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Review

Nanomedicine-based immunotherapy for tissue regeneration

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Abstract

Tissue regeneration is essential for repairing and restoring damaged tissues, which has significant implications for clinical outcomes. Understanding the cellular mechanisms and the role of the immune system in this process provides a basis for improved regenerative techniques. The emergence of nanomedicine has advanced this field by introducing nanoscale technology that offer precise control over therapeutic delivery and cellular interactions. By modulating immune responses, various immunotherapeutic approaches, including cytokine therapy and immune checkpoint inhibitors, can establish an optimal environment for tissue repair. This review summarizes recent findings and applications of nanomedicine-based immunotherapy in tissue regeneration. It highlights the properties and advantages of nanomedicine in immunotherapy, discusses recent progress in using nanocomposite biomaterials for tissue engineering, and addresses the challenges and future directions in this evolving field. This review aims to emphasize the promising potential of nanomedicine-based immunotherapy in tissue engineering, thereby contributing to the functional design and strategic development of next-generation nanomedicine for regenerative medicine.

Keywords: Tissue regeneration; Nanomedicine; Immunotherapy; Nanoparticles; Inflammation; Stem cells

Highlights:

- This review summarizes and discusses recent advancements in nanomedicine-based immunotherapy for tissue regeneration.
- It explores the unique properties and advantages of nanomaterials, progress in nanocomposite biomaterials, and future directions in tissue regeneration.
- Emphasizing the transformative potential of nanomedicine-based immunotherapy in tissue engineering, this review aims to guide the design and development of next-generation regenerative therapies.

Background

The field of tissue regeneration has received significant attention in medical research due to its transformative potential for repairing and restoring damaged tissues. At its core, tissue regeneration seeks to replace or regenerate human cells, tissues, or organs to restore normal function. This objective becomes particularly important in cases where natural healing processes fail, such as severe injuries, chronic wounds, and degenerative diseases. Achieving success in this domain needs an extensive understanding of cellular mechanisms and the critical role of the immune system in regulating these processes [1, 2].

The immune system is essential for tissue regeneration, acting as a significant mediator of healing [3, 4]. During the early stages of tissue injury, immune responses activate a cascade of events that clear debris, combat infection, and prepare the site for repair [3–5]. However, this response can be a double-edged sword; while an effective immune reaction promotes regeneration, excessive or prolonged inflammation can hinder the process, leading to fibrosis or scarring [6–8]. Accordingly, modulating the immune response to provide an optimal environment for tissue repair is a critical aspect of regenerative medicine.

Recent developments in nanomedicine have advanced tissue regeneration methods [9, 10]. Nanomedicine, which involves the use of nanoscale materials and technologies for medical purposes, provides more precision in therapeutic delivery and cellular interaction [11]. Nanomaterials are ideal candidates for enhancing tissue repair due to their unique properties, including high surface area-to-volume ratios, variable surface chemistries, and the ability to interact with biological systems at the molecular level [9, 11]. These materials allow for targeted delivery, sustained drug release, and direct cellular regulation, all of which help optimize regenerative processes.

Immunotherapy is a particularly promising area of nanomedicine in tissue regeneration, which uses the immune system to combat diseases and, increasingly, to promote repair [12]. Nanoparticle-based immunotherapeutics can deliver bioactive factors directly to injury sites, minimizing systemic side effects and enhancing local efficacy [13,

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14]. Such precision enables a controlled modulation of immune responses, promoting a pro-regenerative environment. Nanomedicine-based immunotherapy also drives innovation in tissue engineering, specifically by developing nanocomposite biomaterials. These innovative materials combine nanomaterial properties with traditional biomaterials, mimicking the extracellular matrix (ECM) to support cell growth, differentiation, and tissue development.

For instance, nanoparticles can be tailored to deliver cytokines, which are critical modulators of immune response, thereby enhancing immune cell recruitment and activity at injury sites. Additionally, immune checkpoint inhibitors (ICIs) delivered by nanoparticles can reduce excessive inflammation, hence mitigating chronic immune responses that impair regeneration [15, 16]. Smart delivery systems enhance therapeutic precision by responding to injury-specific microenvironmental stimuli, such as pH changes or enzymatic activity, and releasing payloads only when needed [17]. Nanomedicine-based strategies offer solutions to issues in current regenerative medicine, such as poor graft integration, insufficient vascularization, and uncontrolled immune responses. Nanocomposite biomaterials, resembling the ECM, provide a supportive microenvironment for cell proliferation and tissue repair while mitigating immune rejection and chronic inflammation [18]. Engineered nanoparticles that deliver anti-inflammatory agents or immune modulators to injury sites demonstrate this ability to promote healing while avoiding adverse immune reactions [19, 20].

This review summarizes recent advancements in nanomedicine-based immunotherapy for tissue regeneration, focusing on nanomaterial properties and advantages, progress in nanocomposite biomaterials, and future directions in this field. By highlighting these developments, this review aims to emphasize the transformative potential of nanomedicine-based immunotherapy in tissue engineering and guide the design and development of next-generation regenerative therapies.

Review

Tissue regeneration and immunotherapy

Cellular and molecular basis of tissue regeneration

Tissue regeneration is fundamental to the survival of all living things, necessitating dynamic cellular and molecular adaptation to the wound or damaged environment [21]. A better understanding of the cellular and molecular basis of tissue regeneration would lead to better therapeutic strategies for wounds or injuries.

The process of tissue regeneration involves multiple cells, the most important of which may be the stem cells due to their ability to self-renewal and differentiate into various cell types [22]. The two major types of stem cells are pluripotent stem cells (which can differentiate into lineages of all three embryonic germ layers) and multipotent and unipotent stem cells (which have limited differentiation potential), which are both of great significance in tissue regeneration [23]. When an injury or damage occurs, stem cells in situ and/or recruited stem cells from the neighborhood differentiate into specific cell types to repair the defect and secret cytokines to modulate the immune environment [23, 24]. Therefore, activating stem cells or enhancing their function can improve tissue regeneration. For instance, Charles K. F. Chan and his colleagues promoted articular cartilage regeneration by activating skeletal stem cells (SSCs) [25]. They first conducted microfracture surgery to activate SSCs, which have enhanced chondrogenic potential. The activated SSCs were then guided to differentiate into cartilage with localized co-delivery of BMP2 and soluble VEGFR1. In this way, articular cartilage can be effectively and stably reformed.

Additionally, fibroblasts and immune cells such as macrophages, lymphocytes, granulocytes, and so on play vital roles in tissue regeneration. Fibroblasts, generally described as connective tissue cells with the ability to produce and remodel ECM, serve as key contributors to tissue regeneration by synthesizing and depositing new ECM for repair and differentiating into myofibroblasts for wound contracture [26, 27]. Recent studies have implied interactions between fibroblasts and immune cells, especially macrophages, which may also play an essential role in the repair process [28, 29]. Modulating fibroblasts promptly will contribute to better tissue repair. For instance, Wendy F. Liu *et al.* found that gelatin methacrylate (GelMA) crosslinking may shape wound repair by affecting the interactions between fibroblasts and macrophages [30]. Their results revealed that low crosslinked (lo-GelMA) hydrogels improved macrophage phagocytosis and fibroblast infiltration, resulting in regenerative healing, while high crosslinked (hiGelMA) hydrogels resulted in more pro-inflammatory macrophages with increased inflammation and drove tissue fibrosis, resulting in scarring. Immune cells, the basics of the immune response, are indispensable in tissue regeneration, which will be discussed in the next section.

Proteins such as cytokines and signaling pathways are vital for tissue regeneration because they allow cells to exert their functions and communicate with each other. Inflammation occurs shortly after a wound or injury and is characterized by the recruitment of immune cells and the secretion of inflammatory factors such as interleukins (ILs) and tumor necrosis factor (TNF), among others, which leads to cell death, matrix degradation, or increased production of inflammatory factors in positive feedback [3, 31]. Angiogenesis is also indispensable in tissue regeneration, supporting nutrition and oxygen for cells in the wound site. Some proteins have been proven essential to angiogenesis, including platelet-derived growth factors (PDGFs), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) family, and stromal-cell derived factor-1 (SDF-1), regulation of which can modulate angiogenesis to improve tissue regeneration [32, 33]. Recently, Xin Zhang *et al.* introduced a novel superparamagnetic composite hydrogel scaffold (CHS) loaded with VEGF to treat osteoarthritis [34]. They combined glycidyl methacrylate-modified hyaluronic acid and hydroxyapatite (HAp)-Fe_3O_4 microspheres to create the new CHS and then loaded VEGF in it. The results demonstrated that this novel biomaterial effectively fostered the repair of osteochondral defects and cartilage regeneration by promoting the transition of M1 to M2 of Fe_3O_4 and angiogenesis of VEGF.

Role of immune response in tissue healing and regeneration

Generally, the process of tissue regeneration can be divided into four sequential but overlapping stages: Hemostasis, inflammation, repair, and remodeling [35]. When tissue is injured, the immune system responds to damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) released by damaged cells or invading

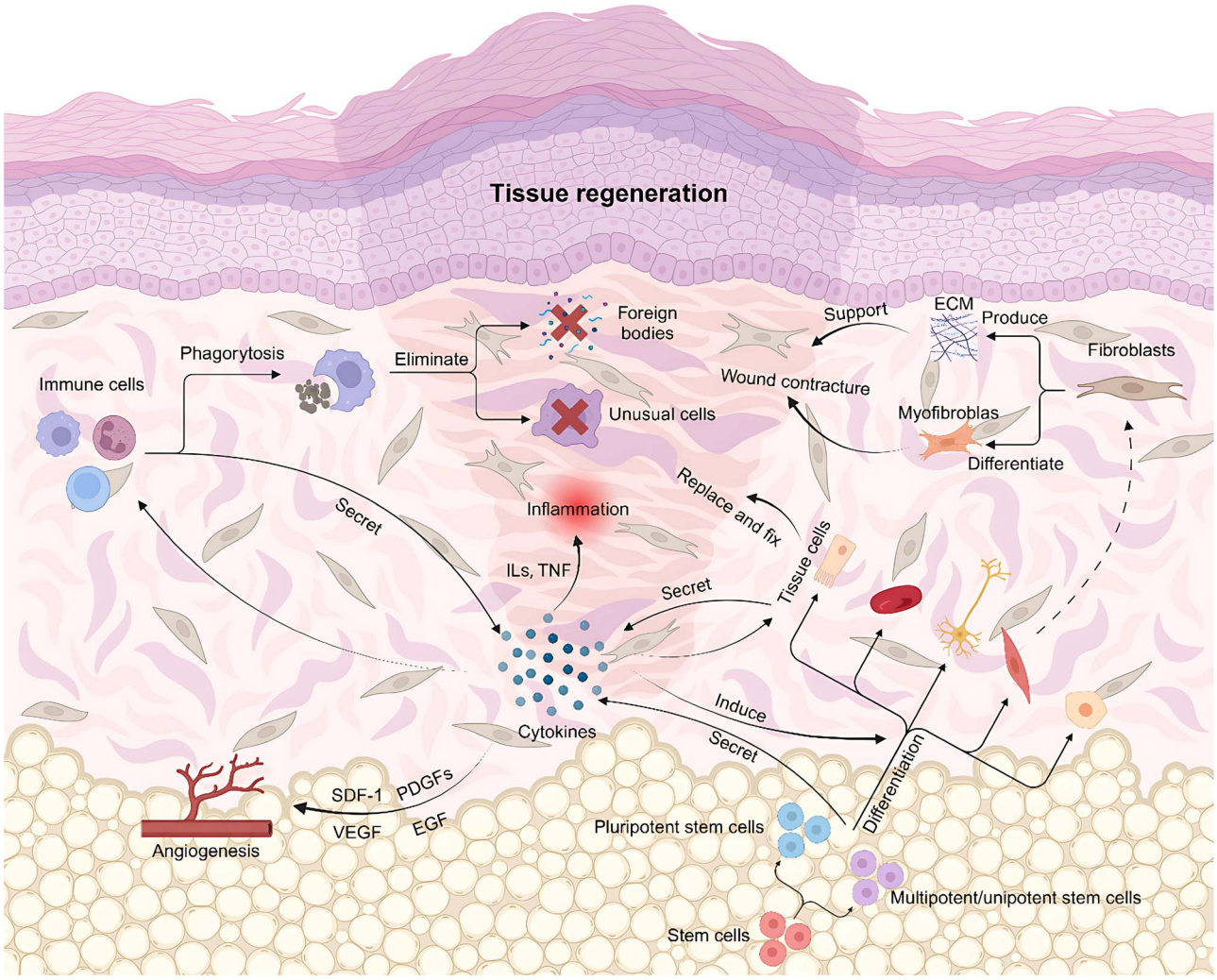

Figure 1. Cellular and molecular basis of tissue regeneration. Multiple cells and molecules are involved in tissue regeneration. These cells, such as stem, tissue, and immune cells, exert their unique functions and interact with each other by secreting some molecules. The balance of these cells and secretion of the molecule is key to the promising outcome of tissue regeneration. *VEGF* vascular endothelial growth factor. The figure was created using BioRender.com

organisms, respectively [36]. The immune response plays a dominating role in the process of tissue regeneration, especially during the inflammation stage, almost determining the outcomes of regeneration. The recruitment and interaction of immune cells and their secretion of cytokine are the key parts of immune response (Figure 1).

Macrophages are among the most important immune cells involved in tissue regeneration. When an injury or damage occurs, macrophages differentiated from the recruited monocytes, accompanied by the tissue-residue ones, are activated to eliminate aberrant cells, debris, and invading organisms or to transform phenotypically and functionally to modulate immune response [37]. The two major and distinct groups of polarized macrophages are M1 macrophages and M2 macrophages. M1 macrophages, induced by DAMPs, PAMPs, interferon-γ (IFN-γ), TNF-α, IL-2, IL-3, and IL-12, produce pro-inflammatory cytokines such as TNF-α and IL-12 in positive feedback, IL-1β, IL-6, C-C motif ligand 2 (CCL2), CCL5, C-X-C motif ligand 9 (CXCL9), and CXCL10, to promote inflammation response to enhance the clearance of unfit bodies. M2 macrophages, induced by transforming growth factor-β (TGF-β), IL-4, IL-10, and IL-13, produce anti-inflammatory cytokines such as TGF-β, IL-4, IL-10, IL-13 in positive feedback, CCL1, CCL17, and CCL18, to repress inflammation and facilitate regeneration [36, 38]. The appropriate polarization and switching of M1 and M2 macrophages are prominent in tissue regeneration; otherwise, repair failure or scarring may occur.

T cells are another important cell type in tissue regeneration, which can be divided into two major groups: $CD4^+$ and $CD8^+$ T cells [39]. $CD4^+$ T cells, also called helper T cells (Th cells), secrete cytokines when activated to regulate immune response. They can be further classified into subgroups such as Th1, Th2, Th17, and regulatory T cells (Tregs) [40]. Th1 secretes pro-inflammatory factors such as IFN-γ, IL-2, and TNF-α to mediate the activation of macrophages. Th2 secretes IL-3, IL-4, IL-5, and others to inhibit inflammation. The balance of Th1 and Th2 is important for homeostasis and tissue regeneration [41]. Th17 expresses a high level of IL-17A, which can recruit other inflammatory factors or chemokines to induce tissue destruction [42]. Tregs have been proven to participate in tissue regeneration, such as bone healing, by suppressing TGFBR1/SMAD2 signaling [43]. Additionally, Tregs can inhibit Th17 in IL-10-dependent ways, preventing

chronic inflammation and regulating the function and secretion of fibroblasts via the production of cytokines such as IL-10 and IL-33 [44, 45]. After activation, $CD8^+$ T cells, also known as cytotoxic T lymphocytes (CTLs), destroy target cells with perforin and granzyme, indicating that they are predominantly involved in adaptive immune response [46]. However, it has been found that $CD8^+$ T cells impair bone regeneration by hampering mesenchymal stem cell (MSC) proliferation and differentiation, indicating its potential role in tissue regeneration [47, 48].

Other immune cells, such as natural killer (NK) cells and dendritic cells (DCs), also play indispensable roles in tissue regeneration. NK cells can recognize foreign bodies and unusual cells and eliminate them at the beginning of tissue repair [49]. Furthermore, NK cells mediate the proliferation and function of stem cells and interact with MSCs to influence tissue regeneration [50, 51]. DCs, on the one hand, direct the differentiation of T cells and modulate macrophages to regulate the immune response of tissue regeneration [52, 53]. On the other hand, the interaction between DCs and tissue cells or MSCs through cytokine production determines the outcomes of tissue repair by regulating their proliferation and differentiation (Figure 2) [54–56].

Role of neutrophils in immune response and tissue repair

Neutrophils, the most abundant type of white blood cell, are key players in both the immune response and tissue healing. They are among the first cells to arrive at the site of tissue injury or infection, having been recruited by a complex array of chemotactic signals, such as cytokines, complement proteins, and DAMPs released from injured tissues [57]. Their primary function in the early stages of injury is pathogen clearance. Neutrophils achieve this through various antimicrobial mechanisms, including the generation of reactive oxygen species (ROS), the release of enzymes such as myeloperoxidase, and the formation of neutrophil extracellular traps, which physically entrap and neutralize pathogens [57]. In addition to defending against infection, neutrophils contribute to tissue homeostasis by phagocytosing dead cells, apoptotic neutrophils, and debris, preventing the release of additional inflammatory mediators that can prolong tissue damage [58]. Neutrophils facilitate the transition from the inflammatory to the repair phase by clearing pathogens and cellular debris, paving the way for tissue regeneration.

Beyond their role in pathogen elimination, neutrophils also participate in the regenerative processes required for tissue repair [59]. These cells secrete various pro-regenerative factors that help orchestrate the healing process. Key cytokines such as IL-1β, IL-6, and TNF-α promote local inflammation, while growth factors like VEGF and the fibroblast growth factor stimulate the proliferation and migration of cells crucial for tissue repair, such as endothelial cells, fibroblasts, and keratinocytes [60]. Neutrophils also release matrix metalloproteinases, which degrade components of the ECM, facilitating the migration of repair cells into the injury site and contributing to wound closure and tissue remodeling. In addition to ECM remodeling, neutrophils support angiogenesis and the formation of new blood vessels through the release of VEGF and other angiogenic factors [57, 58]. This new vascular network is essential for supplying oxygen and nutrients to the regenerating tissue, facilitating the proliferative phase of healing, and ensuring the long-term success of tissue repair.

While neutrophils are necessary for both defense and repair, dysregulated neutrophil activity can have adverse effects on healing results. Excessive neutrophil activation, or the extended presence of neutrophils at the injury site, can lead to chronic inflammation, tissue damage, and fibrosis. The continuous release of ROS, proteases, and pro-inflammatory cytokines can further impair tissue regeneration, prolong wound healing, and increase the formation of chronic wounds [61]. This is most noticeable in conditions where neutrophil activity is unregulated, such as autoimmune diseases, chronic infections, and inflammatory disorders. In contrast, insufficient neutrophil function caused by genetic defects such as chronic granulomatous disease (CGD) or aging-related dysfunction can impair pathogen clearance, extend the inflammatory phase, and hinder tissue repair [62, 63]. For instance, in CGD, neutrophils are unable to produce ROS effectively, increasing susceptibility to infections and delaying healing [63]. Furthermore, dysregulated neutrophil activity can lead to excessive fibrosis. The role of neutrophils in ECM remodeling and matrix deposition can, if unchecked, lead to the development of scar tissue, disrupting normal tissue architecture and impairing function [60, 61].

Types of immunotherapies

Nanomedicine-based immunotherapy uses a variety of strategies to enhance tissue regeneration by modulating the immune system. These strategies include cytokine therapy, ICIs, adoptive cell transfer (ACT), and combination therapies, each offering unique mechanisms to support tissue repair and regeneration [64–66]. Cytokine therapy involves the administration of small proteins known as cytokines, which play important roles in cell signaling and immune response regulation. These proteins can either stimulate or suppress inflammation, depending on their type and context. The goal of cytokine therapy in tissue regeneration is to create a local immune environment conducive to healing [12, 67]. Nanoparticles can be used to deliver pro-regenerative cytokines, such as IL-10 and IL-4, to the injury site. These cytokines help macrophages transition from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype, which promotes tissue repair and reduces fibrosis [20, 67]. Nanoparticles ensure targeted delivery and sustained release of these cytokines, increasing their therapeutic efficacy while reducing systemic side effects. Moreover, growth factors such as VEGF and TGF-β, which are essential for angiogenesis and tissue remodeling, can be incorporated into nanoparticle delivery systems to further support tissue regeneration [12, 66].

Notably, applying ICIs in tissue regeneration represents a novel and rapidly developing field [68, 69]. While primarily used in oncology, recent studies suggest that ICIs may also modulate immune responses in ways that promote tissue repair under certain conditions [70, 71]. In the context of chronic infections, ICIs targeting PD-1 have demonstrated the potential to restore the function of exhausted T cells [72]. This restoration enhances pathogen clearance and reduces inflammation, indirectly supporting tissue repair. In neurodegenerative diseases, PD-1 inhibitors have exhibited promise in facilitating brain repair. A notable study in Alzheimer's disease models demonstrated that PD-1 inhibition reduced cerebral amyloid-β plaques and improved cognitive function in mice [73]. ICIs can affect tissue repair and regeneration in the central nervous system by recruiting macrophages that can remove amyloid-β deposits. Furthermore, emerging evidence

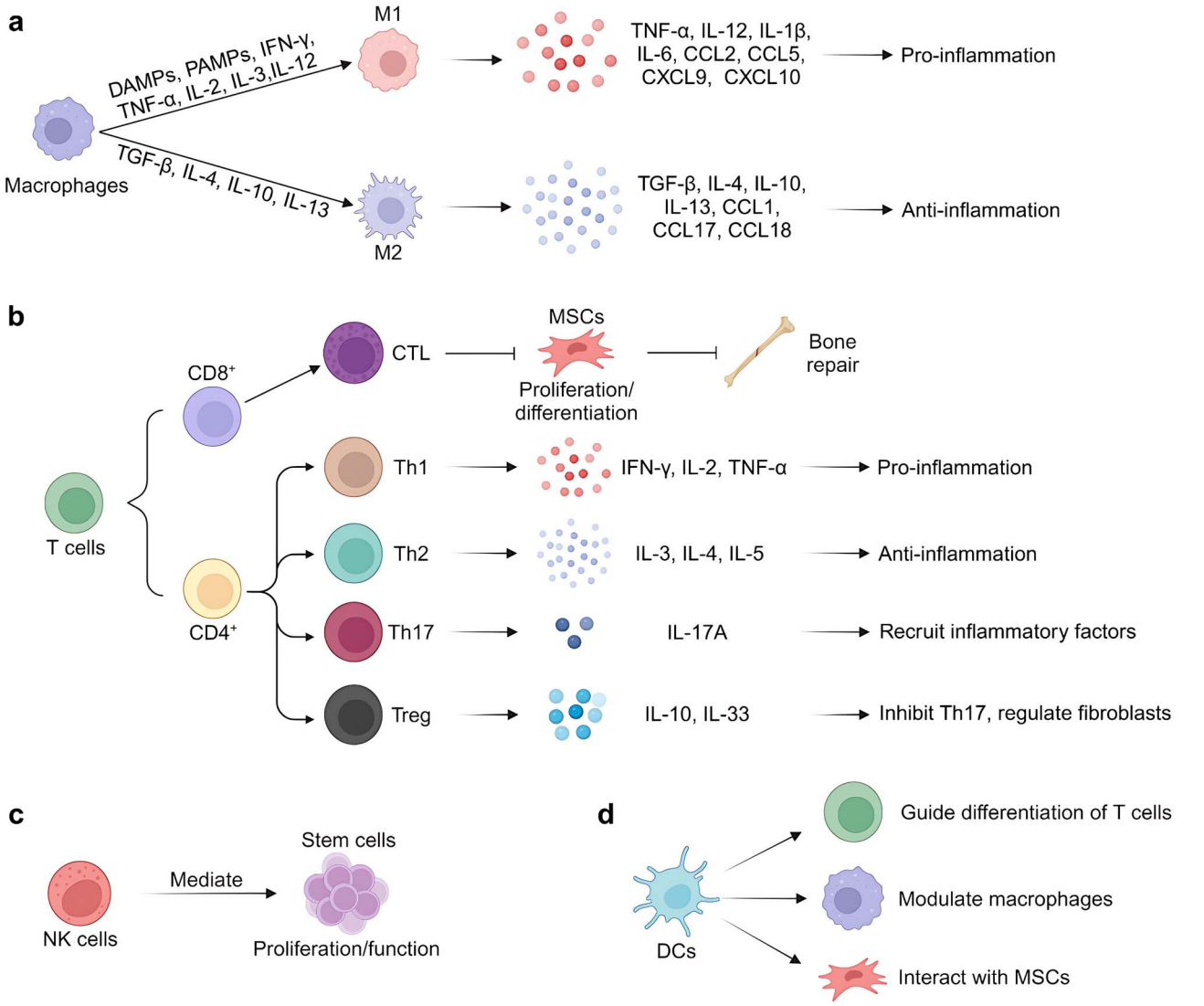

Figure 2. Role of immune cells in tissue regeneration. (**a**) Macrophages differentiate into M1 or M2 under different stimuli to promote or inhibit inflammation. (**b**) T cells can be divided into $CD4^+$ and $CD8^+$ groups. $CD8^+$ transfers into CTL and impairs the proliferation and differentiation of MSCs to hamper bone repair. $CD4^+$ can be further divided into subgroups, which play a role in tissue regeneration by producing diverse cytokines, respectively. (**c**) NK cells mediate the proliferation and function of stem cells to influence tissue regeneration. (**d**) DCs take part in tissue regeneration by guiding the differentiation of T cells, modulating macrophages, and interacting with MSCs. The figure was created using BioRender.com

supports the role of tissue-adapted T cells in repair processes. A recent study identified a distinct tissue-specific state in Vδ1+ T cells defined by PD-1 expression [74]. This subset of T cells may play a role in maintaining tissue homeostasis and regeneration, implying that ICIs can modulate these cells to enhance repair mechanisms. Despite these promising findings, the therapeutic use of ICIs for tissue regeneration remains controversial. Further research is necessary to delineate the mechanisms by which ICIs influence repair processes, to identify specific contexts where they may be beneficial, and to assess potential risks associated with their use in non-cancer settings.

ACT involves the infusion of immune cells that have been engineered or expanded *ex vivo* to improve their regenerative capabilities [75, 76]. This method is very effective in tissue regeneration since the infused cells can directly contribute to the healing process. Nanoparticle-based carriers can deliver genetic material or drugs to these cells, enhancing their therapeutic potential before infusion. ACT provides a targeted approach to immune response modulation and offers personalized treatment options based on individual patient needs [77–79].

Combination therapies that integrate multiple immunotherapy strategies have significant potential to enhance tissue regeneration. For instance, combining cytokine therapy with ICIs can provide a synergistic effect in which cytokines promote a pro-regenerative environment, while checkpoint inhibitors ensure that immune cells remain active and effective in tissue repair [67, 80]. Nanomedicine plays a critical role in combination therapies by providing precise and regulated delivery systems that can simultaneously release numerous therapeutic agents, optimizing their interactions and maximizing their collective therapeutic effects.

Nanomedicine in tissue regeneration

Nanomedicine in tissue regeneration offers novel strategies for enhancing the natural healing processes of the body using the

unique properties of nanoscale materials. In the context of tissue regeneration, nanomedicine enables the direct delivery of drugs, growth factors, and genetic material to injury sites, promoting cell proliferation, differentiation, and tissue repair [81]. Besides, nanoparticles can be engineered to regulate the immune response, reduce inflammation, and create a conducive environment for tissue healing [82, 83]. This targeted approach minimizes systemic side effects while increasing treatment efficacy.

Functional properties of nanomaterials

Nanomaterials have unique properties that make them highly suitable for tissue regeneration applications. One of the most significant properties of nanomaterials is their nanoscale size, which facilitates cellular interactions and uptake. The small dimensions of nanoparticles allow them to closely interact with biological systems at the cellular and molecular levels, resulting in more effective cellular responses. This size advantage enables nanomaterials to penetrate tissues, interact with cell membranes, and even enter cells, thus enhancing therapeutic agent delivery directly to the target sites [84]. For instance, gold nanoparticles can easily cross cell membranes, facilitating intracellular delivery of drugs and bioactive molecules that promote cellular proliferation and differentiation [85].

Another important property of nanomaterials is their high surface area-to-volume ratio, which increases their suitability for tissue regeneration. This high surface area enables a greater density of functional groups on the surface of nanoparticles, which can be used to conjugate diverse bioactive molecules, drugs, and targeting ligands [82]. This property increases the loading capacity of therapeutic agents and also improves their transport efficiency to specific tissues. For instance, liposomes can encapsulate both hydrophilic and hydrophobic drugs, protecting them from degradation and ensuring their sustained release at the site of injury [86].

Tunable surface chemistry is a property that allows nanomaterials to be precisely modified for specific biomedical applications [87]. The interaction of nanomaterials with biological systems can be modified by changing their surface properties, such as charge, hydrophobicity, and functional groups [87]. This customization improves the biocompatibility and targeting capabilities of nanomaterials, making them more effective for tissue regeneration.

Multifunctionality is a unique trait of nanomaterials that allows them to execute numerous roles simultaneously, enhancing their therapeutic potential [88]. Nanomaterials can be designed to deliver medicinal agents, provide structural support, and stimulate cellular responses, all in the same platform. This multifunctionality is particularly beneficial in tissue regeneration, which requires coordinated actions are required to repair and regenerate tissues [89, 90].

Biocompatibility and biodegradability are essential properties for any material used in tissue regeneration. Nanomaterials must be biocompatible to prevent triggering adverse immune responses and enable safe integration with host tissues [91]. Biodegradability is also important because it ensures that the nanomaterials are gradually broken down and removed from the body once they have fulfilled their therapeutic function [92]. Natural polymers such as alginate and gelatin, which are inherently biocompatible and biodegradable, are frequently used to generate nanoparticles that promote tissue regeneration without causing long-term toxicity or inflammatory responses.

Types of nanomaterials used in tissue regeneration

Using nanomaterials in tissue regeneration represents a significant advancement, capitalizing on their unique properties to boost therapeutic efficacy (Table 1).

Metal nanoparticles, including gold, silver, and titanium dioxide, are widely used due to their bioactivity and antimicrobial properties. Gold nanoparticles are notable for their excellent biocompatibility and ability to enhance cellular proliferation and differentiation. They can be functionalized with bioactive molecules to improve interactions with target cells, making them suitable for diverse regenerative applications [93]. However, their high production costs and potential for long-term accumulation in tissues present challenges. Silver nanoparticles are valued for their potent antimicrobial activity, particularly in preventing infections during wound healing [94]. However, their cytotoxicity at higher concentrations necessitates careful dosage control to avoid adverse effects. Titanium dioxide nanoparticles, with their photocatalytic properties, are valuable for light-mediated wound healing. However, their dependency on external light sources limits their application in non-accessible tissue sites [95].

Polymeric nanomaterials, derived from both synthetic and natural sources, provide versatile platforms for tissue repair. Synthetic polymers such as polyethylene glycol (PEG) and polyvinyl alcohol (PVA) are commonly used to create nanoparticles with controlled drug release patterns, ensuring sustained delivery of therapeutic agents. While these polymers enable precise drug delivery, their synthetic origin may elicit inflammatory responses in some circumstances [96]. Natural polymers, such as chitosan, gelatin, and alginate, are highly biocompatible and biodegradable [97]. Chitosan nanoparticles promote collagen synthesis and angiogenesis, which are important processes for tissue repair, although their mechanical properties may need to be improved for load-bearing tissues. Gelatin-based nanoparticles support cell adhesion and proliferation, generating a favorable environment for regeneration; nevertheless, their stability in physiological conditions requires improvement. Alginate nanoparticles are ideal for hydrogel formation, mimicking the ECM, but may require chemical modification to achieve desired mechanical properties.

Lipid-based nanomaterials, such as liposomes and solid lipid nanoparticles (SLNs), are excellent carriers of therapeutic agents. Liposomes, made up of phospholipid bilayers, can encapsulate both hydrophilic and hydrophobic drugs, protecting them from degradation and increasing bioavailability [98]. Their ability to be tailored for targeted delivery improves therapeutic precision, but stability and scalability are still significant challenges. SLNs, with their solid lipid matrices, allow for the controlled release of encapsulated drugs, resulting in sustained therapeutic benefits. Their biocompatibility and low toxicity are advantageous, but their drug-loading capability is relatively limited when compared to other nanomaterials [99].

Carbon nanomaterials, including carbon nanotubes (CNTs) and graphene oxide (GO), are known for their superior mechanical, electrical, and thermal properties. CNTs provide structural support for regenerating tissues while also improving cell adhesion and proliferation, making them ideal for applications such as nerve tissue repair.

Table 1. A summary of the types of nanomaterials for tissue regeneration

Type	Representative examples	Properties	Applications	Ref.
Metal-based nanomaterials	Gold nanoparticles, silver nanoparticles, titanium dioxide nanoparticles	Biocompatibility, antimicrobial activity, photocatalytic properties	Enhance cellular proliferation, prevent infections, promote wound healing under light exposure	[93–95]
Polymeric nanomaterials	PEG, PVA, chitosan, gelatin, alginate	Controlled drug release, biocompatibility, biodegradability	Encapsulate and deliver therapeutic agents, stimulate collagen synthesis, support cell attachment and proliferation, mimic ECM	[96, 97]
Lipid-based nanomaterials	Liposomes, SLNs	Encapsulation of hydrophilic and hydrophobic drugs, controlled release	Targeted delivery of therapeutic agents, sustained drug release, biocompatibility	[98, 99]
Carbon-based nanomaterials	CNTs, GO	Mechanical strength, electrical conductivity, large surface area	Provide structural support, enhance cell adhesion and proliferation, stimulate neuronal growth, facilitate targeted delivery and controlled release, mitigate oxidative stress	[100, 101]
Composite nanomaterials	Combinations of metal-based, polymeric, lipid-based, and carbon-based nanomaterials	Synergistic effects by integrating properties of multiple materials	Enhanced antimicrobial activity, improved cellular response, accelerated wound healing	[102, 103]

However, their potential cytotoxicity and difficulty with biodegradation raise safety concerns [100]. GO, with its large surface area and functionalizable properties, enables targeted drug delivery and controlled release. Furthermore, its antioxidant properties help to reduce oxidative stress, which is a major challenge in tissue repair. However, its long-term biocompatibility and scalability require further investigation [101].

Composite nanomaterials combine the advantages of different nanomaterial types, resulting in synergistic effects that accelerate tissue regeneration. For instance, gold nanoparticles and chitosan composites combine antimicrobial activity with increased cellular responses, promoting rapid wound healing. The ability to customize composite materials to meet specific regenerative needs is a key advantage. However, the complexity of fabrication and the need to balance the properties of individual components present challenges in optimizing their design [102, 103].

Nanomedicine-based immunotherapies for tissue regeneration

Nanoparticles designed for immune modulation are a significant advancement in immunotherapy, offering precise control over immune responses for various therapeutic applications, including cancer, autoimmune diseases, and tissue regeneration [104, 105]. By optimizing parameters such as size, surface charge, and composition, these nanoparticles improve the targeted delivery of immunomodulatory agents, including antigens, cytokines, and drugs, directly to specific cells or tissues, reducing systemic side effects and increasing therapeutic efficacy. Besides, these nanoparticles can be programed to release their therapeutic payload in response to specific physiological stimuli, such as changes in pH or enzymatic activity, ensuring targeted delivery of immune-modulating agents. This controlled release is particularly useful for maintaining immune responses or modulating chronic inflammation [106, 107]. As research evolves, nanoparticle design improves, enabling more precise and effective modulation of immune responses for therapeutic applications.

Nanoparticles for immune modulation

Nanoparticles can modulate immune responses by interacting with different immune cells. Macrophages, for instance, are crucial in the inflammatory response to injury and exist in two main phenotypes: Pro-inflammatory M1 and anti-inflammatory M2 [108]. Effective tissue repair depends on a balanced transition between these phenotypes. Nanoparticles can be engineered to impact macrophage polarization by either delivering agents that promote M2 polarization or directly interacting with macrophages to modify their activity [109]. Prior research has demonstrated that gold nanoparticles, due to their inherent anti-inflammatory properties, can induce M2 polarization of macrophages, reducing inflammation and supporting tissue regeneration [110].

Beyond macrophages, nanoparticles can influence other immune cells, such as DCs and T cells, to shape the entire immune environment. DCs, as antigen-presenting cells, are essential in initiating immune responses [111, 112]. Nanoparticles can be used to deliver specific antigens or immunomodulatory agents, altering dendritic cell function and thereby influencing the adaptive immune response. Similarly, nanoparticles can deliver molecules that activate or suppress T cells, depending on the therapeutic purpose. For instance, nanoparticles can deliver immunosuppressive agents to T cells in cases when immune suppression is necessary to prevent tissue rejection, minimize systemic side effects, and enhance treatment efficacy [113]. In a prior study, Zhou *et al.* proposed a novel strategy to improve tissue regeneration by locally manipulating Tregs, which are essential for modulating the immune microenvironment. The researchers created a multibiologic delivery vehicle by combining poly(l-lactic acid; PLLA) nanofibrous spongy microspheres (NF-SMS), PLLA/PEG co-functionalized mesoporous silica nanoparticles (MSN), and poly(lactic acid-co-glycolic acid) microspheres (PLGA MS). This system is designed to deliver IL-2/TGF-β and miR-10a, which facilitates the recruitment of T cells and their differentiation into Tregs. The PLLA NF-SMS also acts as an injectable scaffold, supporting the adhesion and proliferation of Tregs. In a mouse model of periodontitis,

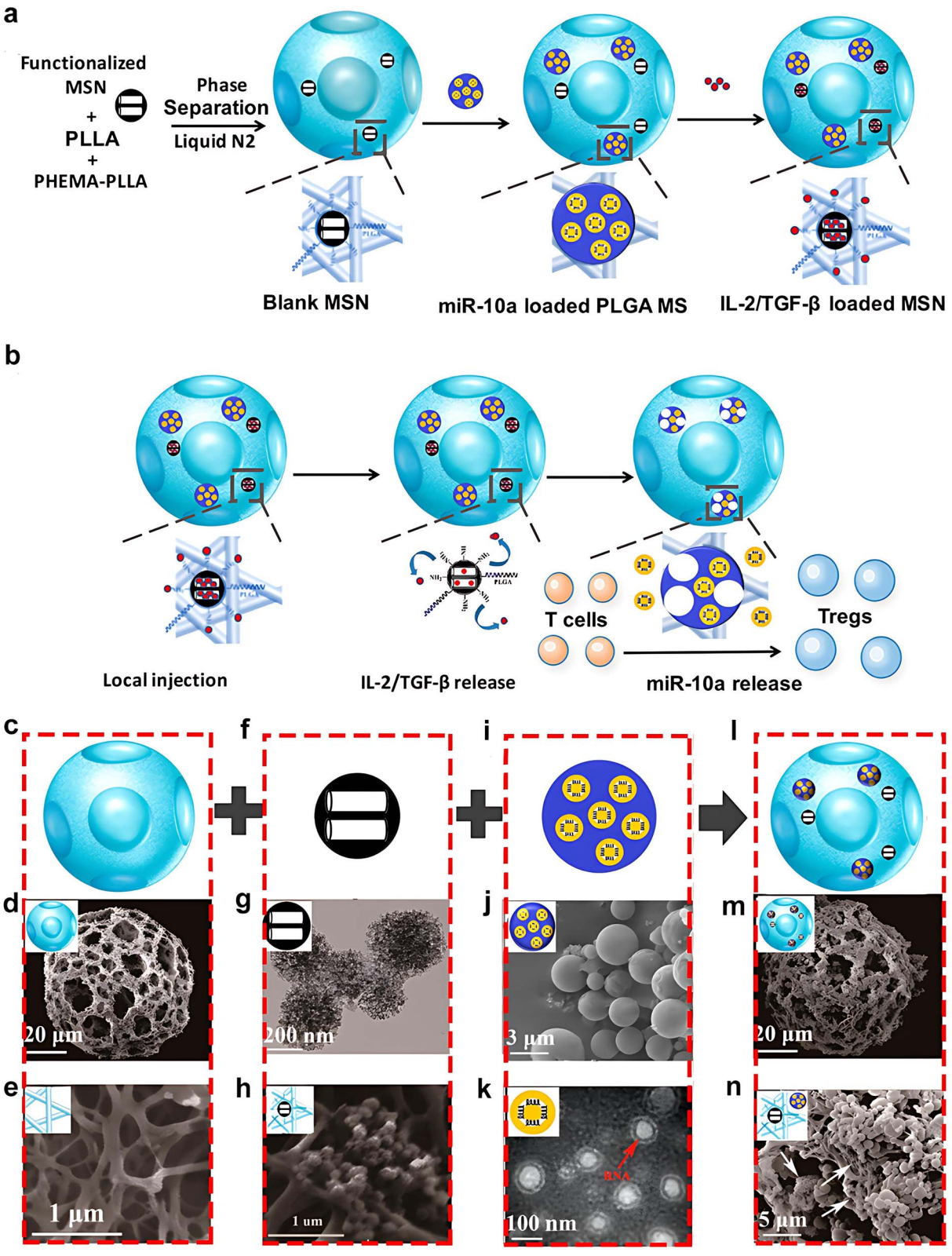

Figure 3. An example of Tregs modulation by nanoparticles. (**a**-**b**) Schematic representation of the fabrication process for multifunctionalized NF-SMS, highlighting their intended release mechanisms and functions. (**c**) Schematic depiction of a PLLA NF-SMS. (**d**) An SEM image of a typical NF-SMS. (**e**) A high-magnification view of the NF-SMS in (d) exhibiting nanofibers with an average diameter of approximately 160 nm. (**f**) Schematic illustration and (**g**) TEM image of MSN, revealing a size of about 300 nm with small pores of around 15 nm. (**h**) A close-up view of the MSN in (g), displaying the MSN attached to the PLLA nanofibers. (**i**) An illustration of microRNA/HP polyplexes loaded into a PLGA microsphere. (**j**) An SEM image of miR-10a/HP polyplexes loaded in PLGA microspheres. (**k**) A TEM image of microRNA encapsulated amino-functionalized multi-armed cationic polymer polyplexes, with a red arrow pointing to the miRNA (dark circle), displaying polyplexes about 100 nm in diameter, sandwiched between inner and outer PEG layers. (**l**) A schematic and (**m**) both schematic and SEM image of MSN and PLGA particles immobilized on PLLA NF-SMS. (**n**) A high-magnification view of MSN clusters (arrows) and PLGA MS on nanofibers. Reproduced with permission [114]. Copyright 2020, American Chemical Society

this delivery system effectively enriched Tregs at the site of inflammation, resulting in a significant reduction in bone loss through Treg-mediated immune modulation [114]. These findings indicate that this approach has potential for broader applications in immunological and regenerative therapies, presenting a promising method for controlled, *in situ* Treg manipulation (Figure 3).

Another innovative application of nanoparticles in immune regulation is their integration with bioactive materials or scaffolds. These hybrid systems can create a localized microenvironment that not only supports tissue growth but also directs the immune response to facilitate healing. For instance, incorporating nanoparticles loaded with anti-inflammatory drugs into hydrogel scaffolds allows for controlled drug release directly at the injury site (Figure 4). This targeted delivery reduces systemic side effects while maintaining therapeutic drug concentrations at the injury site [115–118]. Moreover, nanoparticles can improve the mechanical properties of scaffolds, providing additional support to the regenerating tissue.

Despite their potential, several challenges should be addressed to fully realize the benefits of nanoparticles for immune modulation in tissue regeneration. A major concern is the risk of unexpected immune responses. Although nanoparticles can be tailored to modulate immune activity, there is a possibility that they may cause adverse immune reactions. Factors such as surface properties, including charge and hydrophobicity, can influence interactions with immune cells in unpredictable ways. Consequently, careful design and extensive evaluation of nanoparticles are necessary to reduce the risk of adverse effects while improving therapeutic outcomes.

Nanovaccines for tissue regeneration

Nanovaccines are a transformative development in tissue regeneration, offering novel strategies to trigger and regulate immune responses, hence enhancing healing and repair. Nanovaccines can improve vaccine efficacy and targeting using the unique properties of nanoparticles, facilitating better tissue regeneration [119]. Nanovaccine technology uses nanoparticles to enhance vaccine delivery and effectiveness. Traditional vaccines frequently face issues such as poor antigen stability, inefficient delivery, and suboptimal immune responses [120]. Nanoparticles overcome these problems by acting as carriers, encapsulating and protecting antigens, ensuring stability and controlled release. This approach boosts antigen bioavailability and interaction with the immune system. Furthermore, nanoparticles can be engineered to target specific cells or tissues, increasing the precision of the immune response and reducing unintended effects [120].

One significant advantage of nanovaccines in tissue regeneration is their capability to induce a robust and sustained immune response [121]. Nanoparticles can be designed to include adjuvant agents that enhance the immune response to antigens within their structure. This integration can potentiate the effectiveness of the vaccine by providing a more powerful stimulation of the immune system. For instance, nanovaccines can incorporate toll-like receptor agonists or other immunostimulatory molecules, which activate innate immune pathways and lead to stronger and more durable adaptive immune responses [122]. Such an approach is particularly advantageous in tissue regeneration, where prolonged immune activation is often necessary to support ongoing repair processes.

Nanovaccines can also be customized to target specific components of the immune system involved in tissue regeneration [123]. Nanovaccines can create a balanced immune response that facilitates tissue regeneration by delivering targeted antigens or immunomodulatory factors directly to relevant immune cells. This targeted strategy is essential for conditions requiring precise immune response regulation to avoid excessive inflammation or tissue damage. Chen *et al.* recently presented a novel nanovaccine-based microneedle patch (HVMN) that addresses both skin regeneration and malignant melanoma treatment [123]. Malignant melanoma presents a significant therapeutic challenge due to the persistence of residual tumor cells and severe skin defects after surgical resection. The HVMN patch addresses these issues by incorporating a bioinspired double-layer structure in which HAp and tumor-derived short-chain peptides self-assemble to form a functional nanovaccine (Figure 5). This nanovaccine is then loaded onto microneedle tips, fabricated from methacrylated gelatin (GelMA). The patch demonstrated excellent biocompatibility and immunological activity in a murine model, inhibiting B16 melanoma cell proliferation and inducing apoptosis. Moreover, in a full-thickness skin defect rat model, HVMN facilitated considerable tissue regeneration within 15 days. These findings highlight the potential of the HVMN microneedle patch, which combines anti-tumor and regenerative functions, as a promising strategy for the postoperative treatment of melanoma and skin repair.

Future perspectives

Nanomedicine is advancing the field of immunotherapy for tissue regeneration by developing novel strategies that improve therapeutic efficacy and precision. Major advancements in this field include targeted delivery systems, personalized nanomedicine, and the integration of advanced materials, all of which contribute to better outcomes in tissue repair and regeneration [124, 125].

Targeted delivery systems have become a popular trend in nanomedicine [105, 126]. Nanoparticles can be designed to interact selectively with immune cells or specific tissues involved in the regeneration process. Therapeutic agents can be precisely delivered to their targeted locations by conjugating nanoparticles with antibodies or ligands that bind to receptors on immune cells such as macrophages or DCs. This precision decreases off-target effects while enhancing immunotherapy effectiveness. Such targeted approaches are crucial for regulating chronic inflammation and promoting efficient tissue repair by modulating the immune response more accurately.

Another significant advancement is the emergence of personalized nanomedicine. Developing nanomedicine-based therapies for the unique characteristics of individual patients represents a major leap forward in regenerative medicine [127]. Personalized nanomedicine involves customizing nanoparticle formulations based on the genetic, epigenetic, and immunological profile of the patient. This personalization ensures that treatments are optimized for the specific needs of each patient, enhancing therapeutic efficacy and minimizing potential adverse effects. High-throughput screening and single-cell analysis are increasingly used to gather detailed patient data, facilitating the development of individualized nanomedicine therapies [128].

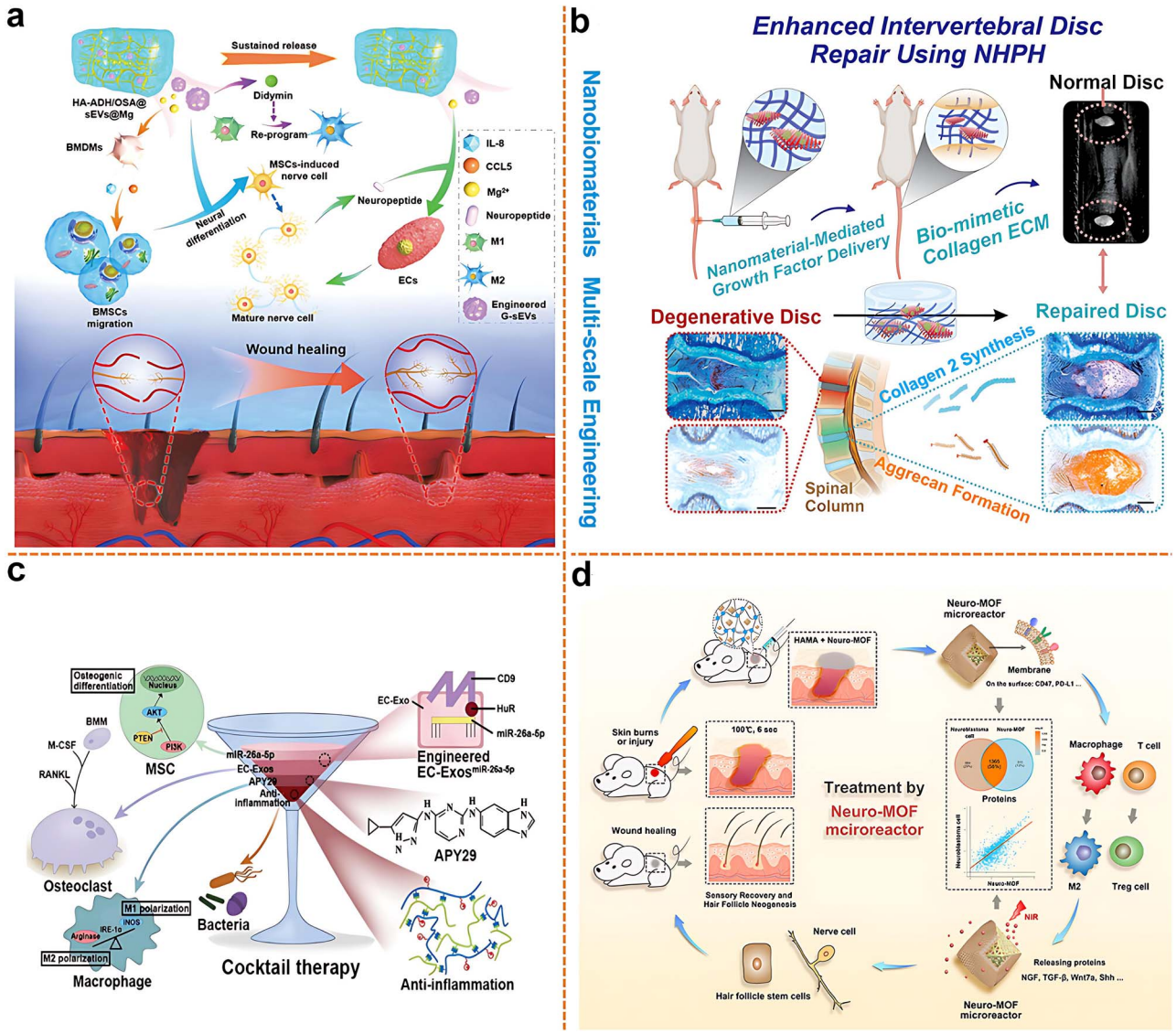

Figure 4. Nanoparticle-based scaffolds for tissue regeneration. (**a**) Engineered extracellular vesicles-loaded hydrogel for diabetic wound healing. Reproduced under the terms of a creative commons attribution 4.0 international license [115]. Copyright 2023, Xiong *et al.* (**b**) An example of nanoparticle-based hydrogel for cartilage regeneration. Reproduced with permission [116]. Copyright 2023, American Chemical Society. (**c**) An example of nanoparticle-based combination therapy for bone regeneration. Reproduced with permission [117]. Copyright 2022, American Chemical Society. (**d**) The application of nanoparticle-based therapy for nerve regeneration. Reproduced with permission [118]. Copyright 2023, American Chemical Society

The incorporation of advanced materials into nanomedicine is also driving progress in immunotherapy [115]. Innovative materials such as functionalized nanoparticles, biodegradable polymers, and stimuli-responsive substances are improving the efficacy of nanomedicine-based treatments. For instance, stimuli-responsive nanoparticles can release therapeutic agents in response to environmental changes such as pH fluctuations or temperature variations, allowing for controlled and localized treatment [84]. Additionally, biodegradable polymers are employed to produce scaffolds that support tissue regeneration while gradually degrading, hence reducing long-term foreign body reactions [129].

Furthermore, the integration of nanomedicine with other emerging technologies, such as gene editing, is creating new possibilities for immunotherapy [130]. Nanoparticles can be designed to deliver gene editing tools, such as CRISPR/Cas9, directly to target cells, allowing for precise genetic modifications that aid in tissue repair and regeneration [131]. This synergy between nanotechnology and gene editing improves the ability to fix genetic abnormalities and improve cellular functioning in regenerative therapies.

However, transitioning nanomedicine-based immunotherapies for tissue regeneration from research to clinical application presents numerous critical challenges that must be addressed to ensure successful implementation. Some limitations are mentioned below:

(i) Safety and biocompatibility are two of the most essential concerns when using nanomedicines clinically. The unique properties of nanoparticles, such as their small size, can cause unanticipated interactions with biological systems, potentially resulting in toxicity or adverse immune responses. Comprehensive preclinical evaluations, including both *in vitro* and *in vivo* studies, are

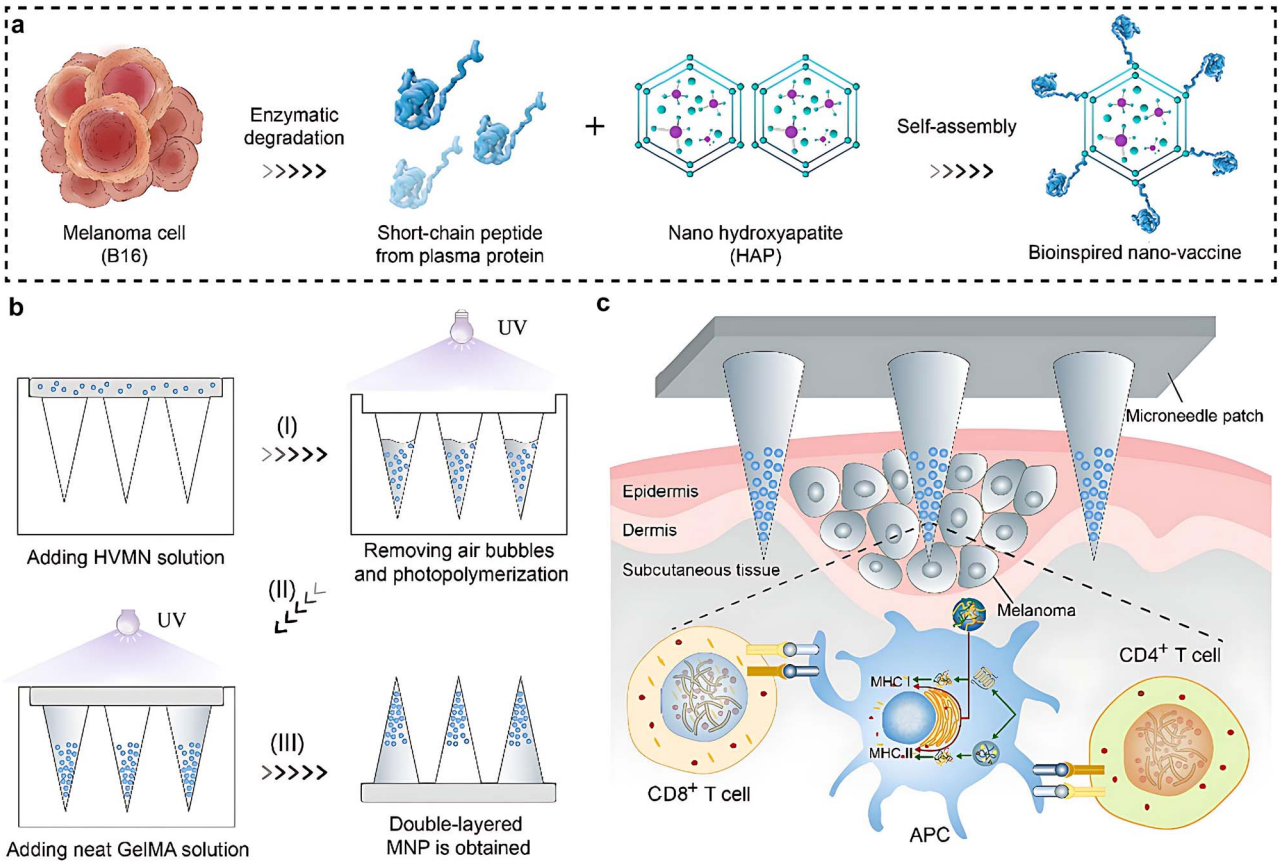

Figure 5. Schematic representation of the design and application of a double-layered MNP. (**a**) A bioinspired nanovaccine was developed through the self-assembly of HAp with short-chain peptides derived from melanoma B16 cells. (**b**) The double-layered MNP was constructed using a mold-casting technique. (**c**) This MNP, possessing both anti-tumor and pro-regenerative properties, is intended for use in postoperative therapy for malignant melanoma. Reproduced with permission [123]. Copyright 2024, Elsevier

essential to detect and mitigate risks. Long-term studies are necessary to monitor any chronic effects and ensure that nanoparticles do not cause undesirable immune reactions or accumulate in organs.

(ii) Optimization of delivery and efficacy is crucial for the success of nanomedicine-based therapies. Nanoparticles must be engineered for precise delivery, controlled release, and interaction with specific cellular or molecular targets to be effective in therapy. This involves fine-tuning nanoparticle design, such as size, surface properties, and release mechanism, to improve therapeutic efficacy while minimizing side effects. Achieving precise control over release kinetics and ensuring efficient cellular uptake is essential for maximizing therapeutic efficacy.

(iii) Designing and executing clinical trials for nanomedicine-based therapies presents specific problems. Trials should be designed comprehensively to assess the safety and efficacy of nanomedicines in humans. This includes determining optimal dose regimens, selecting appropriate endpoints, and identifying suitable patient populations. Advanced analytical techniques and specialized skills are required to accurately analyze the impact of nanomedicines on tissue regeneration and immunological responses.

(iv) The perception and acceptance of the public for nanomedicine-based therapies also influence their clinical use. Effective education of patients and healthcare professionals about the benefits and risks of nanomedicines is essential to garner support and trust. Transparent communication and evidence-based data are required to address concerns and increase acceptance of these advanced therapies.

(v) Integrating with existing therapies is another challenge. Combining nanomedicines with traditional treatment modalities, such as surgery or chemotherapy, necessitates careful consideration of potential interactions and synergies. Developing comprehensive treatment strategies that use nanomedicines while optimizing overall therapeutic approaches is essential for attaining the best clinical outcomes.

Conclusions

To summarize, nanomedicine-based immunotherapy represents a significant development in tissue regeneration, with the potential to significantly improve clinical outcomes. Nanomedicine establishes optimal conditions for effective tissue repair by enabling targeted modulation of immune responses. This review highlighted the substantial progress achieved in using nanomedicine to improve immunotherapeutic strategies, such as cytokine therapy and ICIs, using advanced nanocomposite biomaterials. These innovations provide precise control over the release of therapeutics,

targeted delivery to specific immune cells, and efficient management of the tissue repair environment. Despite these achievements, several important obstacles still exist, such as ensuring safety and biocompatibility, managing complex regulatory requirements, optimizing delivery systems, and scaling up manufacturing processes. Additionally, developing rigorous clinical trials and addressing public perceptions are essential for successful clinical integration. Ongoing research and technological innovation are expected to address these issues and expand the potential applications of nanomedicine in regenerative medicine, resulting in more effective and personalized treatments. As the field progresses, establishing interdisciplinary collaborations will be vital for translating cutting-edge research into practical clinical solutions. Finally, the combination of nanomedicine and immunotherapy has the potential to transform tissue engineering by enhancing both the design and development of next-generation regenerative therapies while also improving patient outcomes.

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Author contributions

Song Li (Data curation [equal], Formal analysis [equal], Software [equal]), Li Lu (Formal analysis [equal], Software [equal]), Yuan Xiong (Conceptualization [lead], Methodology [Lead], Supervision [equal]) and Jun Xiao (Investigation [equal], Project administration [equal], Resources [equal], Supervision [equal])

Conflict of interest

None declared.

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