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REVIEW ARTICLE

Current knowledge of immunomodulation strategies for chronic skin wound repair

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Abstract

In orchestrating the wound healing process, the immune system plays a critical role. Hence, controlling the immune system to repair skin defects is an attractive approach. The highly complex immune system includes the coordinated actions of several immune cells, which can produce various inflammatory and antiinflammatory cytokines and affect the healing of skin wounds. This process can be optimized using biomaterials, bioactive molecules, and cell delivery. The present review discusses various immunomodulation strategies for supporting the healing of chronic wounds. In this regard, following the evolution of the immune system and its role in the wound healing mechanism, the interaction between the extracellular mechanism and immune cells for acceleration wound healing will be firstly investigated. Consequently, the immune-based chronic wounds will be briefly examined and the mechanism of progression, and conventional methods of their treatment are evaluated. In the following, various biomaterials-based immunomodulation strategies are introduced to stimulate and control the immune system to treat and regenerate skin defects. Other effective methods of controlling the immune system in wound healing which is the release of bioactive agents (such as antiinflammatory, antigens, and immunomodulators) and stem cell therapy at the site of injury are reviewed.

KEYWORDS
bioactive agents, biomaterials, cell delivery, immunomodulation, wound healing

1 | INTRODUCTION

Skin is the largest organ of the human body and is the first human defense barrier against pathogenic, physical, chemical, and mechanical attacks.[1] It is regularly subjected to several chronic damages, including trauma, autoimmune skin diseases, burns, skin cancer, and diabetic ulcers.[2,3] Also, skin plays a unique role in body immunomodulation. It is one of the most active organs in immunology due to various types of immune cells.[4,5] Skin defects, called chronic wounds, fail to progress beyond the inflammatory phase and lead to immune system stimulation for a long time.[6] According to the World Health Organization (WHO) report, chronic wounds affect 6.5 million people in the United States, leading to the US $25 billion in annual treatment costs.[7] Therefore, the development of effective strategies to accelerate chronic wound healing is desired.

The immune system is a key player throughout the wound healing process via secreting signaling molecules such as cytokines, chemokines, and growth factors.[8,9] Consequently, to enhance the healing process of chronic wounds, management of the immune system response is necessary. It can be possible by identifying the immune mechanism in the skin, examining the cells involved in the tissue formation and repair process, and studying the interaction between the cells and the extracellular matrix (ECM). Recent studies have shown that ECM properties play a significant role in the regulation and function of the immune system.[10,11] ECM contains bioactive components, which make a range of cellular activities easier.[12] The

interaction between cells and their environment allows the ECM a dynamic homeostatic control bond essential for immune cells to function well.[13] Furthermore, ECM compositions consist of natural immunomodulatory domains which link to receptors on immune cells, supporting their adhesion and regulating their functions.[11] According to the key parameters to control the immune system, various strategies have been examined for chronic wound healing, which can be further divided into biomaterials-based strategies,[14] the release of immunomodulators and antigens,[15–20] and cell therapy.[21,22] Recently, limited review studies have focused on various immune-based strategies to control chronic wound healings.[23] Sheoran et al[7] overviewed the recent immune system mechanism for skin wound healing. The aim of that study was to accurately consider the pathophysiology of both acute and chronic wounds and study the role of the immune system to accelerate chronic wound closure. In another review, Synder et al[24] studied the role of immune cells in wound healing. They summarized studies on the function and interaction of macrophages for wound healing. Park et al[25] also evaluated the interaction of some biomaterials with immune cells such as dendritic cells (DCs). Based on this study, biomaterial-based approaches can be practical tools for manipulating the immune system in order to deliver a range of immunotherapy agents at the right time and place.[25] In another study, Chouhan et al[26] studied the new technologies for healing and regenerating skin wounds that explored the advantages and drawbacks of these methods. Another review article by Andrew et al[11] examined the interaction between the immune system and the ECM. The approaches have provided a wide variety of engineering strategies for immunomodulation based on material interactions.[11] Ben-Ami et al[27] overviewed the functions of mesenchymal stem cells and their potential for the immunomodulatory treatment of autoimmune diseases. Loubna et al[28] also reviewed skin immunomodulation during regeneration and highlighted the role of adipose derived stem cells (ADSCs) in immunomodulatory responses and skin regeneration. In another review, Ghislain et al[29] examined the effect of cytokines, chemokines, matrix metalloproteinases (MMPs), and other biological factors on skin immune function. Despite all review studies in the field of immunology and treatment of chronic skin wounds, there is no complete study in the field of skin immune components, skin diseases related to the immune system, and techniques of treatment by using biomaterials, bioactive agents, and cell therapy. Based on our knowledge, the challenge of previous review articles is to study one face of practical immunomodulation factors and strategies in treating wounds and immune-related skin issues.

The key focus of the present review is to overview various immunomodulation-based technologies to promote the healing of various chronic wounds. In this regard, following the evolution of the immune system and its role in the wound healing mechanism, the interaction between ECM and immune cells to accelerate wound healing will be investigated. Consequently, the immune-based chronic wounds, including autoimmune diseases, diabetic wounds, and skin cancer, will be briefly examined, focusing on the mechanism of progression and their conventional treatment methods. Finally, various immunomodulation-based strategies (e.g., biomaterials-based immunomodulation, the release of bioactive molecules, and cell-based therapy) to stimulate and control the immune system in the regeneration of skin defects are investigated.

2 | SKIN IMMUNE SYSTEM

The skin tissue is divided into two general parts: the epidermis and dermal region with the subcutaneous adipose tissue.[30] Both of them have innate immune and adaptive immune cells and play essential roles in skin regeneration, balance the pre-inflammator, and anti-inflammatory stages and control the wound healing.[7,31] On the other hand, the dynamic structure of ECM controls the function of cells and cellular signals.[13] This section examines the effect of target cells on immune functions, the mechanism of the immune system to repair damaged tissue, and the interaction between the immune system and ECM.

2.1 | Target immune cells in the skin

Several cells are involved in the skin's immunomodulation reactions, including neutrophils, macrophages, keratinocytes, T-cells, Langerhans cells (LCs), and so on.[19] Figure 1 schematically shows the status of cells involved in the immune system in the skin layers. Neutrophils are the primary immune cells, participating in the wound healing process.[32] While the central function of neutrophils is to regulate body's homeostasis by over-proliferation, due to severe inflammation, they are a barrier to wound healing.[33] Macrophages are other important immune cells in the skin. These cells have a critical role in debridement and increase the proliferation of fibroblast.[34]On the other site, keratinocytes are the most abundant cells in the skin epidermis, which act a structural and modulating role in the skin's immune system.[19] These cells can secrete cytokines and chemokines that affect the pro-inflammatory process of the microenvironment and lead to the attract cells such as T-cells and neutrophils.[35] T-cells present in both the epidermis and dermis layers of the skin, and the number of these cells in the skin is twice that of blood. The function of these cells is to modulate the skin's adaptive immune system. Moreover, they usually play a significant role in autoimmune skin problems or allergic cases.[36] LCs are among the primary antigen present cells (APC) in the epidermis.[37] With the same function as keratinocytes, these cells can maintain the pro-inflammatory process in the tissue by secreting inflammatory agents and expressing specific cellular receptors and are effective in the skin's immune system.[38]

2.2 | Function of the immune system in chronic skin wound healing

Wound healing is a dynamic process divided into three phases, hemostasis/inflammation, proliferation, and maturation, which occur approximately 0–5, 5–10, and 10–60 days of wound healing process,

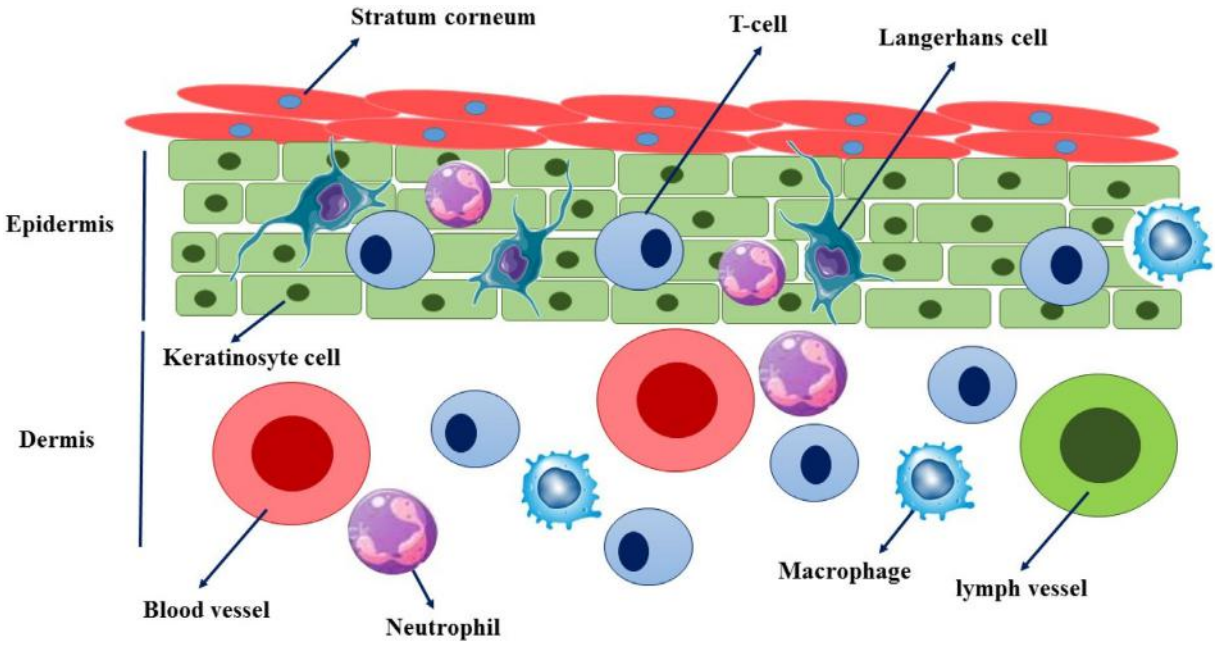

FIGURE 1 Skin cells which involve in immunomodulation and the location of each kind of cells in the skin layers

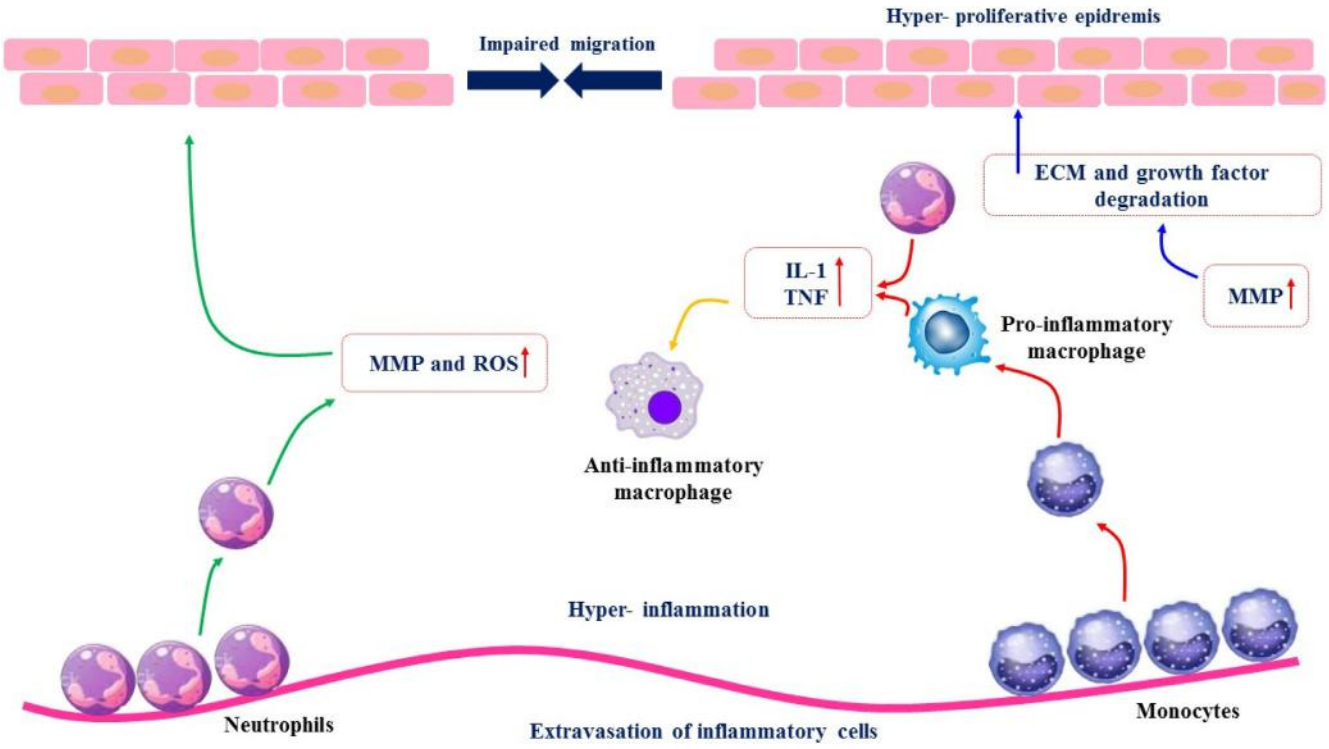

FIGURE 2 A high number of inflammatory cells in chronic wounds, and the secretion of inflammatory agents such as MMP, ROS, and IL-1, leads to the loss of growth factors and ECM and, change the function of macrophages

respectively.[39] The most important factor influencing the wound healing process is the function of immune cells. According to cells actions, they can accelerate wound healing or prevent repair.[40,41] For example, the proliferation of neutrophils in the skin tissue leads to increased reactive oxygen species (ROS) and destruction of the ECM and the other cell membranes.[7] Figure 2 shows the effects of inflammatory immune cells on the chronic wound healing process. At the first phase of chronic wounds healing (inflammation), the number of

innate immune cells, such as macrophages, neutrophils, and monocytes, increases, leading to overactivation of ROS and damaging cells and ECM molecules, or enhanced expression of matrix metalloproteinases (MMPs) at the injury site.[42] Increasing the amount MMPs also results in the degradation of ECM growth factors and structural proteins applied for tissue repair.[43] During the chronic wound healing process, an imbalance between pro-inflammatory and anti-inflammatory signals disrupts the wound healing process.[31] In this phase, the macrophage polarization from pro-inflammatory to anti-inflammatory is also one of the main factors affecting wound healing.[44] In this regard, the control of cell–matrix interactions and inflammatory responses are necessary for the complete inflammation stage in wound healing.[24]

2.3 | Effect of extracellular matrix on immunomodulation

The ECM is a dynamic structure made of proteins such as laminin, collagen, fibronectin, and proteoglycans secreted by skin cells (keratinocytes, fibroblasts, and immune skin cells).[13] ECM plays a fundamental role in coordinating cell signaling and controlling the function of immune cells.[11,13] A slight change in ECM structure and composition lead to change in the immune cell functions.[11] ECM proteins play essential roles in cell signaling.[45] For example, the laminin protein in the ECM structure is necessary to control migration, adhesion, and proliferation of immune cells. Any change in this protein enhances the levels of cytokines and MMPs.[46] Another ECM protein is collagen, which can activate the immune receptors and control the function of immune cells in the skin.[47] The immune system is a critical point for ECM degradation regulators, synthesis, assembly, and remodeling. Its mechanism consists of (I) enzyme synthesis for ECM remodeling, (II) cytokine synthesis and growth factors for ECM synthesis and degradation, and (III) ECM component synthesis.[13]

2.3.1 | ECM remodeling enzymes synthesis

Metalloproteases enzymes are secreted by immune cells and then modify the physical and biochemical ECM characteristics such as activation of bioactive peptides and releasing the growth factors necessary for remodeling.[10]

2.3.2 | Cytokines and growth factors synthesis

The immune cells increase the secretion of cytokines (IL-4, IL-13, and IL-33) and growth factor (TGF-β) by stimulating the synthesis of ECM components.[48] For example, The produce of IL-13 by T-cells alters the differentiation of fibroblasts to myofibroblasts and increases the level of collagen synthesis.[49]

2.3.3 | ECM components synthesis

Immune cells are one of the main factors influencing the secretion of growth factors and protein components in ECM. These cells increase the level of proliferation, adhesion, proteoglycan synthesis, and collagen synthesis.[13] Furthermore, ECM consists of natural immunomodulatory factors which link to immune cells and support their functions.

3 | OVERVIEW OF SKIN DISEASES AND THEIR CONVENTIONAL THERAPEUTIC STRATEGIES

Skin damages are divided into epidermal, superficial partial-thickness, deep partial-thickness, and full-thickness based on the injury depth.[50] All skin diseases, except full-thickness wounds, can regenerate by fibroblasts, keratinocytes, and so on. The main challenge is usually related to the full-thickness wounds and their proper treatment strategy.[51,52] In another category, based on the cause of skin ulcers, skin wounds can be originated from uncontrolled activity of the immune system (e.g., autoimmune skin diseases), abnormal metabolic (e.g., diabetes and skin cancer), or due to external factors (e.g., burns). In these categories, the immune system causes ulcers or is effective in the healing process.[53,54] Table 1 summarizes various types of skin diseases, their symptoms, and treatment methods. In the following, the most common skin diseases such as epidermolysis bullosa (EB), diabetic ulcers, and skin cancer directly or indirectly affected by the immune system, are discussed.

3.1 | Epidermolysis bullosa

Blistering is one of the skin reactions to pathogens such as bacterial, viral infections, trauma, or genetic disorder.[99] Among blistering diseases, autoantibodies play essential roles in skin integrity, such as integrin and skin adhesion molecules.[100] On the other hand, specific antigens against these auto-antibodies change the skin's genetic function, leading to mutations missing or malfunctioning skin proteins.[55,101] EB is one of the genetic skin disorders that leads to instability in the shape and structure of the skin.[102] The leading cause of EB is defects in structural proteins and cytoskeletons in the skin and it is associated with long-term blisters and severe skin lesions.[75] As the patient gets older, the symptoms become more severe and the whole body becomes involved in chronic infectious wounds.[70,103] Generally, EB is categorized into four different types of EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome.[75] According to Figure 3, the change in structure and amount of keratin caused EBS leading to the alteration in the amount of skin integrin and basement membrane proteins such as laminin. In prevalent cases, a significant decrease in collagen type VII leads to DEB.[103] Th faced with EB is severely dry, and its surface layer is brittle due to the separation between two layers of skin epidermis and dermis.

TABLE 1 The list of various types of skin diseases related to the immune system, their diagnostically relevant clinical signs, and the first-line treatments

Skin diseases	Main target for autoantibodies	Clinical sign	Conventional treatments	References
Pemphigus group (PV and PF) Autoimmune skin disorder	Desmogleins (DSG) 1 and 3 Mucosal with cutaneous involvement	Lesions Painful blisters Increasing the level of immunoglobulin1 (Ig1) and Ig4	Corticosteroids Azathioprine Peptide therapy Increasing the level of Ig2	[55–61]
Bullous pemphigoid (BP) Autoimmune skin disorder	BP180 and 230 antibodies	Severe inflammation Tense blisters Increasing the level of IgA and IgE Gap junction between the skin layers	Corticosteroids Oral prednisolone Azathioprine Chlorambucil Dapsone Methotrexate Tetracyclines	[55,56,62–69]
Epidermolysis bullosa (EB) Autoimmune skin disorder	Skin proteins	Mechanobullous Inflammation long-term blisters Severe skin lesions	Cyclosporine Colchicine Plasmapheresis Intravenous gamma globulins Wound dressing Gene delivery	[70–75]
Dermatitis herpetiformis Duhring (DH) Autoimmune skin disorder	Transglutaminases (TG) antibodies such as TG2 and TG3	Inflammation Painful blisters Increasing the level of IgA Increasing neutrophils	Dapsone Sulfone Steroids drugs with a gluten-free diet	[76–82]
Skin cancer	–	Painful lesion Deformation of the skin Changing cell function and level of cytokines	Chemotherapy Radiation therapy Immunotherapy	[83–86]
Diabetic wound	–	Chronic wound	Ozone therapy, laser therapy, and wound dressing	[87–89]
Burn wound	–	Inflammation wound Painful wound Infection Increasing immune cells	Skin grafting, silver wound dressing, skin replacements, and amniotic membranes Stem-cell-based therapeutic controlling immune components	[90–98]

Various treatment approaches for this autoimmune disease include collagen and polyurethane dressings for wound healing and cyclosporine, colchicine, plasmapheresis, extracorporeal photochemotherapy, and intravenous gamma globulins.[72] However, the process of these treatments prevents the development of wounds and cannot affect the synthesis of proteins such as collagen and lead to complete healing disorder.[104] Clinical studies in recent years have shown that stem cells and gene therapy can also be used to accelerate the healing process and regenerate structural proteins in the skin.[70] This process could increase the skin's stability and structural proteins such as collagen type VII and anchoring fibrils in the skin.[14]

3.2 | Skin cancer

The most usual class of human malignancies is skin cancer.[84] Many skin cancer patients had autoimmune skin diseases in the past, which enhances the importance of the link between the immune system and cancer.[84] The function of the immune system in skin cancer is essential because this system controls malignant and cancer cells and prevents their proliferation. On the other hand, increased immune system activity and autoimmune diseases such as Lupus erythematosus, dermatomyositis, and scleroderma can lead to the growth of cancer cells and skin cancer.[83] According to Figure 4, various innate immune cells [macrophages, DCs, natural killer (NK) cells, and adaptive immune cells (T and B lymphocytes)] are present in the skin cancer microenvironment and interact with the cancer cells via direct contact or chemokine and cytokine signaling.[105] Therefore, immunotherapy for skin cancer has been studied extensively using the regulation of inflammatory cytokine dose, reducing the level of immune suppressants, and modulating the adaptive immune system's T-cell activity.[84] Recently, many studies have been performed in immunotherapy and the treatment of skin cancer.[106] The engineering of ex vivo patient-derived lymphocytes injection back into patients is one of these appropriate techniques. The T-cells' function, which naturally can recognize

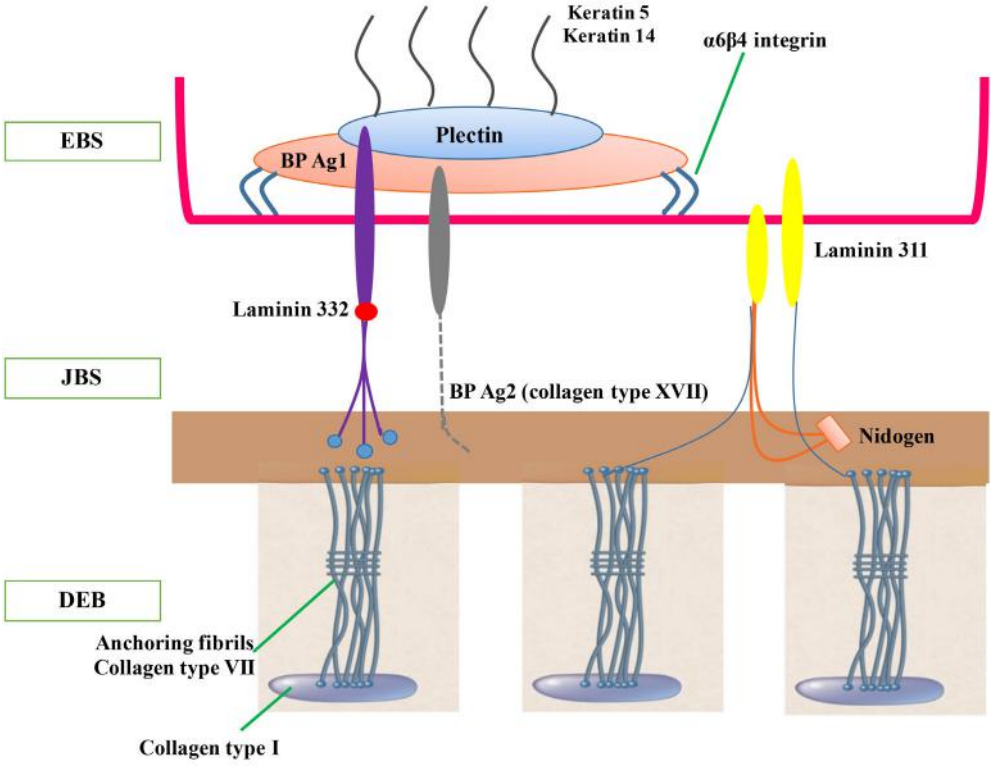

FIGURE 3 The schematic presentation of the structural proteins, skin cytoskeletons in three groups of EB (EBS, JBS, and DEB)

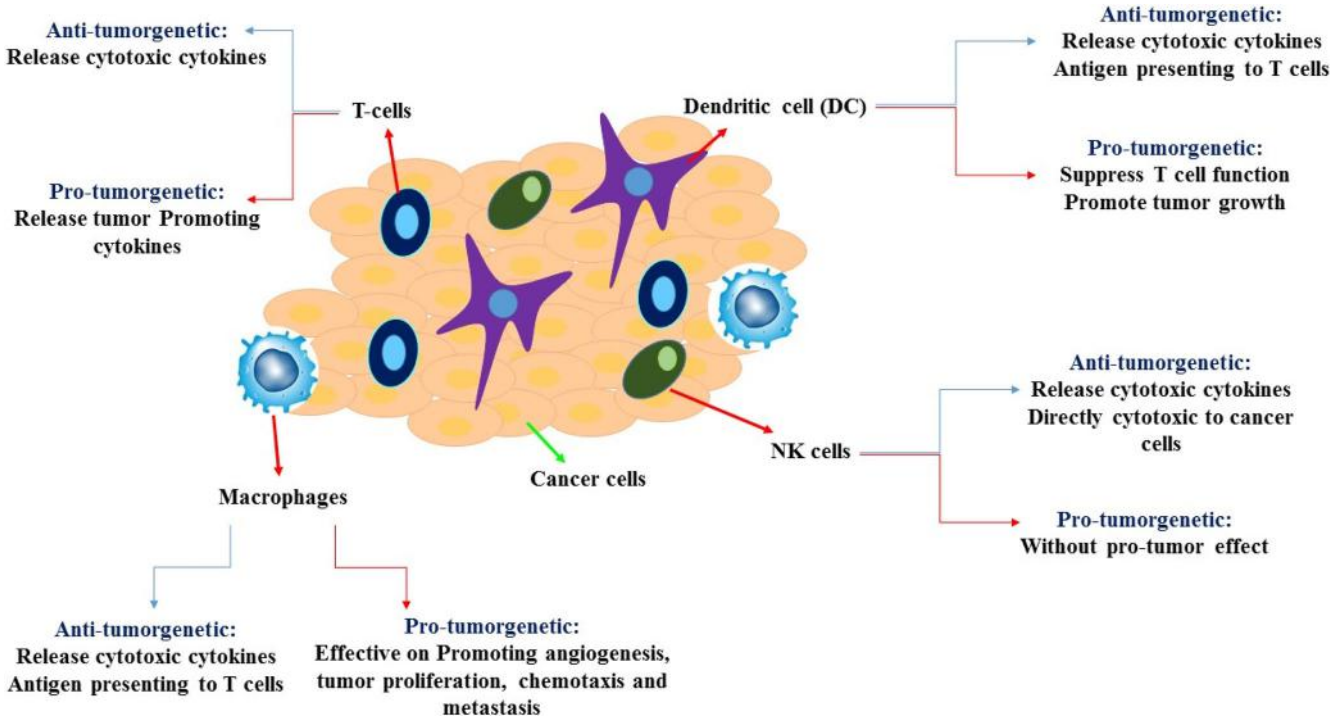

FIGURE 4 Main immune cells in skin cancer microenvironment and their antitumor and protumor functions

tumor tissue but has lost their function and has been suppressed by tumor signals, is the basis of this process.[107] Although this method can be effective in treating skin cancer, the genetic problems in the function of T-cells, lack of control of specific signals, and cellular interactions during the change of function may limit its application.[108]

3.3 | Diabetic chronic wounds

Diabetes mellitus type II (DM2) is a metabolic disorder which is characterized by hyperglycemia caused by insulin resistance. Cardiovascular disease, chronic renal failure, peripheral neuropathy, and diabetic skin wounds or ulcerations are only a few of the co-morbidities linked to DM2.[109] Diabetic skin ulcers are painful wounds without vascularization, which can lead to amputation or even death of the patient.[110–112] The importance of vascularization and vessel proliferation in tissue remodeling, as well as the lack of that in diabetic wound healing, has been highlighted in numerous studies.[99] Recent studies showed, the proliferation of T-cells and B-cells and macrophages are altered in diabetic patients, leading to imbalance in the innate and adaptive immune systems.[113,114] Changes in the immune system of these people lead to severe infection and angiogenic problems in the wound sites which delay wound healing.[88,115] Conventional and modern methods for treating diabetic wounds include ozone and laser therapies, respectivly.[116,117] One way to treat diabetic wounds and control diabetes is to optimize immune system factors.[29,118–120] For instance, MMPs regulate angiogenesis by activating of proangiogenic cytokines, including TNF-α and vascular endothelial growth factor (VEGF) in chronic wound healing.[121]

4 | WOUND TREATMENT STRATEGIES BASED ON IMMUNOMODULATION

Due to the limitations and challenges of conventional treatments of skin diseases, the strategies which can stimulate or control the immune system have been introduced. Wound treatment methods based on immune control can be based on various biomaterials, the release of bioactive molecules, and finally, cell therapy. These methods are described into the following sections.

4.1 | Immunomodulation using biomaterials

Biomaterials-based wound dressings provide a barrier between the wound and the external environment, thus preventing infection, absorbing exudates and promoting tissue remodeling.[122–126] In addition, biomaterials can control or stimulate the immune system responses by modulating their physical, chemical, mechanical, and surface properties.[127–129] The interaction between the immune system and biomaterials is examined based on chemical groups, surface properties, and usual biomaterial. A critical surface characteristic of biomaterials is represented by chemical functional groups.[130] Amino ($-NH_2$), carboxyl (–COOH), hydroxyl (–OH), methyl (–CH3), and sulfide (–SH) groups are the most widely explored groups.[131] Table 2 summarizes the most common chemical groups and their role in the immunological responses. The amino and hydroxyl groups cause the strongest in vivo immune cell interactions.[132] In other words, the anti-inflammatory M2 phenotype is induced by amino groups, while carboxyl groups trigger the inflammatory M1 macrophage phenotype.[133]

Interactions between proteins and biomaterial surfaces are associated with various essential biological reactions such as immune system responses.[139] Therefore, controlling the surface properties and adhesion of proteins can lead to the optimization of immune cell functions.[140] Surface roughness, hydrophilicity, and surface charge are important factors affecting surface interactions with proteins.[141,142] For example, recent studies show that by reducing the surface roughness, the adhesion of proteins and immune responses are minimized, leading to the accelerated healing process.[143–145] The shape and size of biomaterials are also important factors in immunogenicity and immune responses.[146] For example, short rods were more quickly taken up than longer rods and can induce more prominent levels of inflammatory signals (IL-1α and TNF-α).[147] The shape factor of biomaterials-based scaffolds and implants can also be important, since these structures are often too large for engulfment.[131] In another

TABLE 2 Biomaterial surface chemistry and their functions

Groups	Surface charge	Hydrophilicity	Interaction with blood	Interaction with inflammatory cells	Innate immune system responses	Adaptive immune system responses	References
–NH2	Positive	Hydrophilic	Medium	High (in vivo)	Activation antiinflammatory phase	Enhance T-cell activation and improve the lymphocyte proliferation efficiency	[131,133,134]
–COOH	Negative	Hydrophilic	Medium	Low	Inflammatory/low inflammatory	Increased activity of T-cells	[131–133,135]
–OH	Neutral	Hydrophilic	High	High (in vivo)	Low inflammatory	$CD8^+$ T cell proliferation and stimulation adaptive immune cell	[131–133]
–CH3	Neutral	Hydrophobic	Low	High	Antiinflammatory	Without significant changes	[131–133]
–SH	Neutral	Hydrophilic	Low	Low	Low inflammatory/ antiinflammatory	Without significant changes	[136–138]
C–O	Neutral	Hydrophilic	Medium	Low	Low inflammatory	Activation antigen-presenting cells (APCs) and T cell-expressed	[131–133]

TABLE 3 The interactions between immunological cells and biomaterials in wound healing

Cell types	Biomaterials	Finding	References
Neutrophils	Chitosan	Increased level of IL-8 and neutrophils migration, controlling the neutrophil functions, and inflammation by chemical modification of chitosan (surface charge and hydrophobicity)	[149,150]
	Alginate	Increased level of neutrophil migration, chemotaxis, and hexose	[151,152]
	Polycaprolactone (PCL)	Increased level of IL-2, IL-4, and IgG with increasing the activity of neutrophils	[153,154]
	Hyaluronic acid (HA)	Decreased neutrophil migration and induced anti-inflammatory responses	[97,155]
Macrophages	Chitosan	Increased pro-inflammatory cytokines such as TNF-α	[156,157]
	Alginate	Modulate inflammatory phase with increasing presence of macrophages	[158,159]
	Calcium alginate	Increase macrophages in local and TNF-α secretion	[160,161]
	Polycaprolactone (PCL)	Decreased pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6, increased anti-inflammatory responses such as TGF-β and IL-4	[162–164]
Dendritic cells (DCs)	Hyaluronic acid (HA)	Reduced level of activity of DCs and triggered anti-inflammatory responses	[165,166]
	Polytetrafluoroethylene (PTFE)	Increased level of DCs activity and the intensity of inflammatory responses	[167,168]
	Poly(lactic-*co*-glycolic acid) (PLGA)	Increased secretion of IL-4 and pro-inflammatory and anti-inflammatory cytokines	[169,170]
T-cells	Gelatin	Enhanced T helper responses through the TLR4 mediated IL-12 secretion	[171,172]
	Poly(lactic-*co*-glycolic acid) (PLGA)	Increased APC activity and enhanced activation of CD8+ T cell	[173,174]
	Hyaluronic acid (HA)	Activation of TLR and T-cells	[66,175]

study, titanium dioxide with various morphologies (nanoparticles with a diameter of 7–10 nm or 15–20 nm, and nanotubes with a diameter of 10–15 nm and a length 70–150 nm) were synthesized and their interactions with DCs were investigated.[148] Results confirmed the shape dependence across cytokine secretion, ROS production, and DC maturation. In particular, the nanotubes generally caused the largest immunogenic effects.[148] Another critical factor affecting the immune system is the surface charge of biomaterials. For example, the negative charge of carboxyl groups in the materials and its interaction with plasma proteins lead to moderate inflammatory reactions and trigger changes in macrophage functions and T-cells phenotypes.[131,133] Recently, Pan et al[134] showed the influential role of surface modification using amino groups in the triblock polymer of mPEG5k-PAGE15(NH2)-PCL5k(TPCAH). The results demonstrated the positive charge of the amino groups interacted with negatively charged proteins such as ovalbumin (OVA), leading to increasing in the immune responses. The complex TPCAH-OVA could effectively encourage the development of influential individual anti-OVA antibodies, improve the activation of CD4+ and CD8+ T cells, increase the efficiency of lymphocyte proliferation, and promote the secretion of various cytokines. Table 3 presents a list of the common biomaterials used for wound healing and their immune cells' interactions. In the following, the interaction of most common biomaterials with immune system is investigated.

4.2 | Chitosan

Chitosan is a deacetylated polysaccharide which has been widely applied for biomedical applications including wound healing, tissue engineering, and drug delivery due to its unique physico-chemical properties such as biodegradability, biocompatibility, and non-toxicity.[176–178] In another word, chitosan shows immunomodulatory responses due to its structural properties, releasing many cytokines with pro-inflammatory or anti-inflammatory nature.[179] Chitosan can increase the migration of neutrophils, inducing maturation of DCs, promote NK cells activity, and increase the inflammation response in situ.[149,180] The effect of chitosan on macrophages depends on its molecular weight and concentration.[181] Recently, studies have reported that chitosan shows different macrophage responses, depending on the molecular weight.[182] Whether these pro-inflammatory or anti-inflammatory responses are good or bad ultimately depends on the context. The exact difficulty in saying that "chitosan is proinflammatory" is that "inflammation" covers a very wide range of

cellular and molecular reactions. In fact, depending on the type and degree of inflammation, these reactions may be beneficial or harmful.[183–185] Park et al[150] showed that chemical changes in chitosan structure, such as altering the degree of N-acetylation or changing its surface charge, could change the inflammatory responses. However, it has been reported that chitosan with succinylation of amine groups (ZWC) is hydrophilic polymer and water-soluble at physiological pH without pro-inflammatory activities.[186] Lee et al[187] investigated the role of ZWC to suppress the release of pro-inflammatory cytokines and decrease the neutrophil activity. These results found ZWC could be a promising biomaterial for treating diabetic and autoimmune skin defects. In another study, Sunaina et al[188] developed chitosan scaffold with natural crosslinker (genipin). Their results demonstrated that this scaffolds caused no significant immune response while still revealed intrinsic antioxidant and antibacterial properties.

4.3 | Hyaluronic acid

Hyaluronic acid (HA) is a large glycosaminoglycan and an essential extracellular component of skin that has been widely studied to control inflammatory responses in the skin.[189,190] Kim et al[191] revealed that the presence of HA in contact with immune skin cells enhanced the expression of post-inflammatory macrophages (M2) and could essentially control inflammation. This polymer controls the activity of macrophages, neutrophils, DCs, and T-cell. In the presence of HA, the activity of DCs reduces and their interaction is coupled with a decrease in the level of inflammation.[165] HA has been applied for healing of EB or diabetic skins and results found that, HA can control the inflammatory responses, accelerated wound healing, and can be used as a immunomodulatory agent carrier.[192,193] In general, immunogenicity of HA depends on its molecular weight.[194,195] High molecular weight HA has been shown to have anti-inflammatory activity and the low molecular weight HA or its products can induce inflammation responses such as activation of macrophages.[196] Other studies have shown that small fragments of HA can increase the expression of a variety of cytokines and protein production, such as MMP12, macrophage inflammatory protein (MIP)1α and 1β, keratinocyte 8, and IL-12 by macrophages.[197,198] Recently, Fernanda et al[199] evaluated immune responses of HA gels (low and high molecular weight) cross-linked by bis(β-isocyanatoethyl) disulfide (BIED). They found that immune response associated with BIED cross-linked HA hydrogels was directly related to it molecular weight. Low molecular weight HA hydrogel increased fibroblast activation over time, which may be due to delayed and progressive responses, while high molecular weight HA gel decreased fibroblast activation over time, which might be related to inflammation activity.

4.4 | Gelatin

Gelatin is a natural polymer that is widely used for skin wound healing. It is an ideal choice for bonding with other biomaterials or a suitable carrier for the release of biological agents due to its flexibility properties.[200,201] On the other hand, immunomodulation studies showed gelatin affects the progression of inflammation with increasing cytokine release.[202] Recently, Zhao et al[203] investigated the effects of gelatin on the skin cancer cell and immunomodulation pathway. The results showed gelatin could promote immune cell aggregation, suppress the secretion of TNFα cytokine, and promote the secretion of proinflammatory cytokines. Recently, Yuanyuan et al[204] demonstrated that supramolecular host gelatin hydrogels containing resveratrol (Res) and histone 1 (His1) could inhibit inflammation and promote vascularization of skin burns. This hydrogel inhibits the expression of proinflammatory factors such as IL6, IL1β, and TNFα, and increases the expression of TGFβ1 and the platelet endothelial cell adhesion molecule 1 (CD31) leading to promoted wound healing properties.

4.5 | Collagen

Collagen is one of the essential component of ECM and an ideal choice for wound repair.[146] There is a close relationship between the immune system and collagen surface properties which can control or stimulate the immune system.[205,206] It has been proved that the adhesion of immune cells to the hydrophilic surface of collagen is lower than hydrophobic biomaterial surfaces, which results in the decreased level of IL-6 and IL-8 secretion. On the other hand, in fibrous scaffolds, the percentage of porosity and fiber diameter also affect the immune response. Kuyal et al[207] showed that in a collagen-based scaffold, increasing fiber diameter and porosity percentage increased the M1 to M2 macrophage transition and promoted the secretion of the angiogenic cytokines.

4.6 | Poly(lactide-*co*-glycolic acid)

Poly(lactide-*co*-glycolic acid) (PLGA) is a synthetic polymer with controllable degradation capacity that can be effective in damaged tissue repairing.[208] The interactions of PLGA with DCs and T-cells lead to enhance in the secretion of inflammatory cytokines, increasing antigen-presenting cell activity and enhance in the activation of T-cells, respectively, in the wound healing process.[169] Mooney et al[209] evaluated the role of porous PLGA matrix to repair skin cancer. The results showed the presence of PLGA in the structure led to increased DCS activity, generating specific antitumor immunity and healing skin defects.

4.7 | Hybrid biomaterials

The immunomodulation efficiency of biomaterials can be promoted using a mixture of various natural and synthetic biomaterials. Table 4 presents different composites that control inflammation responses and immune function in the wound healing process. You et al[210] developed an antiinflammatory scaffold based on silver nanoparticles (Nag) and collagen-chitosan scaffold (CCS). According to the scratch assay, the NAg-CCS scaffold increased the migration rate of

fibroblasts. On the other hand, histological results showed the full-thickness skin lesions were treated with NAg-CCS and CCS, respectively. The results demonstrated NAg-CCS was an antiinflammatory scaffold, which could potentially facilitate wound healing by controlling fibroblast migration and macrophage activation.[210] Zheng et al[211] also showed wound healing and inflammatory responses of PLGA based

TABLE 4 The role of various composite for control inflammation responses in wound healing

Composites	Application	Finding	References
Collagen-chitosan with silver nanoparticles (Nag)	Diabetic and burn wounds	Fibroblast migration, macrophage activation, anti-inflammatory responses, antibacterials, and accelerated wound healing	[210]
HA/PLGA fibrous scaffold	Diabetic wound healing	Re-epithelialization, collagen deposition, revascularization, increased CD31 expression, and accelerated wound healing	[212]
Dextran-isocyanatoethyl methacrylate-ethylamine (DexIEME)	Cutaneous wound	Differentiated macrophages to the M2 phenotype, reduction in fibrosis, and regenerated skin retains a reticulated endothelial layer	[213]
Decellularized ECM with HA	Full thickness burn wounds	Promoted neovascularization, anti-inflammatory, and proregenerative	[214]
Mesoporous silica/ε-poly-L-lysine with caspase-1 inhibitor	Autoimmune skin defects	Inhibition of pro-inflammatory cytokine and good anti-inflammatory effect	[215]
Glycol chitosan/difunctional polyurethane	Diabetic skin wound	Antimicrobial activity, re-epithelialization, and increased secretion of cytokines TGFβ-1	[89]
Nanofibers bioactive glasses/polydopamine (PDA)	Diabetic wound healing	Increasing re-epithelialization and collagen deposition, decreased inflammatory IL-1β, TNF-α, and IL-6 markers	[216]
PEG-SH with $AgNO_3$ hydrogel	Diabetic wound healing	Increasing angiogenic activity, reduced bacterial infection, and modifying inflammatory response	[110]
Polycaprolactone (PCL)/collagen with nanoparticles	Chronic wounds	Accelerated collagen deposition, anti-inflammatory responses, and full wound closure	[217]
PLGA/cellulose nanocrystals (CNCs) scaffold	Diabetic wound healing	Accelerated collagen deposition and re-epithelialization and optimization inflammatory responses	[211]
Mesoporous silica nanoparticles/ polycaprolactone (PCL) electrospun fibrous scaffold	Chronic wounds	Re-epithelialization, accelerated collagen deposition, and modifying inflammatory response	[218]
Glycol chitosan and difunctional polyurethane	Unhealed diabetic skin wound	Forming granulation tissue with sufficient microvessels and complete re-epithelialization with increased secretion of cytokine TGFβ-1	[89]
S-nitrosated keratin (KSNO)/polyurethane (PU)/gelatin (gel) biocomposite mat	Full-thickness excisional cutaneous wound	Wound healing without inflammatory responses with control nitric oxide release	[219]
Chitosan/cellulose wound dressing	Chronic wounds	Anti-inflammatory activity through the reduction of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), biocompatibility with human fibroblasts	[220]
Nano-titanium oxide/chitosan artificial skin	Chronic wounds	Steady level of TNF-α and IL-6,Unique bactericidal effect of nano-TiO_2 and immune-enhancing effect of chitosan	[221]
Polyvinyl alcohol/chitosan composite hydrogels with Tibetan medicine	Diabetic wounds	Reduced inflammatory responses and improved collagen deposition	[222]
Dibenzaldehyde-grafted poly (ethylene glycol) (PEGDA)/lauric acid-terminated chitosan (Ch-LA), and curcumin (cur)-loaded mesoporous polydopamine nanoparticles	Chronic wounds	Good hemostatic function, prominent antibacterial ability, strong antiinflammatory effect, and good wound healing capacity	[223]

TABLE 5 The role of various bioactive molecules incorporated biomaterials for wound healing

Immunomodulatory type	Application technique	Finding	References
PDGF	Encapsulation in electrospun chitosan-poly ethylene oxide (PEO) scaffold	Promoted fibroblast migration and accelerated diabetic wound healing	[236]
Epidermal growth factor (EGF)	PCL/HA composite emulsion	Promoted cell infiltration, regulated collagen and TGF-β1 gene expression, and accelerated epidermis regeneration in burn wounds	[237]
bFGF and VEGF	Chemical immobilization on PCL/PEG	Promoted diabetic wound healing process, improved re-epithelialization, and increased accumulation of collagen and matrix of keratin	[238]
EGF	Encapsulation in electrospun PLGA/gelatin scaffold	Increased fibroblast proliferation, expression of collagen types I and III genes	[239]
VEGF	Integrated with chitosan microneedle patch	Enhanced wound healing efficiency in skin cancer defects	[240]
IL-2	Conjugation of gel with PCL nanowires	Stimulating the suppressor cells and adjusting immune cells in pemphigus and EB	[241]
IL-22	Gel injection	Induced reepithelialization and tissue remodeling in diabetic wound skin	[242]
Tumor necrosis factor (TNF-α)	Carboxymethylcellulose MN-arrays	Decreased epidermal thickness and enhanced inflammatory responses in skin cancer defects	[243]
bFGF and VEGF	PCL/gelatin co-spun nanofabrics	Newly formed skin appendages, lesser scarring, and lower inflammatory levels in chronic wounds	[244]
Transforming growth factor (TGF-β) and IL-10	Incorporated with chitosan-based cryogels	Enhanced granulation tissue formation, neovascularization, and regenerative epithelialization in burn wounds	[245]
IL-4	Star-shaped poly(ethylene glycol) heparin hydrogels	Supporting (M2) phenotype of macrophage and proinflammatory responses in diabetic wound	[246]
Pyruvate kinase M2	Injection in wound site	Promoting angiogenesis, controlled inflammatory response, and proliferation phase in cancer defects	[247]
VEGF	PLGA nanoparticles	Enhance angiogenesis through sustained VEGF release from biocompatible matrices in cutaneous wounds	[248]
SiRNA	Hyperbranched cationic polysaccharide	Promoting diabetic wound healing	[249]
Collagen VII gene	Highly branched poly(β-aminoester) hydrogel	Increased synthesis of collagen VII and accelerated wound healing in EB wounds	[250]
EGF	Gelatin-methacryloyl (GelMA)/poly (3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV) hydrogels	Promoted migration and proliferation of multiple types of cells (keratinocytes, fibroblasts, and endothelial cells), enhanced angiogenesis, and diabetic wound healing	[251]
Basic fibroblast growth factor (bFGF)/ (VEGF)	PCL/gelatin co-spun nanofibers	Significantly higher number of newly formed skin appendages, lesser scarring, and lower inflammatory levels in newly formed granulation	[244]
EGF	PCL nanofibers functionalized with 6-deoxy-6-amino-β-cyclodextrin	Accelerated wound healing and increased epidermal cell proliferation	[252]
VEGF	GelMA hydrogel	Enhanced migration of endothelial cells and significantly improved quality of healing in porcine wounds	[253]

(Continues)

TABLE 5 (Continued)

Immunomodulatory type	Application technique	Finding	References
Proangiogenic gene stromal-derived factor-1α (SDF-1α)	Collagen-chondroitin sulfate scaffold	Promoted VEGF production, angiogenesis, expression of neurotrophin receptor p75NGFR, and remodeling of the basement matrix	[254]
EGF	Heparin/sulfated derivatives hyaluronan (sHA)/collagen-based hydrogels	Enhanced keratinocyte migration, inducing epithelial tip growth in epithelial and effective wound dressings	[255]
bFGF	Collagen-chitosan composite film modified with graphene oxide	Repairing full-thickness skin wounds, cell proliferation and accelerated wound healing	[256]
EGF	EGF-curcumin bandage bioconjugate	Enhanced wound closure by increasing granulation tissue formation, collagen deposition, and angiogenesis	[257]

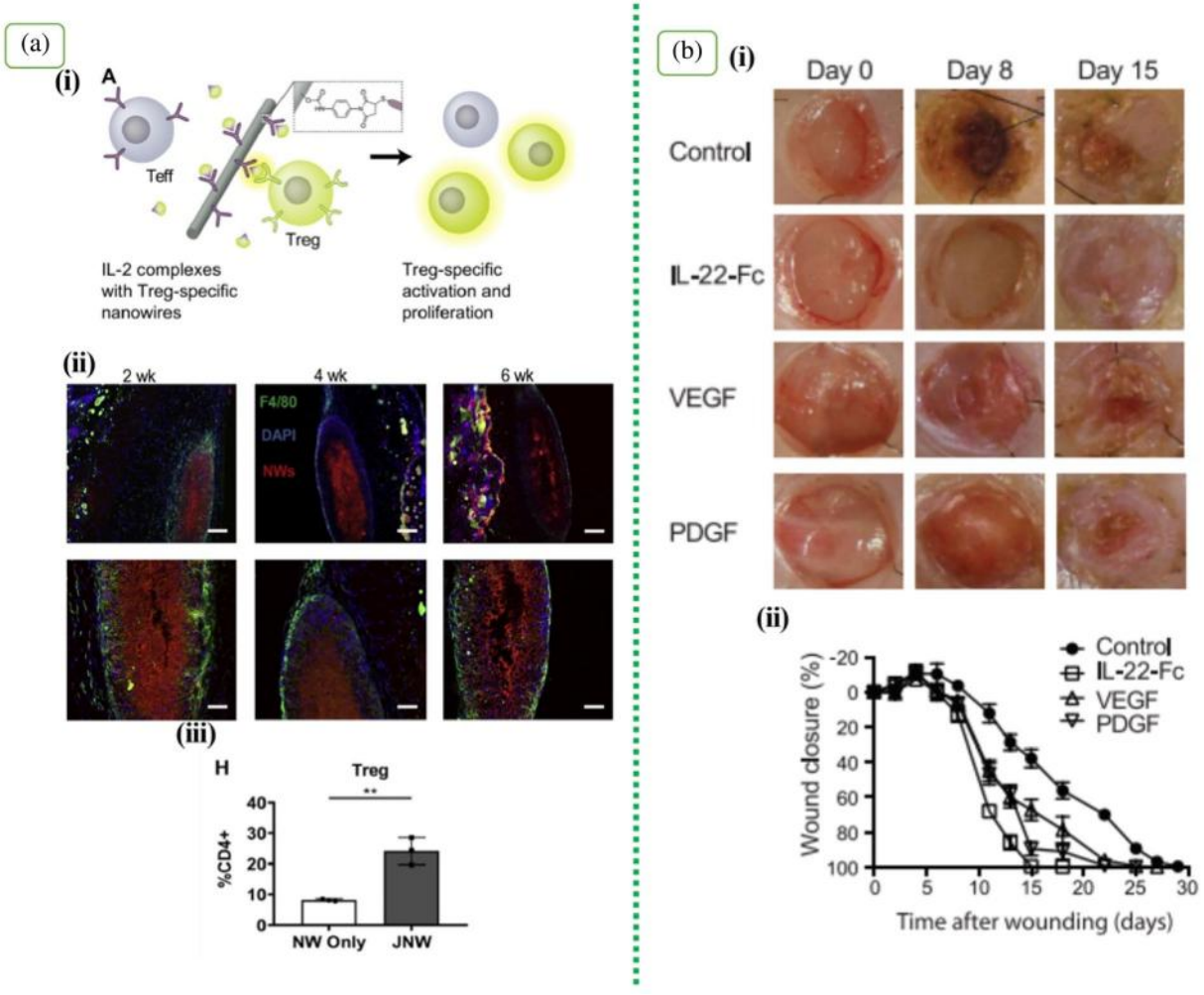

FIGURE 5 The delivery of cytokine by PCL nanowires for control the immune system: (a)—(i) schematic of selective cytokine and immune cell activation, (ii) in vivo PCL nanowire injection at 2, 4, and 6 weeks post-injection, and (iii) *in vitro* cytokine activation with lymphocytes from pooled skin draining lymph nodes in 1 nM IL-2 spiked media after 48 h of culture. Reprinted with permission from Ref. 241. 2020. Elsevier. (b) Wound healing comparison between IL-22, VEGF, and PDGF delivery: (i) The wound region was completely closed by gel injection with IL-22, VEGF and PDGF treatment groups showing IL-22 treated wounds, (ii) the extent of wound closure over 30 days. Reprinted with permission from Ref. 242

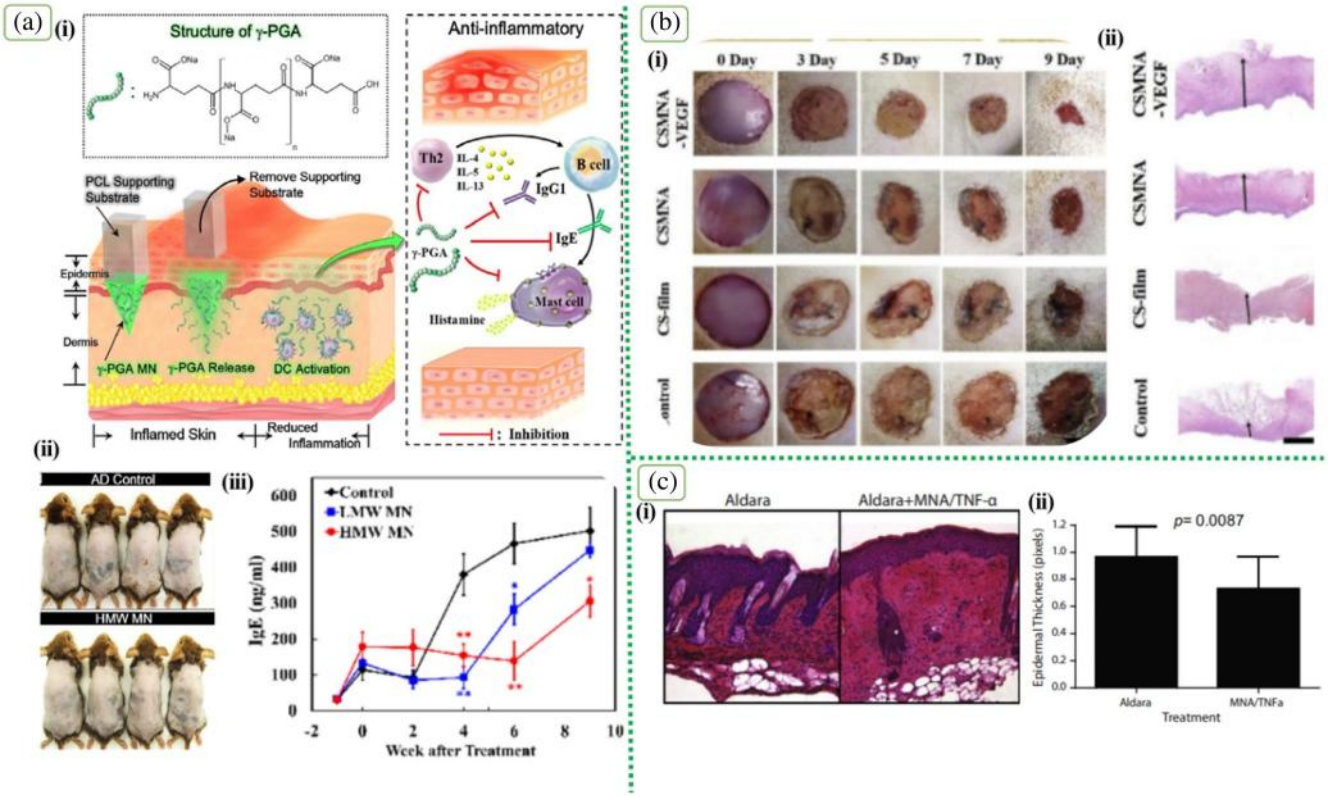

FIGURE 6 (a) Transdermal poly-γ-glutamate MN patch delivery to relieve skin inflammation: (i) Schematic showing the transdermal delivery using a poly- γ-glutamate MN patch to relieve skin inflammation. (ii) Reduction of AD-like skin lesions in the mice following 8 weeks with MN treatment. (iii) Downregulation of serum IgE showing negatively regulated Th2-associated Ig production (IgE) by γ-PGA. Reprinted with permission from Ref. 266. 2020. Elsevier. (b) Wounds treated with CSMNA-VEGF, CSMNA, CS-film, and phosphate buffered saline (PBS) (Control), (i) image of wounds after 3,5,7 and 9 days, (ii) Hematoxylin and eosin (H&E) staining of wounds after 9 days.[240] (c) MN arrays for TNF delivery retracted the development of psoriasiform dermatitis, (i) H&E staining of cutaneous cross-sections collected on day 5 and (ii) Quantitation of epidermal thickness. Reprinted with permission from Ref. 243

membranes incorporated with cellulose nanocrystals (CNCs) (PLGA/CNC). This scaffold accelerated collagen deposition and diabetic wounds re-epithelialization. Also, the immunohistochemical results showed the level of inflammatory cells decreased after 10 days.[211] In another research, Shin et al[212] developed HA/PLGA core/shell fibrous scaffold by coaxial electrospinning for diabetic wound healing. Compared with PLGA and control groups, the wound area was substantially decreased by coverage with HA/PLGA matrices leading to increased re-epithelialization, improved collagen deposition, and increased CD31 expression to test revascularization. In conclusion, the HA/PLGA matrices could theoretically establish strategies for accelerating diabetic wound healing and skin regeneration.[212]

4.8 | Bioactive agent delivery

One of the new strategies for treatment of skin defects is bioactive molecule release such as growth factors, anti-inflammatory, antigens, and immunomodulators to control the immune system.[224–228] Table 5 presents different bioactive agents and immunomodulators that control inflammation responses and accelerate wound healing. Growth factors (GFs) are biologically active polypeptides that regulate cell growth, differentiation, proliferation and migration, and control the immune cell function.[229] A wide range of GFs and cytokines, especially VEGF, epidermal growth factor (EGF), transforming growth factor-β (TGF-β), platelet derived growth factor (PDGF), and fibroblast growth factor (FGF) control various phases of the wound healing process. Another crucial anti-inflammatory factor is cytokines distributed locally and moderate immune system function.[129] For example, the release of TGF-β or IL-10 through hydrogels demonstrates their effectiveness in suppressing the maturation of DCs.[230,231] The transition M1 to M2 macrophages phenotype was also promoted by controlled delivery of IL-4 from biomaterials.[232] Cytokines such as IL-4 and IL-10 are essential for skin repair and regeneration owing to their role in M1 to M2 switching.[127] On the other hand, TGF-β1 is an exciting factor necessary for the early stages of tissue repair. Depending on the cell type, this molecule may use either inflammatory or antiinflammatory properties.[233] For instance, although TGF-β1 inhibits lymphocyte activity and proliferation, it can induce regulatory T-cells simultaneously.[234] In other words, TGF-β3 can be used to accelerate regeneration and prevent scarring.[235]

TABLE 6 Summary of in vivo studies of cell therapy for wound healing

Wound types	Cell source	Carrier	Findings	References
Chronic ulcers wound	BM-MSCs	Topical fibrin spray	Accelerated wound healing	[272]
Radiation burn	BM-MSCs	Treated collagen sponge	Wound healing without scar formation	[273]
Skin cancer	BM.MSCs	Injectable hydrogel	Isolated tumors and metastatic with anti-proliferative, proapoptotic, and anti-angiogenic properties	[274]
Diabetic wounds	AMSCs	Gelatin sponge	Accelerated granulation tissue formation, and increased reepithelialization and neovascularization	[275]
Physical full-thickness wound	hSDMSC	Carrageenan or poly (vinyl alcohol) hydrogel	Increased angiogenesis and accelerated wound closure	[276]
Burn wounds	rMSCs	Chitosan-porcine decellularized small intestinal submucosal (SIS) matrix supplemented with recombinant murine EGF	Accelerated angiogenesis and epithelialization	[277]
Cutaneous wounds	hUCMSC	Cellulose-based hydrogel	Promoted angiogenesis, proliferation, wound healing, and reduced scar formation in radiation induced skin wounds and better than hydrogel contain EGF	[278]
Diabetic wound	hSMSC	Chitosan hydrogels	Promoted healing and angiogenesis in skin wounds when delivered in chitosan hydrogels	[279]
Diabetic wound	mASC	Oxidized hyaluronic acid (HA), and poly-ε-lysine hydrogel	Reduced wound healing duration and enhanced angiogenesis in wounds	[280]
Diabetic wound	hGMSC	Chitosan/silk hydrogel	Promoted cutaneous wound healing, increased angiogenesis, collagen deposition, and nerve fiber density	[281]
Physical full-thickness wound	hUCMSC	HydroMatrix hydrogel	Prevented α-SMA expression and scar formation	[282]
Cutaneous wounds	MSCs	PEG hydrogel	Support wound re-epithelialization, possibly due to its ability to increase PDGF expression and decrease IL-6 expression	[283]
Cutaneous wounds	ADSC	Thin layer of acrylic acid	Accelerated wound healing through differentiation and vasculogenesis	[284]
Cutaneous wounds	MSCs	Collagen scaffolds	Vascularized more than control scaffolds	[285]
Diabetic wounds	MSCs	Fibrin spray	Accelerated angiogenesis and wound healing	[286]
Diabetic wounds	ADSCs	Hybrid injectable hydrogel from hyperbranched PEG macromer	Promoted angiogenesis and re-epithelialization	[287]
Diabetic ulcers	ADSCs	Injectable gelatin microcryogels	Enhanced wound healing and generated intact skin with regeneration after full-thickness injury	[288]
Diabetic wounds	MSCs	Gelatin scaffold	Enhanced reepithelialization, antiinflammatory response, and proangiogenic functions	[289]
Diabetic wounds	MSCs	Pretreated with salidroside and PEG hydrogel	Improved the wound closure rate and re-epithelialization	[290]
EB	ABCB5+ MSCs	Injection	Decreased anti-inflammatory interleukin1, improvement of migration of endothelial and epithelial cells	[291]
Diabetic wounds	ADSCs	Scaffold of human acellular amniotic membrane (hAAM)	Accelerated wound healing by regulating inflammation, stimulating vascularization, and promoting the production of ECM	[292]
Surgically created full-thickness skin excision	ADSC	PLGA nanofibrous	Improved wound healing process	[293]

TABLE 6 (Continued)

Wound types	Cell source	Carrier	Findings	References
Third-degree burn wounds	MSCs	Arginine-based poly(ester amide) (UArg-PEA) and chitosan	Promoted re-epithelialization, granulation tissue formation, vascularization and induction of reparative, antiinflammatory interleukin-10, and M2-like macrophages, the reduction of inflammatory cytokine TNF-α and M1-like macrophages at late inflammatory phase of burn wound healing	[294]
Full-thickness burn wounds	MSCs	Direct injection	Promoted wound healing process	[295]
Chronic wounds	MSCs	Injectable hydrogel composed of sodium alginate (SA) and collagen type I (Col)	Exhibited low immunogenicity, promoted granulation formation, enhanced collagen deposition and angiogenesis, increased VEGF and TGF-β1, and mitigated inflammation	[296]
Chronic wounds	Adipose-derived mesenchymal stem cells (AMSCs)	Direct injection exosomes derived from AMSCs (AEXOs)	Alleviated inflammation response, promoted wound healing, and antiinflammatory responses	[297]
Diabetic wounds	Menstrual blood-derived mesenchymal stem cells (MenSCs)	Exosomes isolated from MenSCs	Enhanced neoangiogenesis through VEGF release, accelerated re-epithelialization and less scar formation	[298]

Zamecnil et al[241] studied the role of an injectable cytokine delivery system for local treatment of pemphigus and EB skin defects. In this study, PCL nanowires were conjugated to IL-2 and assembled into injectable porous matrices to enable regulatory T-cells resident in tissue (Tregs) (Figure 5a(i)). Injection of this nanomaterial induced long-term inflammatory responses. After 2, 4, and 6 weeks, nanowire nodules were cryosectioned in OCT and stained with macrophage-labeling antibody around the nodules (Figure 5a(ii)), and minimal inflammatory was detected. The results showed the level of CD4+ Tregs for PCL nanowires increased (Figure 5a(iii)) and this hybrid structure stimulated the suppressor cells, which were necessary to control immune system function.[241] In another study, Kolumam et al[242] compared the wound healing process by simultaneous injection of IL-22 and growth factors such as VEGF and PDGF. The results showed IL-22 induced re-epithelialization and tissue remodeling in diabetic wound skin (Figure 5b(i,ii)).

Antigen delivery is another effective method used to treat skin diseases and control the function of the immune system. The appropriate release of an antigen to the target tissue is a crucial point to achieve antigen-specific immune tolerance.[258,259] In this regard, various skin patches,[259] microneedle (MNs) patches[17] and injectable polymers[260] have been applied. One of the most common ways to release drugs, growth factors and antigens is to use MN patches. MNs are micron-sized needles made from various materials and shapes, varying in height from 25 to 2000 μm.[261,262] MNs can be applied to the skin to build micron-sized transport pathways that allow various pharmaceutical, protein agents, and drug molecules to be distributed better.[19,156,263] This method has been widely used to deliver immunomodulatros to treat skin defects and autoimmune diseases.[264,265] An example of a recent study of the release of immunomodulators by MNs patches is the study by Chen et al.[266] They developed dissolvable poly-γ-glutamate (γ-PGA) MNs as transdermal immunomodulators for atopic dermatitis (AD) skin diseases. According to Figure 6a(i), the γ-PGA MNs with a PCL-supporting substrate were mixed. The dissolved γ-PGA induced the increased production level of IgE and IgG1 (Th2-associated antibodies) and reduced infiltration of mast cells that directly stimulated dermal DCs, regulated immune responses and improved AD pathology. In addition, treatment with γ-PGA MNs upon 8 weeks showed immunomodulatory effects in mice (Figure 6a(ii)) and had the potential to be a mild, easy and efficient treatment choice for the management of AD by decreasing the development of Th2-dependent IgE (Figure 6a(iii)).[266] In another study, Chi et al[240] evaluated skin patches of MNs/chitosan hydrogel with the delivery of VEGF in the wound site. The results showed this skin patch promoted the wound healing in comparison with CS film (Figure 6b). Moreover, Korkmaz et al[243] assessed using tip-loaded dissolvable carboxymethylcellulose (CMC) MN patches for localized intradermal delivery of TNF-α in inflammatory cases. This study showed that MN encapsulated anti-TNF-α was biologically active after 5 days compared with Aldara cream and had a therapeutic impact in an animal model with skin defects. Reduced epidermal thickness preserved positions compared with untreated control (Figure 6c).

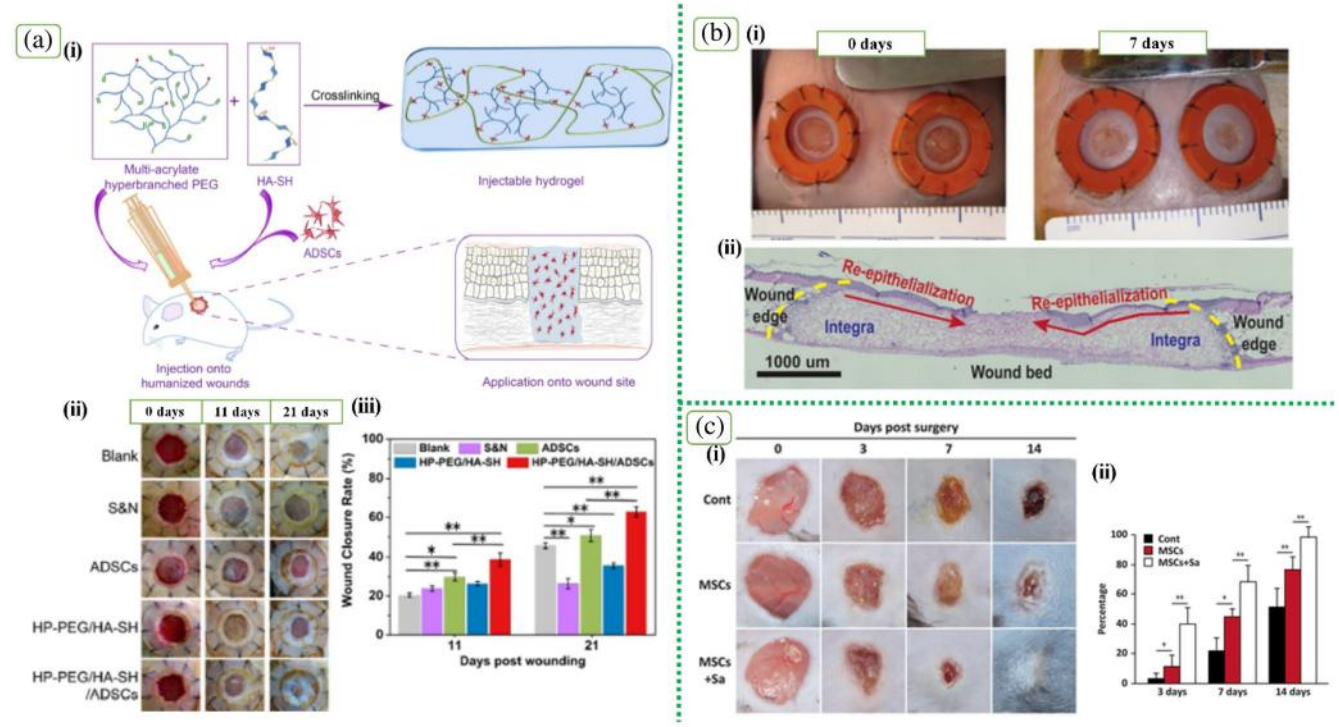

FIGURE 7 Immunomodulation therapy using cell delivery: (a) An injectable HP-PEG-based hydrogel with ADSCs for the healing of diabetic wounds; (i) Schematic principle of the development of injectable HP-PEG-based hydrogel with ADSCs and incorporation into a humanized diabetic wound model. (ii) The images of wounds during 21-day *in vivo* experiments, (iii) wound closure rate quantification (%) over 21-day period. Reprinted with permission from Ref. 287. 2020. Elsevier. (b) Diabetic wound healing with MSCs, (i) *In vivo* wounding assay treatment of MSC and enhanced wound healing in diabetic mice after 7 days, (ii) H&E stained image showing wound edge location and re-epithelialization on day 7 (red arrows).[289] (c) The effect of MSCs and salidroside on diabetic wounds. (i) Image of wound closure of diabetic mice transplanted with salidroside-pretreated MSCs after 14 days and (ii) the wound closure rate in various time points after wounding. Reprinted with permission from Ref. 290

4.9 | Immunomodulation using cell delivery

One of the traditional techniques for immunosuppression or immune system modification is cell therapy.[28,89,267] An overview of immunomodulatory strategies based on cell delivery is provided in Table 6. The mesenchymal stem cells (MSCs) are critical cells applied to control the immune system.[268] MSCs, the resident in most adult tissues, are non-hematopoietic, multipotent stromal precursor cells.[269] Initially, MSCs are found to prevent in vitro mitogen-induced T-cell proliferation and escape immune surveillance.[270] Studies have shown that MSCs can modulate immune responses in the innate and adaptive immune systems during chronic inflammation. All of these characteristics make MSCs an attractive candidate to cure chronic inflammatory diseases.[21] Antiinflammatory mediators such as prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), TGF-β, and IL-6 may be generated by MSCs in skin immunomodulation.[271] For the treatment of EB diseases, recent studies have used direct injection of MSCs. Structural proteins such as collagen III, VII, and XVII have been secreted by MSCs, resulting in increased re-epithelization of the wound areas. Additionally, cytokine preconditioning of MSCs with TGFβ and TNFα increases in COL7 expression and healing of the EB wounds.[104]

Sigen et al[287] have developed an injectable hydrogel system based on ADSCs with hyperbranched multiacrylated poly(ethylene glycol) macromers (HP-PEGs) and thiolated hyaluronic acid (HA-SH) to heal diabetic wounds (Figure 7a(i)). Compared with the control groups receiving no care and wounds treated with cells alone, HP-PEG/HA-SH/ADSCs considerably accelerated wound healing at days 11 and 21 postwounding by hindering inflammation, encouraging angiogenesis, and re-epithelialization (Figure 7a(ii,iii)). In another study, Yang et al[289] fabricated a scaffold comprising hypoxia-preconditioned, allogeneic human MSCs combined with the beta-adrenergic antagonist timolol, to enhance weakened wound healing in diabetic mice. Figure 7b(i) shows that in diabetic mice, MSCs accelerated healing ratio after 7 days and facilitated wound healing. Additionally, this hybrid structure enhanced re-epithelialization, anti-inflammatory responses, and proangiogenic functions (Figure 7b(ii)). In another research study, Zhang et al[290] examined the role of salidroside pretreatment on the therapeutic effect of MSC-based therapy loaded on PEG hydrogel for diabetic wound healing. The finding showed that mice transplanted with MSCs increased the anti-inflammatory responses and wound closure rate relative to the control group. On the other hand, pretreatment with salidroside further encouraged the therapeutic effect of MSCs (Figure 7c(i,ii)).

5 | CONCLUDING REMARKS

In various skin diseases, such as ulcers diabetes, burn wound, skin cancer and autoimmune skin defects, the immune system, and its interaction with tissue environment are known as crucial parameters to control wound healing. In the wound repair process, ECM plays an essential role in moderating the immune system and its function. The interaction between cells and their environment makes the ECM a dynamic bond for the healthy function of immune cells. Furthermore, ECM compositions have natural immunomodulatory domains which interact with receptors on immune cells, providing the regulation of their function. Based on the importance of immune system elements and their interaction with ECM, the most appropriate way to treat autoimmune diseases is to use factors controlling the immune system. One of the factors that can improve or suppress the immune system function is biomaterials-based structures. Various natural and synthetic biomaterials can have different immune responses and react with immune cells in a controlled manner based on their chemical properties, side groups, mechanical properties, and morphology. For example, coating carboxylic groups on the biomaterial surface can alter the immune cell responses and be effective in the healing process of chronic wounds. In addition, controlled release of bioactive molecules such as immunomodulators and cytokines by polymeric skin patches and MN patches can dramatically alter the immune system function in autoimmune diseases and skin ulcers. One of the new methods to suppress or regulate the immune system is the cell delivery technique. In this method, the skin immune system function and immune cells signal control by injection of stem cells such as MSCs or modify biomaterials by loading cells.

According to the recent findings, it can be demonstrated the crucial roles of the immune system in the wound healing process. However, various common therapies failed because none of them have fundamentally repaired skin defects while using the immunomodulation strategies can accelerate the process of repair of autoimmune skin diseases, diabetic wounds, and skin cancer. Perhaps specific strategies that failed clinical trials in the past may become successful using immune system-based strategies.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

REFERENCES

1. Zhong SP, Zhang YZ, Lim CT. Tissue scaffolds for skin wound healing and dermal reconstruction. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2010;*2*(5):510-525. https://doi.org/10.1002/wnan.100
2. Szilveszter KP, Németh T, Mócsai A. Tyrosine kinases in autoimmune and inflammatory skin diseases. *Front Immunol*. 2019;*10*:1862.
3. Kamel RA, Ong JF, Eriksson E, Junker JPE, Caterson EJ. Tissue engineering of skin. *J Am Coll Surg*. 2013;*217*(3):533-555.
4. Barak Y. The immune system and happiness. *Autoimmun Rev*. 2006;*5*(8):523-527.
5. Rustemeyer T, Fartasch M. Immunology and barrier function of the skin. In: John SM, Johansen JD, Rustemeyer T, Elsner P, Maibach HI, eds. *Kanerva's Occupational Dermatology*. Switzerland: Springer; 2020:3-10.
6. MacLeod AS, Mansbridge JN. The innate immune system in acute and chronic wounds. *Adv Wound Care*. 2016;*5*(2):65-78.
7. Larouche J, Sheoran S, Maruyama K, Martino MM. Immune regulation of skin wound healing: mechanisms and novel therapeutic targets. *Adv Wound Care*. 2018;*7*(7):209-231.
8. Strbo N, Yin N, Stojadinovic O. Innate and adaptive immune responses in wound epithelialization. *Adv Wound Care*. 2014;*3*(7):492-501.
9. Moura J, Madureira P, Leal EC, Fonseca AC, Carvalho E. Immune aging in diabetes and its implications in wound healing. *Clin Immunol*. 2019;*200*:43-54.
10. Tomlin H, Piccinini AM. A complex interplay between the extracellular matrix and the innate immune response to microbial pathogens. *Immunology*. 2018;*155*(2):186-201.
11. Rowley AT, Nagalla RR, Wang S, Liu WF. Extracellular matrix-based strategies for immunomodulatory biomaterials engineering. *Adv Healthc Mater*. 2019;*8*(8):1801578.
12. Ventura RD, Padalhin AR, Park CM, Lee BT. Enhanced decellularization technique of porcine dermal ECM for tissue engineering applications. *Mater Sci Eng C*. 2019;*104*:109841.
13. Bhattacharjee O, Ayyangar U, Kurbet AS, Ashok D, Raghavan S. Unraveling the ECM-immune cell crosstalk in skin diseases. *Front Cell Dev Biol*. 2019;*7*:68.
14. Chung L, Maestas DR Jr, Housseau F, Elisseeff JH. Key players in the immune response to biomaterial scaffolds for regenerative medicine. *Adv Drug Deliv Rev*. 2017;*114*:184-192.
15. Patel HJ, Trivedi DG, Bhandari AK, Shah DA. Penetration enhancers for transdermal drug delivery system: a review. *J Pharm Cosmetol*. 2011;*1*(2):67-80.
16. Bachhav YG, Heinrich A, Kalia YN. Controlled intra-and transdermal protein delivery using a minimally invasive erbium: YAG fractional laser ablation technology. *Eur J Pharm Biopharm*. 2013;*84*(2):355-364.
17. Lee JW, Prausnitz MR. Drug delivery using microneedle patches: not just for skin. *Expert Opin Drug Deliv*. 2018;*15*:541.
18. Park J, Lee H, Lim G-S, Kim N, Kim D, Kim Y-C. Enhanced transdermal drug delivery by sonophoresis and simultaneous application of sonophoresis and iontophoresis. *AAPS PharmSciTech*. 2019;*20*(3):96.
19. Zhao Z, Ukidve A, Dasgupta A, Mitragotri S. Transdermal immunomodulation: principles, advances and perspectives. *Adv Drug Deliv Rev*. 2018;*127*:3-19.
20. Srinivasan S, Babensee JE. Controlled delivery of immunomodulators from a biomaterial scaffold niche to induce a tolerogenic phenotype in human dendritic cells. *ACS Biomater Sci Eng*. 2020;*6*(7):4062-4076.
21. Munir H, McGettrick HM. Mesenchymal stem cell therapy for autoimmune disease: risks and rewards. *Stem Cells Dev*. 2015;*24*(18):2091-2100.
22. Petrof G, Martinez-Queipo M, Mellerio JE, Kemp P, McGrath JA. Fibroblast cell therapy enhances initial healing in recessive dystrophic epidermolysis bullosa wounds: results of a randomized, vehicle-controlled trial. *Br J Dermatol*. 2013;*169*(5):1025-1033.
23. Mokarram N, Bellamkonda RV. A perspective on immunomodulation and tissue repair. *Ann Biomed Eng*. 2014;*42*(2):338-351.
24. Snyder RJ, Lantis J, Kirsner RS, Shah V, Molyneaux M, Carter MJ. Macrophages: a review of their role in wound healing and their therapeutic use. *Wound Repair Regen*. 2016;*24*(4):613-629.

25. Park W, Song KH, Lim J, Park CG, Doh J, Han DK. Biomaterial-based strategies to prime dendritic cell-mediated anti-cancer immune responses. *Int Mater Rev*. 2020;*65*(7):1-18.
26. Chouhan D, Dey N, Bhardwaj N, Mandal BB. Emerging and innovative approaches for wound healing and skin regeneration: current status and advances. *Biomaterials*. 2019;*216*:119267.
27. Ben-Ami E, Berrih-Aknin S, Miller A. Mesenchymal stem cells as an immunomodulatory therapeutic strategy for autoimmune diseases. *Autoimmun Rev*. 2011;*10*(7):410-415.
28. Mazini L, Rochette L, Hamdan Y, Malka G. Skin immunomodulation during regeneration: emerging new targets. *J Pers Med*. 2021;*11*(2):85.
29. Opdenakker G, Van Damme J, Vranckx JJ. Immunomodulation as rescue for chronic atonic skin wounds. *Trends Immunol*. 2018;*39*(4):341-354.
30. Sun BK, Siprashvili Z, Khavari PA. Advances in skin grafting and treatment of cutaneous wounds. *Science*. 2014;*346*(6212):941-945.
31. Eming SA, Koch M, Krieger A, et al. Differential proteomic analysis distinguishes tissue repair biomarker signatures in wound exudates obtained from normal healing and chronic wounds. *J Proteome Res*. 2010;*9*(9):4758-4766.
32. Nathan C. Neutrophils and immunity: challenges and opportunities. *Nat Rev Immunol*. 2006;*6*(3):173-182.
33. Wilgus TA. Immune cells in the healing skin wound: influential players at each stage of repair. *Pharmacol Res*. 2008;*58*(2):112-116.
34. Yanez DA, Lacher RK, Vidyarthi A, Colegio OR. The role of macrophages in skin homeostasis. *Pflug Arch Eur J Phy*. 2017;*469*(3–4):455-463.
35. Klicznik MM, Szenes-Nagy AB, Campbell DJ, Gratz IK. Taking the lead–how keratinocytes orchestrate skin T cell immunity. *Immunol Lett*. 2018;*200*:43-51.
36. Park CO, Fu X, Jiang X, et al. Staged development of long-lived T-cell receptor αβ TH17 resident memory T-cell population to *Candida albicans* after skin infection. *J Allergy Clin Immunol*. 2018;*142*(2):647-662.
37. Polak ME, Singh H. Tolerogenic and immunogenic states of Langerhans cells are orchestrated by epidermal signals acting on a core maturation gene module. *Bioessays*. 2021;*43*(5):2000182.
38. Iwamoto K, Moriwaki M, Niitsu Y, et al. *Staphylococcus aureus* from atopic dermatitis skin alters cytokine production triggered by monocyte-derived Langerhans cell. *J Dermatol Sci*. 2017;*88*(3):271-279.
39. Xu Z, Han S, Gu Z, Wu J. Advances and impact of antioxidant hydrogel in chronic wound healing. *Adv Healthc Mater*. 2020;*9*(5):1901502.
40. Brazil JC, Quiros M, Nusrat A, Parkos CA. Innate immune cell–epithelial crosstalk during wound repair. *J Clin Invest*. 2019;*129*(8):2983-2993.
41. Rakita A, Nikolić N, Mildner M, Matiasek J, Elbe-Bürger A. Re-epithelialization and immune cell behaviour in an ex vivo human skin model. *Sci Rep*. 2020;*10*(1):1-11.
42. Kabashima K, Honda T, Ginhoux F, Egawa G. The immunological anatomy of the skin. *Nat Rev Immunol*. 2019;*19*(1):19-30.
43. Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: molecular and cellular mechanisms. *J Invest Dermatol*. 2007;*127*(3):514-525.
44. Cano Sanchez M, Lancel S, Boulanger E, Neviere R. Targeting oxidative stress and mitochondrial dysfunction in the treatment of impaired wound healing: a systematic review. *Antioxidants*. 2018;*7*(8):98.
45. Rosińczuk J, Taradaj J, Dymarek R, Sopel M. Mechanoregulation of wound healing and skin homeostasis. In: Shiffman MA, Low M, eds. *Chronic Wounds, Wound Dressings and Wound Healing*. Switzerland: Springer; 2021:461-477.
46. Simon T, Bromberg JS. Regulation of the immune system by laminins. *Trends Immunol*. 2017;*38*(11):858-871.
47. An B, Lin Y-S, Brodsky B. Collagen interactions: drug design and delivery. *Adv Drug Deliv Rev*. 2016;*97*:69-84.
48. Rankin AL, Mumm JB, Murphy E, et al. IL-33 induces IL-13–dependent cutaneous fibrosis. *J Immunol*. 2010;*184*(3):1526-1535.
49. Fichtner-Feigl S, Strober W, Kawakami K, Puri RK, Kitani A. IL-13 signaling through the IL-13α 2 receptor is involved in induction of TGF-β 1 production and fibrosis. *Nat Med*. 2006;*12*(1):99-106.
50. Groeber F, Holeiter M, Hampel M, Hinderer S, Schenke-Layland K. Skin tissue engineering—in vivo and in vitro applications. *Adv Drug Deliv Rev*. 2011;*63*(4):352-366.
51. Kobsa S, Kristofik NJ, Sawyer AJ, Bothwell ALM, Kyriakides TR, Saltzman WM. An electrospun scaffold integrating nucleic acid delivery for treatment of full-thickness wounds. *Biomaterials*. 2013;*34*(15):3891-3901.
52. Avenue H. Effects of substrate deformability on cell behaviors: elastic modulus versus thickness. *J Mech Med Biol*. 2017;*17*(5):1-14. https://doi.org/10.1142/S0219519417500889
53. Dainichi T, Hanakawa S, Kabashima K. Classification of inflammatory skin diseases: a proposal based on the disorders of the three-layered defense systems, barrier, innate immunity and acquired immunity. *J Dermatol Sci*. 2014;*76*(2):81-89.
54. Hong Y, Chen H-D, Gao X-H. Immunological skin diseases: Boundaries and relationships. *Global Dermatology*, 2014;*1*(1). https://doi.org/10.15761/god.1000102.
55. Sticherling M, Erfurt-Berge C. Autoimmune blistering diseases of the skin. *Autoimmun Rev*. 2012;*11*(3):226-230.
56. Mutasim DF. Autoimmune bullous dermatoses in the elderly. *Drugs Aging*. 2010;*27*(1):1-19.
57. Di Bisceglie MB, Lucchese A, Crincoli V. Pemphigus: the promises of peptide immunotherapy. *Immunopharmacol Immunotoxicol*. 2009;*31*(4):509-515.
58. Ghaedi F, Etesami I, Aryanian Z, et al. Drug-induced pemphigus: a systematic review of 170 patients. *Int Immunopharmacol*. 2021;*92*:107299.
59. Memis I, Andreadis D, Apessos I, Georgakopoulou E, Poulopoulos A. Paraneoplastic autoimmune multi-organ syndrome and oral mucosa involvement: an intriguing disorder. *Cancer Res Front*. 2015;*1*(3):268-279.
60. Papara C, Zillikens D, Sadik CD, Baican A. MicroRNAs in pemphigus and pemphigoid diseases. *Autoimmun Rev*. 2021;*20*(7):102852.
61. Fang H, Li Q, Wang G. The role of T cells in pemphigus vulgaris and bullous pemphigoid. *Autoimmun Rev*. 2020;*19*(11):102661.
62. Schmidt E, Zillikens D. Pemphigoid diseases. *Lancet*. 2013;*381*(9863):320-332.
63. Ludwig RJ, Kalies K, Köhl J, Zillikens D, Schmidt E. Emerging treatments for pemphigoid diseases. *Trends Mol Med*. 2013;*19*(8):501-512.
64. van Beek N, Schulze FS, Zillikens D, Schmidt E. IgE-mediated mechanisms in bullous pemphigoid and other autoimmune bullous diseases. *Expert Rev Clin Immunol*. 2016;*12*(3):267-277.
65. Daniel BS, Murrell DF. Review of autoimmune blistering diseases: the pemphigoid diseases. *J Eur Acad Dermatol Venereol*. 2019;*33*(9):1685-1694.
66. Amber KT, Valdebran M, Kridin K, Grando SA. The role of eosinophils in bullous pemphigoid: a developing model of eosinophil pathogenicity in mucocutaneous disease. *Front Med*. 2018;*5*:201.
67. Abdat R, Waldman RA, de Bedout V, et al. Dupilumab as a novel therapy for bullous pemphigoid: a multicenter case series. *J Am Acad Dermatol*. 2020;*83*(1):46-52.
68. Patel PM, Jones VA, Murray TN, Amber KT. A review comparing international guidelines for the management of bullous pemphigoid, pemphigoid gestationis, mucous membrane pemphigoid, and epidermolysis bullosa acquisita. *Am J Clin Dermatol*. 2020;*21*:1-9.

69. Verheyden MJ, Bilgic A, Murrell DF. A systematic review of drug-associated bullous pemphigoid. *Acta Derm Venereol*. 2020;*100*(8): adv00224.
70. Vanden OM, Twaroski K, Osborn MJ, Wagner JE, Tolar J. Inside out: regenerative medicine for recessive dystrophic epidermolysis bullosa. *Pediatr Res*. 2018;*83*(1):318-324.
71. Cooper TW, Bauer EA. Epidermolysis bullosa: a review. *Pediatr Dermatol*. 1984;*1*(3):181-188.
72. Engineer L, Ahmed AR. Emerging treatment for epidermolysis bullosa acquisita. *J Am Acad Dermatol*. 2001;*44*(5):818-828.
73. Smith BRC, Nyström A, Nowell CJ, et al. Mouse models for dominant dystrophic epidermolysis bullosa carrying common human point mutations recapitulate the human disease. *Dis Model Mech*. 2021;*14* (6):dmm048082.
74. Tang JY, Marinkovich MP, Lucas E, et al. A systematic literature review of the disease burden in patients with recessive dystrophic epidermolysis bullosa. *Orphanet J Rare Dis*. 2021;*16*(1):1-25.
75. Bardhan A, Bruckner-Tuderman L, Chapple ILC, et al. Epidermolysis bullosa. *Nat Rev Dis Primers*. 2020;*6*(1):1-27.
76. Salmi TT. Dermatitis herpetiformis. *Clin Exp Dermatol*. 2019;*44*(7):728-731.
77. Antiga E, Caproni M. The diagnosis and treatment of dermatitis herpetiformis. *Clin Cosmet Investig Dermatol*. 2015;*8*:257.
78. Maglie R, Anitga E, Quintarelli L, et al. Dermatitis herpetiformis: novel perspectives. *Front Immunol*. 2019;*10*:1290.
79. Collin P, Salmi TT, Hervonen K, Kaukinen K, Reunala T. Dermatitis herpetiformis: a cutaneous manifestation of coeliac disease. *Ann Med*. 2017;*49*(1):23-31.
80. Reunala T, Hervonen K, Salmi T. Dermatitis herpetiformis: an update on diagnosis and management. *Am J Clin Dermatol*. 2021;*22*: 329-338.
81. Lee R, Lobo Y, Spelman L. Development of dermatitis herpetiformis in chronic plaque psoriasis. *Case Rep Dermatol*. 2021;*13*(1):141-147.
82. Gofur NRP, Gofur ARP, Gofur RNRP, Kahdina M, Putri HM. Duhring disease, a rare autoimmune disease diagnosis and management: a review article. *Biomed J Sci Tech Res*. 2021;*34*(1):26417-26424.
83. Grosu-Bularda A, Lăzărescu L, Stoian A, Lascăr I. Immunology and skin cancer. *Arch Clin Cases*. 2018;*5*(3):109-119.
84. Rangwala S, Tsai KY. Roles of the immune system in skin cancer. *Br J Dermatol*. 2011;*165*(5):953-965.
85. Schierbeck J, Vestergaard T, Bygum A. Skin cancer associated genodermatoses: a literature review. *Acta Derm Venereol*. 2019;*99* (3):360-369.
86. Angeles CV, Sabel MS. Immunotherapy for Merkel cell carcinoma. *J Surg Oncol*. 2021;*123*(3):775-781.
87. Yoon DS, Lee Y, Ryu HA, et al. Cell recruiting chemokine-loaded sprayable gelatin hydrogel dressings for diabetic wound healing. *Acta Biomater*. 2016;*38*:59-68.
88. Shah SA, Sohail M, Khan S, et al. Biopolymer-based biomaterials for accelerated diabetic wound healing: a critical review. *Int J Biol Macromol*. 2019;*139*:975-993.
89. Chen T-Y, Wen T-K, Dai N-T, Hsu S. Cryogel/hydrogel biomaterials and acupuncture combined to promote diabetic skin wound healing through immunomodulation. *Biomaterials*. 2021;*269*:120608.
90. Wang Y, Beekman J, Hew J, et al. Burn injury: challenges and advances in burn wound healing, infection, pain and scarring. *Adv Drug Deliv Rev*. 2018;*123*:3-17.
91. Rahman MS, Islam R, Rana MM, et al. Characterization of burn wound healing gel prepared from human amniotic membrane and Aloe vera extract. *BMC Complement Altern Med*. 2019;*19*(1):115.
92. Uehara M, Li X, Sheikhi A, et al. Anti-IL-6 eluting immunomodulatory biomaterials prolong skin allograft survival. *Sci Rep*. 2019;*9* (1):1-13.
93. Morgado PI, Aguiar-Ricardo A, Correia IJ. Asymmetric membranes as ideal wound dressings: an overview on production methods, structure, properties and performance relationship. *J Membr Sci*. 2015;*490*:139-151.
94. Gindraux F, Laurent R, Nicod L, et al. Human amniotic membrane: clinical uses, patents and marketed products. *Recent Pat Regen Med*. 2013;*3*(3):193-214.
95. Rowan MP, Cancio LC, Elster EA, et al. Burn wound healing and treatment: review and advancements. *Crit Care*. 2015;*19*(1):243.
96. Li Y, Xia W, Van der Merwe L, Dai W, Lin C. Efficacy of stem cell therapy for burn wounds: a systematic review and meta-analysis of preclinical studies. *Stem Cell Res Ther*. 2020;*11*(1):1-12.
97. Julier Z, Park AJ, Briquez PS, Martino MM. Promoting tissue regeneration by modulating the immune system. *Acta Biomater*. 2017;*53*: 13-28.
98. Zuhriddinovich SK, Anatolevich AA, Raufjanovich KM, Anvarovna NZ. Current aspects in the treatment of burn wounds. *Вопросы науки и образования*. 2020;*13*:93-97.
99. Tampoia M, Giavarina D, Di Giorgio C, Bizzaro N. Diagnostic accuracy of enzyme-linked immunosorbent assays (ELISA) to detect anti-skin autoantibodies in autoimmune blistering skin diseases: a systematic review and meta-analysis. *Autoimmun Rev*. 2012;*12*(2): 121-126.
100. Egu DT, Sigmund AM, Schmidt E, Spindler V, Walter E, Waschke J. A new ex vivo human oral mucosa model reveals that p38 MAPK inhibition is not effective in preventing autoantibody-induced mucosal blistering in pemphigus. *Br J Dermatol*. 2020;*182*(4):987-994.
101. Daoud YJ, Amin KG. Comparison of cost of immune globulin intravenous therapy to conventional immunosuppressive therapy in treating patients with autoimmune mucocutaneous blistering diseases. *Int Immunopharmacol*. 2006;*6*(4):600-606.
102. Has C, South A, Uitto J. Molecular therapeutics in development for epidermolysis bullosa: update 2020. *Mol Diagn Ther*. 2020;*24*(3): 299-309.
103. March OP, Reichelt J, Koller U. Gene editing for skin diseases: designer nucleases as tools for gene therapy of skin fragility disorders. *Exp Physiol*. 2018;*103*(4):449-455.
104. Naso G, Petrova A. Cellular therapy options for genetic skin disorders with a focus on recessive dystrophic epidermolysis bullosa. *Br Med Bull*. 2020;*136*:30-45.
105. Schrom KP, Kim I, Baron ED. The immune system and pathogenesis of melanoma and non-melanoma skin cancer. In: Reichrath J, ed. *Sunlight, Vitamin D and Skin Cancer*. Cham: Springer; 2020: 211-226.
106. Paulson KG, Lahman MC, Chapuis AG, Brownell I. Immunotherapy for skin cancer. *Int Immunol*. 2019;*31*(7):465-475.
107. Borgheti-Cardoso LN, Viegas JSR, Silvestrini AVP, et al. Nanotechnology approaches in the current therapy of skin cancer. *Adv Drug Deliv Rev*. 2020;*153*:109-136.
108. Eggermont LJ, Hammink R, Blank KG, Rowan AE, Tel J, Figdor CG. Cytokine-functionalized synthetic dendritic cells for T cell targeted immunotherapies. *Adv Ther*. 2018;*1*(6):1800021.
109. Centers for Disease Control and Prevention. *National Diabetes Statistics Report: Estimates of Diabetes and its Burden in the United States, 2014*. Atlanta, GA: US Department of Health and Human Services; 2014.
110. Chen H, Cheng R, Zhao X, et al. An injectable self-healing coordinative hydrogel with antibacterial and angiogenic properties for diabetic skin wound repair. *NPG Asia Mater*. 2019;*11*(1):1-12.
111. Alavi A, Sibbald RG, Mayer D, et al. Diabetic foot ulcers: part I. Pathophysiology and prevention. *J Am Acad Dermatol*. 2014;*70*(1): 1-e1.
112. Martins-Mendes D, Monteiro-Soares M, Boyko EJ, et al. The independent contribution of diabetic foot ulcer on lower extremity amputation and mortality risk. *J Diabetes Complications*. 2014;*28*(5): 632-638.
113. Murano I, Barbatelli G, Parisani V, et al. Dead adipocytes, detected as crown-like structures, are prevalent in visceral fat depots of genetically obese mice. *J Lipid Res*. 2008;*49*(7):1562-1568.

114. Stentz FB, Kitabchi AE. Activated T lymphocytes in type 2 diabetes: implications from in vitro studies. *Curr Drug Targets*. 2003;*4*(6):493-503.
115. Rajendran NK, Kumar SSD, Houreld NN, Abrahamse H. A review on nanoparticle based treatment for wound healing. *J Drug Deliv Sci Technol*. 2018;*44*:421-430.
116. Wainstein J, Feldbrin Z, Boaz M, Harman-Boehm I. Efficacy of ozone–oxygen therapy for the treatment of diabetic foot ulcers. *Diabetes Technol Ther*. 2011;*13*(12):1255-1260.
117. Mathur RK, Sahu K, Saraf S, Patheja P, Khan F, Gupta PK. Low-level laser therapy as an adjunct to conventional therapy in the treatment of diabetic foot ulcers. *Lasers Med Sci*. 2017;*32*(2):275-282.
118. Baeyens A, Pérol L, Fourcade G, et al. Limitations of IL-2 and rapamycin in immunotherapy of type 1 diabetes. *Diabetes*. 2013;*62*(9):3120-3131.
119. Luo X, Huang P, Yuan B, et al. Astragaloside IV enhances diabetic wound healing involving upregulation of alternatively activated macrophages. *Int Immunopharmacol*. 2016;*35*:22-28.
120. Caley MP, Martins VLC, O'Toole EA. Metalloproteinases and wound healing. *Adv Wound Care*. 2015;*4*(4):225-234.
121. Singh WR, Devi HS, Kumawat S, et al. Angiogenic and MMPs modulatory effects of icariin improved cutaneous wound healing in rats. *Eur J Pharmacol*. 2019;*858*:172466.
122. Chouhan D, Mandal BB. Silk biomaterials in wound healing and skin regeneration therapeutics: from bench to bedside. *Acta Biomater*. 2020;*103*:24-51.
123. Shariati A, Moradabadi A, Azimi T, Ghaznavi-Rad E. Wound healing properties and antimicrobial activity of platelet-derived biomaterials. *Sci Rep*. 2020;*10*(1):1-9.
124. Kumar SSD, Rajendran NK, Houreld NN, Abrahamse H. Recent advances on silver nanoparticle and biopolymer-based biomaterials for wound healing applications. *Int J Biol Macromol*. 2018;*115*:165-175.
125. Castano O, Pérez-Amodio S, Navarro-Requena C, Mateos-Timoneda MÁ, Engel E. Instructive microenvironments in skin wound healing: biomaterials as signal releasing platforms. *Adv Drug Deliv Rev*. 2018;*129*:95-117.
126. Zarei F, Soleimaninejad M. Role of growth factors and biomaterials in wound healing. *Artif Cells Nanomed Biotechnol*. 2018;*46*:906-911.
127. Wynn TA, Vannella KM. Macrophages in tissue repair, regeneration, and fibrosis. *Immunity*. 2016;*44*(3):450-462.
128. Vishwakarma A, Bhise NS, Evangelista MB, et al. Engineering immunomodulatory biomaterials to tune the inflammatory response. *Trends Biotechnol*. 2016;*34*(6):470-482.
129. Hume PS, He J, Haskins K, Anseth KS. Strategies to reduce dendritic cell activation through functional biomaterial design. *Biomaterials*. 2012;*33*(14):3615-3625.
130. Maitra R, Clement CC, Crisi GM, Cobelli N, Santambrogio L. Immunogenecity of modified alkane polymers is mediated through TLR1/2 activation. *PLoS One*. 2008;*3*(6):e2438.
131. Andorko JI, Jewell CM. Designing biomaterials with immunomodulatory properties for tissue engineering and regenerative medicine. *Bioeng Transl Med*. 2017;*2*(2):139-155.
132. Christo SN, Diener KR, Bachhuka A, Vasilev K, Hayball JD. Innate immunity and biomaterials at the nexus: friends or foes. *Biomed Res Int*. 2015;*2015*:1-23.
133. Christo SN, Bachhuka A, Diener KR, Mierczynska A, Hayball JD, Vasilev K. The role of surface nanotopography and chemistry on primary neutrophil and macrophage cellular responses. *Adv Healthc Mater*. 2016;*5*(8):956-965.
134. Pan Y, Qi Y, Shao N, Tadle AC, Huang Y. Amino-modified polymer nanoparticles as adjuvants to activate the complement system and to improve vaccine efficacy in vivo. *Biomacromolecules*. 2019;*20*(9):3575-3583.
135. Chen Z, Bachhuka A, Han S, et al. Tuning chemistry and topography of nanoengineered surfaces to manipulate immune response for bone regeneration applications. *ACS Nano*. 2017;*11*(5):4494-4506.
136. Liu H, May K. Disulfide bond structures of IgG molecules: structural variations, chemical modifications and possible impacts to stability and biological function. *MAbs*. 2012;*4*:17-23.
137. Srivastava P, Hira SK, Paladhi A, et al. Studies on interaction potency model based on drug synergy and therapeutic potential of triple stimuli-responsive delivery of doxorubicin and 5-fluoro-2-deoxyuridine against lymphoma using disulfide-bridged cysteine over mesoporous silica nanoparticles. *J Mater Chem B*. 2020;*8*(7):1411-1421.
138. Xu X, Chiu J, Chen S, Fang C. Pathophysiological roles of cell surface and extracellular protein disulfide isomerase and their molecular mechanisms. *Br J Pharmacol*. 2021;*178*:2911-2930.
139. Khan TA, Reddy ST. Immunological principles regulating immunomodulation with biomaterials. *Acta Biomater*. 2014;*10*(4):1720-1727.
140. Visalakshan RM, MacGregor MN, Sasidharan S, et al. Biomaterial surface hydrophobicity-mediated serum protein adsorption and immune responses. *ACS Appl Mater Interfaces*. 2019;*11*(31):27615-27623.
141. Pacelli S, Manoharan V, Desalvo A, et al. Tailoring biomaterial surface properties to modulate host-implant interactions: implication in cardiovascular and bone therapy. *J Mater Chem B*. 2016;*4*(9):1586-1599.
142. Roach P, Eglin D, Rohde K, Perry CC. Modern biomaterials: a review—bulk properties and implications of surface modifications. *J Mater Sci Mater Med*. 2007;*18*(7):1263-1277.
143. Chang S, Popowich Y, Greco RS, Haimovich B. Neutrophil survival on biomaterials is determined by surface topography. *J Vasc Surg*. 2003;*37*(5):1082-1090.
144. Giovambattista N, Debenedetti PG, Rossky PJ. Enhanced surface hydrophobicity by coupling of surface polarity and topography. *Proc Natl Acad Sci*. 2009;*106*(36):15181-15185.
145. Yu Y, Wu R-X, Yin Y, Chen F-M. Directing immunomodulation using biomaterials for endogenous regeneration. *J Mater Chem B*. 2016;*4*(4):569-584.
146. Bartneck M, Keul HA, Singh S, et al. Rapid uptake of gold nanorods by primary human blood phagocytes and immunomodulatory effects of surface chemistry. *ACS Nano*. 2010;*4*(6):3073-3086.
147. Padmore T, Stark C, Turkevich LA, Champion JA. Quantitative analysis of the role of fiber length on phagocytosis and inflammatory response by alveolar macrophages. *Biochim Biophys Acta Gen Subj*. 2017;*1861*(2):58-67.
148. Schanen BC, Karakoti AS, Seal S, Drake DR III, Warren WL, Self WT. Exposure to titanium dioxide nanomaterials provokes inflammation of an in vitro human immune construct. *ACS Nano*. 2009;*3*(9):2523-2532.
149. Furlani F, Sacco P, Decleva E, et al. Chitosan acetylation degree influences the physical properties of polysaccharide nanoparticles: implication for the innate immune cells response. *ACS Appl Mater Interfaces*. 2019;*11*(10):9794-9803.
150. Park CJ, Gabrielson NP, Pack DW, Jamison RD, Johnson AJW. The effect of chitosan on the migration of neutrophil-like HL60 cells, mediated by IL-8. *Biomaterials*. 2009;*30*(4):436-444.
151. Mai GT, Seow WK, Pier GB, McCormack JG, Thong YH. Suppression of lymphocyte and neutrophil functions by *Pseudomonas aeruginosa* mucoid exopolysaccharide (alginate): reversal by physicochemical, alginase, and specific monoclonal antibody treatments. *Infect Immun*. 1993;*61*(2):559-564.
152. König B, Friedl P, Pedersen SS, König W. Alginate–its role in neutrophil responses and signal transduction towards mucoid *Pseudomonas aeruginosa* bacteria. *Int Arch Allergy Immunol*. 1992;*99*(1):98-106.
153. Florindo HF, Pandit S, Lacerda L, Gonçalves LMD, Alpar HO, Almeida AJ. The enhancement of the immune response against

S. equi antigens through the intranasal administration of poly-ϵ-caprolactone-based nanoparticles. *Biomaterials*. 2009;*30*(5):879-891.
154. Hao D, Zhang G, Gong Y, Ma Z. Development and biological evaluation of cerium oxide loaded polycaprolactone dressing on cutaneous wound healing in nursing care. *Mater Lett*. 2020;*265*:127401.
155. Zamboni F, Vieira S, Reis RL, Oliveira JM, Collins MN. The potential of hyaluronic acid in immunoprotection and immunomodulation: chemistry, processing and function. *Prog Mater Sci*. 2018;*97*:97-122.
156. Oliveira MI, Santos SG, Oliveira MJ, Torres AL, Barbosa MA. Chitosan drives anti-inflammatory macrophage polarisation and pro-inflammatory dendritic cell stimulation. *Eur Cell Mater*. 2012;*24*(136):133-136.
157. Caires HR, Esteves T, Quelhas P, Barbosa MA, Navarro M, Almeida CR. Macrophage interactions with polylactic acid and chitosan scaffolds lead to improved recruitment of human mesenchymal stem/stromal cells: a comprehensive study with different immune cells. *J R Soc Interface*. 2016;*13*(122):20160570.
158. Koga AY, Pereira AV, Lipinski LC, Oliveira MRP. Evaluation of wound healing effect of alginate films containin g *Aloe vera* (*Aloe barbadensis* Miller) gel. *J Biomater Appl*. 2018;*32*(9):1212-1221.
159. Koga AY, Felix JC, Silvestre RGM, et al. Evaluation of wound healing effect of alginate film containing *Aloe vera* gel and cross-linked with zinc chloride. *Acta Cir Bras*. 2020;*35*:e202000507.
160. Thomas A, Harding KG, Moore K. Alginates from wound dressings activate human macrophages to secrete tumour necrosis factor-α. *Biomaterials*. 2000;*21*(17):1797-1802.
161. Witherel CE, Graney PL, Freytes DO, Weingarten MS, Spiller KL. Response of human macrophages to wound matrices in vitro. *Wound Repair Regen*. 2016;*24*(3):514-524.
162. Yoo Y-J, Oh J-H, Zhang Q, Lee W, Woo KM. Dimethyloxalylglycine-embedded poly (ε-caprolactone) fiber meshes promote odontoblastic differentiation of human dental pulp–derived cells. *J Endod*. 2018;*44*(1):98-103.
163. Schwinté P, Mariotte A, Anand P, et al. Anti-inflammatory effect of active nanofibrous polymeric membrane bearing nanocontainers of atorvastatin complexes. *Nanomedicine*. 2017;*12*(23):2651-2674.
164. Merrell JG, McLaughlin SW, Tie L, Laurencin CT, Chen AF, Nair LS. Curcumin loaded poly (ε-caprolactone) nanofibers: diabetic wound dressing with antioxidant and anti-inflammatory properties. *Clin Exp Pharmacol Physiol*. 2009;*36*(12):1149-1156.
165. van den Berg LM, Cardinaud S, van der Aar AMG, et al. Langerhans cell–dendritic cell cross-talk via langerin and hyaluronic acid mediates antigen transfer and cross-presentation of HIV-1. *J Immunol*. 2015;*195*(4):1763-1773.
166. Leifer CA. Dendritic cells in host response to biologic scaffolds. *Semin Immunol*. 2017;*29*:41-48.
167. Shokouhi B, Coban C, Hasirci V, et al. The role of multiple toll-like receptor signalling cascades on interactions between biomedical polymers and dendritic cells. *Biomaterials*. 2010;*31*(22):5759-5771.
168. Roch T, Kratz K, Ma N, Lendlein A. Inflammatory responses of primary human dendritic cells towards polydimethylsiloxane and polytetrafluoroethylene. *Clin Hemorheol Microcirc*. 2016;*64*(4):899-910.
169. Babensee JE. Interaction of dendritic cells with biomaterials. *Semin Immunol*. 2008;*20*:101-108.
170. Elamanchili P, Diwan M, Cao M, Samuel J. Characterization of poly (D, L-lactic-co-glycolic acid) based nanoparticulate system for enhanced delivery of antigens to dendritic cells. *Vaccine*. 2004;*22*(19):2406-2412.
171. Chen H, Li P, Yin Y, et al. The promotion of type 1 T helper cell responses to cationic polymers in vivo via toll-like receptor-4 mediated IL-12 secretion. *Biomaterials*. 2010;*31*(32):8172-8180.
172. Suraiya AB, Hun ML, Truong VX, Forsythe JS, Chidgey AP. Gelatin-based 3D microgels for in vitro T lineage cell generation. *ACS Biomater Sci Eng*. 2020;*6*(4):2198-2208.
173. Sunshine JC, Green JJ. Nanoengineering approaches to the design of artificial antigen-presenting cells. *Nanomedicine*. 2013;*8*(7):1173-1189.
174. Iranpour S, Nejati V, Delirezh N, Biparva P, Shirian S. Enhanced stimulation of anti-breast cancer T cells responses by dendritic cells loaded with poly lactic-co-glycolic acid (PLGA) nanoparticle encapsulated tumor antigens. *J Exp Clin Cancer Res*. 2016;*35*(1):1-11.
175. Do Y, Nagarkatti PS, Nagarkatti M. Role of CD44 and hyaluronic acid (HA) in activation of alloreactive and antigen-specific T cells by bone marrow-derived dendritic cells. *J Immunother*. 2004;*27*(1):1-12.
176. Moran HBT, Turley JL, Andersson M, Lavelle EC. Immunomodulatory properties of chitosan polymers. *Biomaterials*. 2018;*184*:1-9.
177. Antunes BP, Moreira AF, Gaspar VM, Correia IJ. Chitosan/arginine–chitosan polymer blends for assembly of nanofibrous membranes for wound regeneration. *Carbohydr Polym*. 2015;*130*:104-112.
178. Iacob A-T, Drăgan M, Ghețu N, et al. Preparation, characterization and wound healing effects of new membranes based on chitosan, hyaluronic acid and arginine derivatives. *Polymers*. 2018;*10*(6):607.
179. Fong D, Hoemann CD. Chitosan immunomodulatory properties: perspectives on the impact of structural properties and dosage. *Future Sci OA*. 2018;*4*:FSO225.
180. Carroll EC, Jin L, Mori A, et al. The vaccine adjuvant chitosan promotes cellular immunity via DNA sensor cGAS-STING-dependent induction of type I interferons. *Immunity*. 2016;*44*(3):597-608.
181. Wu N, Wen Z-S, Xiang X-W, Huang Y-N, Gao Y, Qu Y-L. Immunostimulative activity of low molecular weight chitosans in RAW264. 7 macrophages. *Mar Drugs*. 2015;*13*(10):6210-6225.
182. Fong D, Grégoire-Gélinas P, Cheng AP, et al. Lysosomal rupture induced by structurally distinct chitosans either promotes a type 1 IFN response or activates the inflammasome in macrophages. *Biomaterials*. 2017;*129*:127-138.
183. McNab F, Mayer-Barber K, Sher A, Wack A, O'garra A. Type I interferons in infectious disease. *Nat Rev Immunol*. 2015;*15*(2):87-103.
184. Vasconcelos DP, Fonseca AC, Costa M, et al. Macrophage polarization following chitosan implantation. *Biomaterials*. 2013;*34*(38):9952-9959.
185. Gudmundsdottir S, Lieder R, Sigurjonsson OE, Petersen PH. Chitosan leads to downregulation of YKL-40 and inflammasome activation in human macrophages. *J Biomed Mater Res A*. 2015;*103*(8):2778-2785.
186. Xu P, Bajaj G, Shugg T, Van Alstine WG, Yeo Y. Zwitterionic chitosan derivatives for pH-sensitive stealth coating. *Biomacromolecules*. 2010;*11*(9):2352-2358.
187. Lee SW, Park HJ, Pei Y, Yeo Y, Hong S. Topical application of zwitterionic chitosan suppresses neutrophil-mediated acute skin inflammation. *Int J Biol Macromol*. 2020;*158*:1184-1193.
188. Sapru S, Ghosh AK, Kundu SC. Non-immunogenic, porous and antibacterial chitosan and Antheraea mylitta silk sericin hydrogels as potential dermal substitute. *Carbohydr Polym*. 2017;*167*:196-209.
189. Toole BP. Hyaluronan: from extracellular glue to pericellular cue. *Nat Rev Cancer*. 2004;*4*(7):528-539.
190. Lee Y, Sugihara K, Gillilland MG, Jon S, Kamada N, Moon JJ. Hyaluronic acid–bilirubin nanomedicine for targeted modulation of dysregulated intestinal barrier, microbiome and immune responses in colitis. *Nat Mater*. 2019;*19*(1):118-126.
191. Kim H, Cha J, Jang M, Kim P. Hyaluronic acid-based extracellular matrix triggers spontaneous M2-like polarity of monocyte/macrophage. *Biomater Sci*. 2019;*7*(6):2264-2271.
192. Wollina U, Konrad H, Fischer T. Recessive epidermolysis bullosa dystrophicans (Hallopeau-Siemens)—improvement of wound healing by autologous epidermal grafts on an esterified hyaluronic acid membrane. *J Dermatol*. 2001;*28*(4):217-220.
193. Tokatlian T, Cam C, Segura T. Porous hyaluronic acid hydrogels for localized nonviral DNA delivery in a diabetic wound healing model. *Adv Healthc Mater*. 2015;*4*(7):1084-1091.

194. Cowman MK, Lee H-G, Schwertfeger KL, McCarthy JB, Turley EA. The content and size of hyaluronan in biological fluids and tissues. *Front Immunol*. 2015;*6*:261.
195. Jiang D, Liang J, Noble PW. Hyaluronan as an immune regulator in human diseases. *Physiol Rev*. 2011;*91*(1):221-264.
196. Litwiniuk M, Krejner A, Speyrer MS, Gauto AR, Grzela T. Hyaluronic acid in inflammation and tissue regeneration. *Wounds*. 2016;*28*(3):78-88.
197. Termeer C, Benedix F, Sleeman J, et al. Oligosaccharides of Hyaluronan activate dendritic cells via toll-like receptor 4. *J Exp Med*. 2002;*195*(1):99-111.
198. Horton MR, Shapiro S, Bao C, Lowenstein CJ, Noble PW. Induction and regulation of macrophage metalloelastase by hyaluronan fragments in mouse macrophages. *J Immunol*. 1999;*162*(7):4171-4176.
199. Zamboni F, Ryan E, Culebras M, Collins MN. Labile crosslinked hyaluronic acid via urethane formation using bis (β-isocyanatoethyl) disulphide with tuneable physicochemical and immunomodulatory properties. *Carbohydr Polym*. 2020;*245*:116501.
200. Tanaka A, Nagate T, Matsuda H. Acceleration of wound healing by gelatin film dressings with epidermal growth factor. *J Vet Med Sci*. 2005;*67*(9):909-913.
201. Ferriol A, Morán MC. Enhanced performance of gelatin 5-fluorouracil-containing nanoparticles against squamous cell carcinoma in simulated chronic wounds conditions. *Mater Sci Eng C*. 2021;*124*:112073.
202. Yu G, Ye L, Tan W, Zhu X, Li Y, Jiang D. A novel dermal matrix generated from burned skin as a promising substitute for deep-degree burns therapy. *Mol Med Rep*. 2016;*13*(3):2570-2582.
203. Zhao Y-L, Lu Z-Y, Zhang X, et al. Gelatin promotes cell aggregation and pro-inflammatory cytokine production in PMA-stimulated U937 cells by augmenting endocytosis-autophagy pathway. *Int J Biochem Cell Biol*. 2018;*95*:132-142.
204. Zheng Y, Yuan W, Liu H, Huang S, Bian L, Guo R. Injectable supramolecular gelatin hydrogel loading of resveratrol and histatin-1 for burn wound therapy. *Biomater Sci*. 2020;*8*(17):4810-4820.
205. Lynn AK, Yannas IV, Bonfield W. Antigenicity and immunogenicity of collagen. *J Biomed Mater Res B: Appl Biomater*. 2004;*71*(2):343-354.
206. Chang DT, Jones JA, Meyerson H, et al. Lymphocyte/macrophage interactions: biomaterial surface-dependent cytokine, chemokine, and matrix protein production. *J Biomed Mater Res A*. 2008;*87*(3):676-687.
207. Madden LR, Mortisen DJ, Sussman EM, et al. Proangiogenic scaffolds as functional templates for cardiac tissue engineering. *Proc Natl Acad Sci*. 2010;*107*(34):15211-15216.
208. Das A, Fishero BA, Christophel JJ, et al. Poly (lactic-co-glycolide) polymer constructs cross-linked with human BMP-6 and VEGF protein significantly enhance rat mandible defect repair. *Cell Tissue Res*. 2016;*364*(1):125-135.
209. Ali OA, Huebsch N, Cao L, Dranoff G, Mooney DJ. Infection-mimicking materials to program dendritic cells in situ. *Nat Mater*. 2009;*8*(2):151-158.
210. You C, Li Q, Wang X, et al. Silver nanoparticle loaded collagen/chitosan scaffolds promote wound healing via regulating fibroblast migration and macrophage activation. *Sci Rep*. 2017;*7*(1):1-11.
211. Zheng Z, Liu Y, Huang W, et al. Neurotensin-loaded PLGA/CNC composite nanofiber membranes accelerate diabetic wound healing. *Artif Cells Nanomed Biotechnol*. 2018;*46*:493-501.
212. Shin YC, Shin D, Lee EJ, et al. Hyaluronic acid/PLGA core/shell fiber matrices loaded with EGCG beneficial to diabetic wound healing. *Adv Healthc Mater*. 2016;*5*(23):3035-3045.
213. Sun G. Pro-regenerative hydrogel restores Scarless skin during cutaneous wound healing. *Adv Healthc Mater*. 2017;*6*(23):1700659.
214. Kuna VK, Padma AM, Håkansson J, et al. Significantly accelerated wound healing of full-thickness skin using a novel composite gel of porcine acellular dermal matrix and human peripheral blood cells. *Cell Transplant*. 2017;*26*(2):293-307.
215. García-Fernández A, García-Laínez G, Ferrándiz ML, et al. Targeting inflammasome by the inhibition of caspase-1 activity using capped mesoporous silica nanoparticles. *J Control Release*. 2017;*248*:60-70.
216. Jiang Y, Li Y, Li J, et al. A mussel-inspired extracellular matrix-mimicking composite scaffold for diabetic wound healing. *ACS Appl Biomater*. 2020;*3*(7):4052-4061.
217. Ehterami A, Salehi M, Farzamfar S, et al. In vitro and in vivo study of PCL/COLL wound dressing loaded with insulin-chitosan nanoparticles on cutaneous wound healing in rats model. *Int J Biol Macromol*. 2018;*117*:601-609.
218. Dong R-H, Jia Y-X, Qin C-C, et al. In situ deposition of a personalized nanofibrous dressing via a handy electrospinning device for skin wound care. *Nanoscale*. 2016;*8*(6):3482-3488.
219. Wan X, Liu S, Xin X, et al. S-nitrosated keratin composite mats with NO release capacity for wound healing. *Chem Eng J*. 2020;*400*:125964.
220. Harkins AL, Duri S, Kloth LC, Tran CD. Chitosan–cellulose composite for wound dressing material. Part 2. Antimicrobial activity, blood absorption ability, and biocompatibility. *J Biomed Mater Res B Appl Biomater*. 2014;*102*(6):1199-1206.
221. Peng C, Yang M, Chiu W, et al. Composite nano-titanium oxide–chitosan artificial skin exhibits strong wound-healing effect—an approach with anti-inflammatory and bactericidal kinetics. *Macromol Biosci*. 2008;*8*(4):316-327.
222. Wang Z, Gao S, Zhang W, et al. Polyvinyl alcohol/chitosan composite hydrogels with sustained release of traditional Tibetan medicine for promoting chronic diabetic wound healing. *Biomater Sci*. 2021;*9*(10):3821-3829.
223. Tao B, Lin C, Yuan Z, et al. Near infrared light-triggered on-demand cur release from gel-PDA@ cur composite hydrogel for antibacterial wound healing. *Chem Eng J*. 2021;*403*:126182.
224. Majtan J. Honey: an immunomodulator in wound healing. *Wound Repair Regen*. 2014;*22*(2):187-192.
225. Boehler RM, Graham JG, Shea LD. Tissue engineering tools for modulation of the immune response. *Biotechniques*. 2011;*51*(4):239-254.
226. Miguel SP, Sequeira RS, Moreira AF, et al. An overview of electrospun membranes loaded with bioactive molecules for improving the wound healing process. *Eur J Pharm Biopharm*. 2019;*139*:1-22.
227. Huh J-E, Nam D-W, Baek Y-H, et al. Formononetin accelerates wound repair by the regulation of early growth response factor-1 transcription factor through the phosphorylation of the ERK and p38 MAPK pathways. *Int Immunopharmacol*. 2011;*11*(1):46-54.
228. Kim H, Lee S, Ki CS. Modular formation of hyaluronic acid/β-glucan hybrid nanogels for topical dermal delivery targeting skin dendritic cells. *Carbohydr Polym*. 2021;*252*:117132.
229. Yang HS, Shin J, Bhang SH, et al. Enhanced skin wound healing by a sustained release of growth factors contained in platelet-rich plasma. *Exp Mol Med*. 2011;*43*(11):622-629.
230. Mariani E, Lisignoli G, Borzì RM, Pulsatelli L. Biomaterials: foreign bodies or tuners for the immune response? *Int J Mol Sci*. 2019;*20*(3):636.
231. Hotaling NA, Tang L, Irvine DJ, Babensee JE. Biomaterial strategies for immunomodulation. *Annu Rev Biomed Eng*. 2015;*17*:317-349.
232. Spiller KL, Nassiri S, Witherel CE, et al. Sequential delivery of immunomodulatory cytokines to facilitate the M1-to-M2 transition of macrophages and enhance vascularization of bone scaffolds. *Biomaterials*. 2015;*37*:194-207.
233. Penn JW, Grobbelaar AO, Rolfe KJ. The role of the TGF-β family in wound healing, burns and scarring: a review. *Int J Burn Trauma*. 2012;*2*(1):18-28.

234. Johnston CJC, Smyth DJ, Dresser DW, Maizels RM. TGF-β in tolerance, development and regulation of immunity. *Cell Immunol*. 2016; *299*:14-22.
235. Ferguson MWJ, Duncan J, Bond J, et al. Prophylactic administration of avotermin for improvement of skin scarring: three double-blind, placebo-controlled, phase I/II studies. *Lancet*. 2009;*373*: 1264-1274.
236. Yuan TT, Foushee AMD, Johnson MC, Jockheck-Clark AR, Stahl JM. Development of electrospun chitosan-polyethylene oxide/fibrinogen biocomposite for potential wound healing applications. *Nanoscale Res Lett*. 2018;*13*(1):1-12.
237. Wang Z, Qian Y, Li L, et al. Evaluation of emulsion electrospun polycaprolactone/hyaluronan/epidermal growth factor nanofibrous scaffolds for wound healing. *J Biomater Appl*. 2016;*30*(6):686-698.
238. Choi JS, Choi SH, Yoo HS. Coaxial electrospun nanofibers for treatment of diabetic ulcers with binary release of multiple growth factors. *J Mater Chem*. 2011;*21*(14):5258-5267.
239. Norouzi M, Shabani I, Ahvaz HH, Soleimani M. PLGA/gelatin hybrid nanofibrous scaffolds encapsulating EGF for skin regeneration. *J Biomed Mater Res A*. 2015;*103*(7):2225-2235.
240. Chi J, Zhang X, Chen C, Shao C, Zhao Y, Wang Y. Antibacterial and angiogenic chitosan microneedle array patch for promoting wound healing. *Bioactive Mater*. 2020;*5*(2):253-259.
241. Zamecnik CR, Levy ES, Lowe MM, Zirak B, Rosenblum MD, Desai TA. An injectable cytokine trap for local treatment of autoimmune disease. *Biomaterials*. 2020;*230*:119626.
242. Kolumam G, Wu X, Lee WP, et al. IL-22R ligands IL-20, IL-22, and IL-24 promote wound healing in diabetic db/db mice. *PLoS One*. 2017;*12*(1):e0170639.
243. Korkmaz E, Friedrich EE, Ramadan MH, et al. Therapeutic intradermal delivery of tumor necrosis factor-alpha antibodies using tip-loaded dissolvable microneedle arrays. *Acta Biomater*. 2015;*24*: 96-105.
244. Joshi A, Xu Z, Ikegami Y, et al. Exploiting synergistic effect of externally loaded bFGF and endogenous growth factors for accelerated wound healing using heparin functionalized PCL/gelatin co-spun nanofibrous patches. *Chem Eng J*. 2021;*404*:126518.
245. Jimi S, Jaguparov A, Nurkesh A, Sultankulov B, Saparov A. Sequential delivery of Cryogel released growth factors and cytokines accelerates wound healing and improves tissue regeneration. *Front Bioeng Biotechnol*. 2020;*8*:345.
246. Schirmer L, Atallah P, Werner C, Freudenberg U. StarPEG-heparin hydrogels to protect and sustainably deliver IL-4. *Adv Healthc Mater*. 2016;*5*(24):3157-3164.
247. Zhang Y, Li L, Liu Y, Liu Z. PKM2 released by neutrophils at wound site facilitates early wound healing by promoting angiogenesis. *Wound Repair Regen*. 2016;*24*(2):328-336.
248. Catanzano O, Quaglia F, Boateng JS. Wound dressings as growth factor delivery platforms for chronic wound healing. *Expert Opin Drug Deliv*. 2021;*18*:737-759.
249. Lan B, Wu J, Li N, et al. Hyperbranched cationic polysaccharide derivatives for efficient siRNA delivery and diabetic wound healing enhancement. *Int J Biol Macromol*. 2020;*154*:855-865.
250. Zhou D, Gao Y, Aied A, et al. Highly branched poly (β-amino ester) s for skin gene therapy. *J Control Release*. 2016;*244*:336-346.
251. Augustine R, Hasan A, Dalvi YB, et al. Growth factor loaded in situ photocrosslinkable poly (3-hydroxybutyrate-co-3-hydroxyvalerate)/gelatin methacryloyl hybrid patch for diabetic wound healing. *Mater Sci Eng C*. 2021;*118*:111519.
252. Moyers-Montoya ED, Escobedo-González RG, Vargas-Requena CL, Garcia-Casillas PE, Martínez-Pérez CA. Epithelial growth factor-anchored on polycaprolactone/6-deoxy-6-amino-β-cyclodextrin nanofibers: in vitro and in vivo evaluation. *Polymers*. 2021;*13*(8): 1303.
253. Nuutila K, Samandari M, Endo Y, et al. In vivo printing of growth factor-eluting adhesive scaffolds improves wound healing. *Bioactive Mater*. 2021.
254. Laiva AL, O'Brien FJ, Keogh MB. SDF-1α gene-activated collagen scaffold drives functional differentiation of human Schwann cells for wound healing applications. *Biotechnol Bioeng*. 2021;*118*(2): 725-736.
255. Thönes S, Rother S, Wippold T, et al. Hyaluronan/collagen hydrogels containing sulfated hyaluronan improve wound healing by sustained release of heparin-binding EGF-like growth factor. *Acta Biomater*. 2019;*86*:135-147.
256. Liu T, Dan W, Dan N, Liu X, Liu X, Peng X. A novel grapheme oxide-modified collagen-chitosan bio-film for controlled growth factor release in wound healing applications. *Mater Sci Eng C*. 2017;*77*: 202-211.
257. Mohanty C, Pradhan J. A human epidermal growth factor-curcumin bandage bioconjugate loaded with mesenchymal stem cell for in vivo diabetic wound healing. *Mater Sci Eng C*. 2020;*111*:110751.
258. Islam M. Immunomodulators of tissue regeneration and morphogenesis. 2020.
259. Shakya AK, Nandakumar KS. Antigen-specific tolerization and targeted delivery as therapeutic strategies for autoimmune diseases. *Trends Biotechnol*. 2018;*36*(7):686-699.
260. Phan VHG, Duong HTT, Thambi T, et al. Modularly engineered injectable hybrid hydrogels based on protein-polymer network as potent immunologic adjuvant in vivo. *Biomaterials*. 2019;*195*: 100-110.
261. Guillot AJ, Cordeiro AS, Donnelly RF, Montesinos MC, Garrigues TM, Melero A. Microneedle-based delivery: an overview of current applications and trends. *Pharmaceutics*. 2020;*12*(6):569.
262. Bhatnagar S, Dave K, Venuganti VVK. Microneedles in the clinic. *J Control Release*. 2017;*260*:164-182.
263. Patel D, Chaudhary SA, Parmar B, Bhura N. Transdermal drug delivery system: a review. *Pharma Innov*. 2012;*1*(4):66-75.
264. Ye Y, Wang C, Zhang X, et al. A melanin-mediated cancer immunotherapy patch. *Sci Immunol*. 2017;*2*(17):eaan5692.
265. Sivamani RK, Liepmann D, Maibach HI. Microneedles and transdermal applications. *Expert Opin Drug Deliv*. 2007;*4*(1):19-25.
266. Chen M-C, Chen C-S, Wu Y-W, Yang Y-Y. Poly-γ-glutamate microneedles as transdermal immunomodulators for ameliorating atopic dermatitis-like skin lesions in Nc/Nga mice. *Acta Biomater*. 2020; *114*:183-192.
267. Mirzadegan E, Golshahi H, Kazemnejad S. Current evidence on immunological and regenerative effects of menstrual blood stem cells seeded on scaffold consisting of amniotic membrane and silk fibroin in chronic wound. *Int Immunopharmacol*. 2020;*85*:106595.
268. Brennan MÁ, Layrolle P, Mooney DJ. Biomaterials functionalized with MSC secreted extracellular vesicles and soluble factors for tissue regeneration. *Adv Funct Mater*. 2020;*30*(37):1909125.
269. Casado-Díaz A, Quesada-Gómez JM, Dorado G. Extracellular vesicles derived from mesenchymal stem cells (MSC) in regenerative medicine: applications in skin wound healing. *Front Bioeng Biotechnol*. 2020;*8*:146.
270. Hombach AA, Geumann U, Günther C, Hermann FG, Abken H. IL7-IL12 engineered mesenchymal stem cells (MSCs) improve a CAR T cell attack against colorectal cancer cells. *Cell*. 2020;*9*(4):873.
271. Trivanović D, Mojsilović S, Ilić V, et al. Immunomodulatory capacity of human mesenchymal stem cells isolated from adipose tissue, dental pulp, peripheral blood and umbilical cord Wharton's jelly. *Cent Eur J Immunol*. 2013;*38*(4):421-429.
272. Masłowski L, Paprocka M, Czyżewska-Buczyńska A, et al. Autotransplantation of the adipose tissue-derived mesenchymal stromal cells in therapy of venous stasis ulcers. *Arch Immunol Ther Exp (Warsz)*. 2020;*68*(1):1-9.

273. Lataillade JJ, Doucet C, Bey E, et al. New approach to radiation burn treatment by dosimetry-guided surgery combined with autologous mesenchymal stem cell therapy. *Regen Med*. 2007;*2*(5):785-794.
274. Shah K. Mesenchymal stem cells engineered for cancer therapy. *Adv Drug Deliv Rev*. 2012;*64*(8):739-748.
275. Álvaro-Afonso FJ, Sanz-Corbalán I, Lázaro-Martínez JL, Kakagia D, Papanas N. Adipose-derived mesenchymal stem cells in the treatment of diabetic foot ulcers: a review of preclinical and clinical studies. *Angiology*. 2020;*71*(9):853-863.
276. Robert AW, Azevedo Gomes F, Rode MP, Marques da Silva M, Veleirinho MB, Maraschin M, Hayashi L, Wosgrau Calloni G, Stimamiglio MA. The skin regeneration potential of a pro-angiogenic secretome from human skin-derived multipotent stromal cells. *J Tissue Eng* 2019;*10*:1-10.
277. Palakkara S, Maiti SK, Mohan D, et al. Healing potential of chitosan and decellularized intestinal matrix with mesenchymal stem cells and growth factor in burn wound in rat. *Wound Med*. 2020;*30*: 100192.
278. Sun J, Zhang Y, Song X, Zhu J, Zhu Q. The healing effects of conditioned medium derived from mesenchymal stem cells on radiation-induced skin wounds in rats. *Cell Transplant*. 2019;*28*(1):105-115.
279. Tao SC, Guo SC, Li M, Ke QF, Guo YP, Zhang CQ. Chitosan wound dressings incorporating exosomes derived from microRNA-126-overexpressing synovium mesenchymal stem cells provide sustained release of exosomes and heal full-thickness skin defects in a diabetic rat model. *Stem Cells Transl Med*. 2017;*6*:736.
280. Wang C, Wang M, Xu T, et al. Engineering bioactive self-healing antibacterial exosomes hydrogel for promoting chronic diabetic wound healing and complete skin regeneration. *Theranostics*. 2019;*9* (1):65-76.
281. Shi Q, Qian Z, Liu D, et al. GMSC-derived exosomes combined with a chitosan/silk hydrogel sponge accelerates wound healing in a diabetic rat skin defect model. *Front Physiol*. 2017;*8*:904.
282. Fang S, Xu C, Zhang Y, et al. Umbilical cord-derived mesenchymal stem cell-derived exosomal microrna suppress myofibroblast differentiation by inhibiting the transforming growth factor-β/SMAD2 pathway during wound healing. *Stem Cells Transl Med*. 2016;*5*(10): 1425-1439.
283. Marusina AI, Merleev AA, Luna JI, et al. Tunable hydrogels for mesenchymal stem cell delivery: integrin-induced transcriptome alterations and hydrogel optimization for human wound healing. *Stem Cells*. 2020;*38*(2):231-245.
284. Jiang D, Qi Y, Walker NG, et al. The effect of adipose tissue derived MSCs delivered by a chemically defined carrier on full-thickness cutaneous wound healing. *Biomaterials*. 2013;*34*(10):2501-2515.
285. Egaña JT, Fierro FA, Krüger S, et al. Use of human mesenchymal cells to improve vascularization in a mouse model for scaffold-based dermal regeneration. *Tissue Eng Part A*. 2009;*15*(5):1191-1200.
286. Falanga V, Iwamoto S, Chartier M, et al. Autologous bone marrow–derived cultured mesenchymal stem cells delivered in a fibrin spray accelerate healing in murine and human cutaneous wounds. *Tissue Eng*. 2007;*13*(6):1299-1312.
287. Xu Q, Sigen A, Gao Y, et al. A hybrid injectable hydrogel from hyperbranched PEG macromer as a stem cell delivery and retention platform for diabetic wound healing. *Acta Biomater*. 2018;*75*:63-74.
288. Zeng Y, Zhu L, Han Q, et al. Preformed gelatin microcryogels as injectable cell carriers for enhanced skin wound healing. *Acta Biomater*. 2015;*25*:291-303.
289. Yang H, Fierro F, So M, et al. Combination product of dermal matrix, human mesenchymal stem cells, and timolol promotes diabetic wound healing in mice. *Stem Cells Transl Med*. 2020;*9*(11):1353-1364.
290. Ariyanti AD, Zhang J, Marcelina O, et al. Salidroside-pretreated mesenchymal stem cells enhance diabetic wound healing by promoting paracrine function and survival of mesenchymal stem cells under hyperglycemia. *Stem Cells Transl Med*. 2019;*8*(4): 404-414.
291. Riedl J, Pickett-Leonard M, Eide C, et al. ABCB5+ dermal mesenchymal stromal cells with favorable skin homing and local immunomodulation for recessive dystrophic epidermolysis bullosa treatment. *Stem Cells*. 2021;*39*(7):897-903.
292. Xiao S, Xiao C, Miao Y, et al. Human acellular amniotic membrane incorporating exosomes from adipose-derived mesenchymal stem cells promotes diabetic wound healing. *Stem Cell Res Ther*. 2021;*12* (1):1-16.
293. Tang K-C, Yang K-C, Lin C-W, et al. Human adipose-derived stem cell secreted extracellular matrix incorporated into electrospun poly (lactic-co-glycolic acid) nanofibrous dressing for enhancing wound healing. *Polymers*. 2019;*11*(10):1609.
294. Alapure BV, Lu Y, He M, et al. Accelerate healing of severe burn wounds by mouse bone marrow mesenchymal stem cell-seeded biodegradable hydrogel scaffold synthesized from arginine-based poly (ester amide) and chitosan. *Stem Cells Dev*. 2018;*27*(23): 1605-1620.
295. Abo-Elkheir W, Hamza F, Elmofty AM, et al. Role of cord blood and bone marrow mesenchymal stem cells in recent deep burn: a case-control prospective study. *Am J Stem Cell*. 2017;*6*(3):23-35.
296. Zhang Z, Li Z, Li Y, et al. Sodium alginate/collagen hydrogel loaded with human umbilical cord mesenchymal stem cells promotes wound healing and skin remodeling. *Cell Tissue Res*. 2021;*383*(2): 809-821.
297. Heo JS, Kim S, Yang CE, Choi Y, Song SY, Kim HO. Human Adipose Mesenchymal Stem Cell-Derived Exosomes: A Key Player in Wound Healing. *Tissue Engineering and Regenerative Medicine*, 2021. https://doi.org/10.1007/s13770-020-00316-x.
298. Dalirfardouei R, Jamialahmadi K, Jafarian AH, Mahdipour E. Promising effects of exosomes isolated from menstrual blood-derived mesenchymal stem cell on wound-healing process in diabetic mouse model. *J Tissue Eng Regen Med*. 2019;*13*(4):555-568.

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