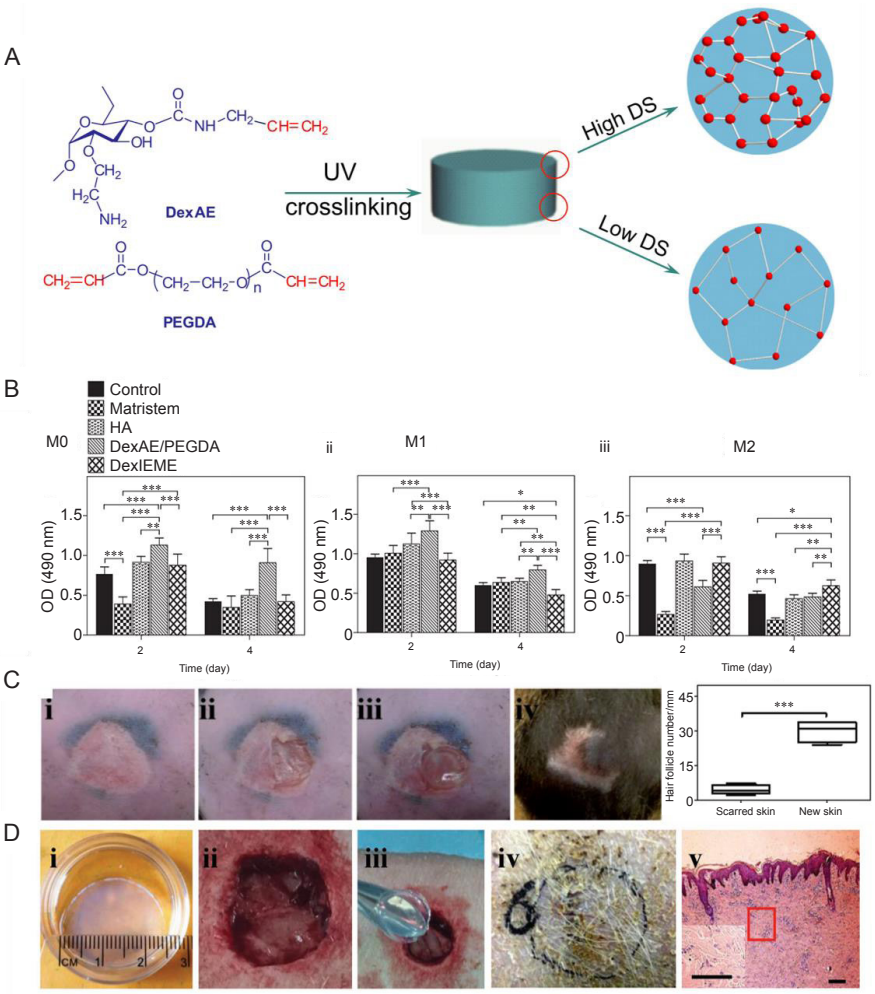

Figure 5. Integrating chemi-physical properties into biomaterials. (A) Increasing the DS of the crosslinkable functional group leads to a less porous structure. Reprinted from Sun et al.[81] Copyright 2011, with permission from Elsevier. (B) Macromers affect macrophage differentiation and polarization; DexIEME promotes M2 phenotype transformation. Reprinted from Sun.[80] Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission. (C) A pre-existing skin scar (i) that was partially promoted (ii) and treated with DexIEME hydrogel (iii) exhibited scarless skin healing (iv) with skin appendages (e.g., hair follicles). (D) A full-thickness skin injury (ii) in a preclinical swine model demonstrated that DexIEME (i, iii) regenerated complete skin (iv) structures (v) after 10 weeks. DexAE/PEGDA: dextran-allyl isocyanate-ethylamine and polyethylene glycol-diacrylate hydrogel; DexIEME: dextran-isocyanatoethyl methacrylate-ethylamine; DS: degree of substitution; HA: hyaluronic acid; OD: optical density; PEGDA: poly(ethylene glycol) diacrylate; UV: ultraviolet.

IL-8).[83, 84, 92] Macrophages cocultured with MSCs also showed a transformation into the anti-inflammatory type.[93] The secretion of CD206 was also significantly increased. In addition, prostaglandin E2 inhibited mitogenesis and proliferation of T cells in the wound and assisted the transition from Th1 to Th2 cells, which resolved inflammation and induced tissue regeneration, respectively.[83, 94, 95] The delivery of ASCs was also investigated, and they were found to promote wound healing leading to a similar outcome as that of MSCs.[96-98] Compared with MSCs, ASCs are plentiful in adipose tissue and 500 times the number of cells can be isolated from the same amount of tissue.[99-101] Thus ASCs may be more promising for use in clinical treatment because of their high yield and ease of isolation.[85, 98]

MSC-derived small extracellular vesicles (EVs) were developed to regulate immune cells,[102, 103] and they were examined for treatment of fibrotic liver disease.[104, 105] The data showed that the transmission of exosomes inhibited the TGF-β1 signalling pathway and hepatocyte transition from epithelium to mesenchyme, which further reduced formation of fibrosis in the liver. Wei et al.[106] evaluated the immunomodulatory function of MSC-derived EVs in promoting vascular graft regeneration. They prepared EV-functionalized electrospun vascular grafts, and transplanted them into a rat model of hyperlipidaemia for 3 months. Their results suggested that vascular grafts with MSC-derived EVs showed immunomodulatory function and could effectively improve vascular regeneration. Immune cells such as macrophages were also used as therapeutic cells to regulate the immune response and promote regeneration. Chen et al.[107] induced the switch to the M2 macrophage phenotype, and then collected the conditioned medium to induce bone marrow-derived MSCs to differentiate into osteoblasts. The

introduction of conditioned medium increased the expression of osteogenic differentiation markers. Collectively, these results suggest that EVs are a potential treatment for tissue regeneration through immune regulation.

Future Perspectives

Bio-fabricating an equivalent skin substitute is a classical treatment for wound healing, but it is unable to restore complete skin. Skin regeneration is a very complex process, which requires more than 50 different cell lineages to self-assemble into perfect structures.[108] Until now, the skin engineering field has yet to achieve a major breakthrough. Recent studies indicate that the immune response has a greater impact on tissue engineering and regenerative medicine than stem cells, and engineering immune-responsive scaffolds has thus attracted great attention. The design of biomaterials based on immunoregulation provides a new strategy for perfect skin regeneration. In addition to harnessing the regenerative potential to restore dermal structures, exploring the interaction between inmunomodulation and skin appendages (e.g., hair follicles) will have great potential to promote wound healing. Further progress in unveiling the mechanism of the immune response will help us design immunoregulatory scaffolds in a more pro-regeneration manner. The infiltration and proliferation of skin cells as well as the immune cells around the wound surface should be considered when designing the scaffold composition and pore structure. Although great strides have been made in promoting wound healing, there is still a long way to go to achieve complete skin regeneration in the clinic. A well-designed and fabricated scaffold that can promote inflammatory cell infiltration and the secretion of anti-inflammatory cytokines will further promote tissue regeneration. Moreover, the pro-regenerative properties can be further improved once biomaterials are coupled with bioactive components, which will result in more efficient products to treat deep skin injury.

The application of the immune response to promote perfect skin regeneration relies on a full understanding of the mechanisms of immune regulation. Progress in single cell sequencing technology may help us to explore the regulatory mechanism, which could guide us in how to design biomaterials. Meanwhile, the rapid development of manufacturing technology is desirable to enable the production of complex scaffolds. The realization of perfect wound healing requires the advancement of many fields.[109]

Conclusion

The immune response plays a greater role than traditional tissue-engineering strategies in regenerative medicine. The correlation between biomaterials and immune response empowers us to design immunomodulatory scaffolds to create a pro-regenerative microenvironment for skin regeneration. Many biomaterial strategies can be used to modulate the immune response of implants. Understanding and taking advantage of the important function of immune cells in tissue remodelling and regeneration would overcome the current bottleneck of tissue engineering regeneration. However, immune responses are spatiotemporally regulated, and a through grounding in the immune reactions to biomaterial scaffolds will undoubtedly help us develop regenerative treatments for wound healing. Therefore, further advancement is still dependent on continued progress in skin biology and biomaterial science.

Author contributions

PW and GS designed the manuscript and wrote the manuscript; GS conducted literature search; PW and YL performed literature search; YL helped write the manuscript. All authors approved the final version of this manuscript.

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Conflicts of interest statement

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