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Review

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Emerging Strategies for Biomaterials-Mediated Reprogramming of Macrophages in Tissue Repair and Regeneration

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Abstract: Adult tissue repair is often limited, resulting in fibrotic scar formation rather than functional regeneration. Macrophages are central regulators of this process, driving inflammation, tissue formation, and remodeling. Increasing evidence demonstrates that macrophages exhibit substantial heterogeneity and plasticity, transitioning along a continuum of phenotypes in response to evolving microenvironmental cues rather than existing as discrete M1/M2 subsets. This functional diversity reflects their critical role across all stages of tissue repair, from early inflammatory responses to later regenerative and remodeling phases. Recent advances in bioengineering have enabled the development of biomaterial-based strategies to reprogram macrophages and enhance tissue repair. These include the controlled delivery of immunomodulatory biochemical signals, such as cytokines, proteins, and metabolites; the engineering of matrix biophysical properties, including stiffness, viscoelasticity, and topography; and the enhancement of efferocytosis to promote inflammation resolution and tissue homeostasis. These approaches demonstrate that macrophage behavior can be modulated through both biochemical and physical cues to improve regenerative outcomes across diverse tissue contexts. This review summarises current understanding of macrophage heterogeneity and plasticity during tissue repair and highlights emerging biomaterials-driven strategies for macrophage reprogramming, providing a framework for leveraging macrophage function to support effective tissue regeneration.

Keywords: biomaterial; macrophage; tissue regeneration; immunomodulation; reprogramming

1. Introduction

Adult tissue repair after injury exhibits limited regenerative capacity, leading to fibrotic scar tissue that replaces damaged tissue but lacks tissue-specific structures and functionality, particularly in key organs such as the heart, brain, spinal cord, and cartilage [1,2]. While this limitation partly reflects the low proliferative capacity of resident cells, repair outcomes are critically determined by the regulation of immune response following tissue injury [1]. Effective healing and regeneration require a tightly coordinated transition from inflammation to resolution, whereas dysregulation of this process leads to chronic inflammation, fibrosis, or impaired regeneration [3,4]. For

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instance, a persistent pro-inflammatory response leads to sustained tissue damage and impaired healing in chronic wounds [5,6]. Conversely, excessive or prolonged macrophage anti-inflammatory activity can drive fibrosis and scar formation, or lead to non-healing wounds [7].

Macrophages are essential mediators for effective tissue regeneration in all stages of tissue repair by regulating inflammation, promoting tissue formation, and guiding remodelling [8–10]. They exhibit substantial heterogeneity arising from differences in ontogenetic origins, tissue residency, and environmental exposure [10]. In response to injury, both monocyte-derived macrophages (MDMs) and tissue-resident macrophages (TRMs) exhibit plasticity, meaning they can undergo phenotypic/functional switching between polarisation states in response to the dynamically local microenvironmental cues and the transition is reversible [11–14]. The functional plasticity enables macrophages to transition between pro-inflammatory and pro-reparative states, making them critical determinants of healing outcomes [15–17]. Traditionally, macrophage activation has been described using the M1/M2 paradigm, which classifies macrophages into two polarised states: classically activated M1 macrophages and alternatively activated M2 macrophages [18]. M2 macrophages have been further subdivided into M2a, M2b, M2c, and M2d subsets based on their inducing stimuli and functional properties [19–22]. However, this classification remains largely derived from *in vitro* studies and fails to reflect the complexity of macrophage phenotypes observed *in vivo*. Recent advances in single-cell transcriptomics have demonstrated that macrophages exist along a continuum of activation states, shaped by dynamic microenvironmental signals and epigenetic regulation, with M1 and M2 representing two extremes rather than discrete subsets [23,24]. Multiple tissue-specific macrophage populations have also been identified, including subsets associated with inflammatory, degenerative, and reparative functions across tissues such as the skin [25], spinal cord [26], peritoneal membrane [27], arteries [28], atherosclerotic plaques [29], cardiac tissue [30] and skeletal muscle [31], all of which contribute to tissue repair and regeneration.

Given their central role in regulating inflammation and repair, macrophages have emerged as promising therapeutic targets, particularly in cancer therapy [32–34]. However, translational knowledge on targeting macrophages to promote tissue regeneration after injury is limited. Conventional approaches, such as systemic delivery of cytokines or anti-inflammatory drugs, often fail to replicate the dynamic and spatially regulated nature of immune responses during tissue repair. In particular, the precise timing and localisation of macrophage activation states are critical for successful healing, yet remain difficult to control using traditional strategies [35]. By directing macrophages toward desired functional states, it is possible to enhance tissue repair or mitigate disease progression. In this context, bioengineering approaches have gained significant attention. Biomaterials can serve as drug-delivery platforms for the local, programmed delivery of immunomodulatory biomolecules to modulate macrophage polarisation [36–43]. The biophysical properties of the biomaterials can also influence macrophage phenotype through mechanotransduction [44,45]. Furthermore, efferocytosis by macrophages can be enhanced by modulating the recognition process through mimicking apoptotic signals, delivering bridging molecules, and engineering efferocytosis receptors [46–53].

This review summarises the current understanding of macrophage polarisation as a continuum and discusses the mechanisms of plasticity during tissue repair. We consider emerging bioengineering strategies for macrophage reprogramming, highlight how controlled modulation of macrophage function can improve wound-healing outcomes, and outline key challenges and future directions for translating these approaches into clinical applications.

2. Macrophage Heterogeneity and Plasticity during Tissue Repair

2.1. Origins of Macrophages

Macrophages are a highly heterogeneous and plastic cell population that rapidly responds to microenvironmental signalling. Macrophages can be divided into two groups based on their ontogenetic origins: TRMs and MDMs [54,55]. TRMs have a prenatal origin (yolk sac- or fetal liver-derived) and reside in specific organs, exhibiting heterogeneous phenotypes that are specific to the tissue in which they reside [12,30]. They are important for maintaining tissue homeostasis, clearing cell debris, and regulating metabolism and tissue development, such as angiogenesis and fibrosis [10,12,56,57]. In contrast, circulating MDMs originate from the bone marrow and are recruited to the site of injury in response to chemokine and cytokine gradients generated by inflammation [55]. MDMs and TRMs exhibit different gene expression profiles and therefore have distinct roles in wound healing, which will be discussed in a later section [55,58].

2.2. Temporal Phenotypic Changes of Macrophage Populations during Wound Healing

Macrophage phenotypes and functions evolve dynamically across wound healing stages [59–61]. Upon wounding, TRMs are activated by the danger-associated molecular patterns (DAMPs) released by damaged cells

or pathogen-associated molecular patterns (PAMPs) released by invading pathogens, thereby contributing to a pro-inflammatory environment and initiating the inflammatory phase [62]. This results in the rapid influx of additional leukocyte populations, including neutrophils and monocytes, within hours of injury [63]. These recruited monocytes differentiate into MDMs and join the TRM populations, contributing to wound healing [63]. MDMs rapidly dominate the macrophage population due to increased influx and depletion of TRMs, contributing primarily to inflammatory amplification and debris clearance [10,55,64]. In this early inflammatory phase, macrophages predominantly adopt pro-inflammatory, phagocytic M1-like phenotypes, producing cytokines such as tumour necrosis factor alpha (TNF-α), interleukin 1β (IL-1β), and interleukin-6 (IL-6) to clear pathogens, dead cells, and matrix debris [65]. For example, pro-inflammatory CC chemokine receptor 2-expressing (*Ccr2*^{high}) MDMs are closely associated with myocardial inflammation [56,66], and their inhibition enhanced revascularisation following ischemia-reperfusion injury [67]. Similarly, pro-inflammatory *S100a9*^{high}*Ly6c*^{high} MDMs are early responders to tissue injury in the heart [64] and kidney [68], mediating initiation and amplification of inflammation. As healing progresses, macrophage efferocytosis of apoptotic neutrophils promotes a transition towards pro-resolving macrophage phenotypes, assisted by increased oxidative phosphorylation and anti-inflammatory signalling [15,61,65]. Phagocytosis of apoptotic cell debris triggers the release of growth factors, such as vascular endothelial growth factor (VEGF), and anti-inflammatory mediators, including transforming growth factor-beta (TGF-β), interleukin 10 (IL-10), and interleukin-1 receptor antagonist (IL-1Ra), from macrophages [63]. For example, triggering receptor expressed on myeloid cells 2-expressing (*Trem2*^{high}) macrophages expand from day 3 post-myocardial infarction, peaking at 5 days, then gradually decrease. They exhibit anti-inflammatory characteristics, including high expression of anti-inflammatory genes and of arginase 1 (ARG1) and osteopontin, which are related to pro-fibrotic potential [66]. *In vivo* injection of soluble TREM2 has been shown to promote the functional and structural improvements of infarcted hearts [66]. In tendon healing, secreted phosphoprotein 1-expressing (SPP1^{+}) TREM2^{+} MDMs were found 3 days post-injury in the tendon adhesion tissue, exhibiting a pro-fibrotic phenotype by upregulating the mRNA level of collagen type I alpha 1 chain (COL1A1) in fibroblasts [69]. In contrast, folate receptor beta-expressing (FOLR2^{+}) MDMs constitute the dominant macrophage population in normal tendon adhesion tissue and at 12 weeks post-injury [69]. These FOLR2^{+} macrophages exert antifibrotic effects by reducing the mRNA level of COL1A1 in fibroblasts *in vitro* via pathways such as oxidative phosphorylation or the mitogen-activated protein kinase (MAPK) signalling pathway [69]. During the remodelling phase, macrophages ingest cell debris and help degrade excess extracellular matrix (ECM) by secreting matrix metalloproteinases (MMPs) [59]. However, depletion studies suggested that macrophages may play a less critical role during this phase, indicating partial redundancy in tissue remodelling [70].

2.3. Macrophage Population Dynamics during Wound Healing

Changes in macrophage phenotypes during wound healing arise not only from reprogramming of existing macrophages but also from dynamic shifts in population composition mediated by monocyte recruitment, macrophage differentiation, local proliferation, and cellular turnover. Many studies interpret temporal changes as phenotype switching of existing macrophages; however, lineage-tracing studies indicated that different macrophage subsets enter and leave wounds over time. Therefore, an increase in the abundance of a phenotype does not necessarily imply reprogramming.

Recruitment of circulating monocytes is a major mechanism by which macrophage populations are reshaped during tissue repair. The phenotype of recruited monocytes can influence those of the macrophages they subsequently differentiate into [71]. For example, during skin repair, classical Ly6C^{high}CCR2^{+} and non-classical Ly6C^{low}CX3CR1^{+} monocytes sequentially infiltrate the wound site. CCR2^{+} monocytes give rise to pro-inflammatory macrophages that contribute to defence against microorganisms and neo-angiogenesis, while CX3CR1^{+} monocytes are important in wound closure and ECM deposition [72,73]. Nevertheless, the ultimate fate and function of infiltrating monocytes are strongly influenced by local microenvironmental signals [63]. Therefore, the appearance of distinct macrophage phenotypes during wound healing may result from selective recruitment and differentiation of monocyte subsets rather than solely from phenotypic switching of pre-existing macrophages.

In addition to monocyte recruitment, local proliferation of TRMs can substantially contribute to macrophage accumulation and functional specialisation during tissue repair. Although TRMs often represent a minority of the macrophage population after injury, their expansion has been associated with improved regenerative outcomes. For example, neonatal heart repair following myocardial infarction is characterised by expansion of cardiac CCR2^{-} TRMs through local proliferation, whereas the adult heart predominantly recruits CCR2^{+} monocytes and MDMs, resulting in cardiomyocyte hypertrophy and interstitial fibrosis [55]. These different healing outcomes are attributed to the reparative nature of CCR2^{-} cardiac TRMs, which promote tissue regeneration while triggering

minimal inflammatory response, compared with the predominantly inflammatory activity of the recruited $CCR2^+$ MDMs [55,74]. Further studies demonstrated that the reparative TRMs can be characterised by the co-expression of genes such as T-cell immunoglobulin and mucin domain-containing protein 4 (*Timd4*), lymphatic vessel endothelial, hyaluronan receptor 1 (*Lyve1*), *Folr2*, and insulin-like growth factor 1 (*Igf1*), which are not expressed in recruited MDMs [58]. These findings suggest that expansion of the TRMs can directly influence wound healing outcomes and contribute to the emergence of reparative macrophage phenotypes during tissue repair.

Together, these findings highlight that macrophage heterogeneity during wound healing is governed by both phenotypic plasticity and population dynamics. Therefore, temporal changes in macrophage phenotypes should be interpreted as the combined result of activation-state transitions, selective monocyte recruitment, local macrophage proliferation, and population turnover. The complexity and context-dependent nature of macrophage heterogeneity pose significant challenges for traditional therapies, which often cannot precisely regulate macrophage behaviour across different locations and times [35]. This has increased interest in bioengineering methods that mimic essential features of the tissue microenvironment and influence macrophage activity. By combining biochemical, mechanical, and structural signals, these strategies provide a promising approach to leverage macrophage plasticity for regenerative medicine.

3. Emerging Bioengineering Strategies for Macrophage Reprogramming

Owing to their plasticity, macrophages can be reprogrammed to acquire the desired phenotype/function to enhance tissue repair and regeneration. Rather than a binary switch, macrophage reprogramming often produces intermediate or hybrid phenotypes [75]. This section summarises novel bioengineering strategies to induce macrophage reprogramming to enhance tissue repair and regeneration, including the use of biomaterials for programmed delivery of immunomodulatory bioactive molecules, modulation of substrate physical properties, and enhancement of efferocytosis. While macrophage heterogeneity goes beyond the traditional M1/M2 classification, many biomaterial immunomodulation studies still rely on a narrow range of M1- and M2-related markers. This reliance may overlook diverse macrophage states induced by biomaterials, highlighting the need for more comprehensive approaches to characterising macrophage heterogeneity.

3.1. Programmed Delivery of Immunomodulatory Biochemical Signals via Biomaterials

Biomaterials, including fibrous scaffolds [36], porous scaffolds [37,38], hydrogels [39,40], and micro- and nanoparticles [41–43], can serve as versatile platforms for the controlled delivery of bioactive molecules to modulate macrophage polarisation. These immunomodulatory cues include cytokines [36], magnesium ions (Mg^{2+}) [38], bioactive proteins [76], extracellular vesicles (EVs) [77], and metabolic intermediates of macrophage activation [40]. The cytokine interleukin-4 (IL-4) is widely used to promote M2-like polarisation and has been incorporated into diverse biomaterials, such as silk films [36], hyaluronic acid particles [41], gellan gum beads [78], and gold nanoparticles [43]. These systems consistently enhanced M2-associated marker expression *in vitro* [36,41,78] and improved tissue regeneration outcomes, including bone repair [78] and muscle repair [43] *in vivo*. Co-delivery strategies, such as nanogels delivering IL-4 and IL-10, further modulated inflammatory signalling and macrophage phenotype, although they still lack temporal precision [79]. Magnesium-based systems also exhibit strong immunomodulatory effects. Magnesium-loaded fibrinogen scaffold suppressed nuclear factor kappa B (NF-κB) signalling pathway, reduced pro-inflammatory cytokine secretion, and promoted M2 polarisation both *in vitro* and *in vivo* [38]. Similarly, Mg^{2+}-crosslinked alginate hydrogels enabled transient release of Mg^{2+}, thereby modulating cytokine profiles by decreasing IL-1β and increasing interleukin-8 (IL-8) *in vivo* [39]. Macrophage phenotype can also be modulated via the delivery of bioactive proteins [76] and EVs [77]. For example, a tropoelastin/polyglycerol sebacate (PGS) scaffold enhanced M2-associated markers and IL-10 production *in vitro* and increased the M2-like macrophages *in vivo,* generating a pro-healing environment that enhances full-thickness wound repair and regeneration [76]. Similarly, gelatin methacryloyl (GelMA) hydrogels comprising bioactive glass-elicited mesenchymal stem cell (MSC)-derived EVs enabled sustained EV release and induced an M1-to-M2 phenotypic shift, thereby enhancing angiogenesis and tendon regeneration *in vivo* [77].

To further improve specificity and efficacy, targeted delivery systems utilising cell membrane-coated nanoparticles have been developed that enable immune evasion, prolonged blood circulation, and homologous targeting [80,81]. For example, hybrid membrane nanovesicles, fused from membranes derived from induced pluripotent stem cell-derived endothelial cells and M1 macrophages, were embedded in GelMA hydrogels and could deliver the anti-inflammatory metabolite 4-octyl itaconate (4OI) to both M1 macrophages and endothelial cells [40]. By inhibiting glycolysis through suppression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH),

4OI reduced macrophage pro-inflammatory activation and enhanced vascularisation and tissue repair, particularly in diabetic wound models [40].

Despite these advances, most systems rely on single or simultaneous delivery of bioactive factors, producing relatively static macrophage phenotypes that do not reflect the dynamic progression of tissue repair. As discussed above, macrophages transition from an early pro-inflammatory state (M1-like) to a later pro-reparative (M2-like) phenotype, a shift that is essential for coordinated angiogenesis and tissue regeneration. Additionally, macrophages release stage-specific growth factors that regulate blood vessel formation and tissue repair [82,83], and premature suppression of inflammation can disrupt this sequence and impair healing [16]. Therefore, sequential and programmable delivery systems that provide temporal control of macrophage polarisation are more effective in enhancing wound healing. These systems utilise macrophage plasticity by delivering distinct signals at defined stages using different release mechanisms (Figure 1). For example, physisorbed interferon-gamma (IFN-γ) on the surface of a decellularised bone scaffold enables rapid early release to induce M1-like activation, while covalently bound IL-4 provides sustained release to promote M2-like polarisation [83]. This sequential delivery drives time-dependent changes in macrophage gene expression *in vitro* [83]. Similarly, a composite polycaprolactone (PCL)/poly(lactic-*co*-glycolic acid) (PLGA) scaffold incorporating surface-bound lipopolysaccharide (LPS) and delayed-release strontium ions induced early M1 macrophage recruitment, followed by reprogramming into an M2-like phenotype *in vivo*, thereby enhancing neovascularisation and osteogenesis [84].

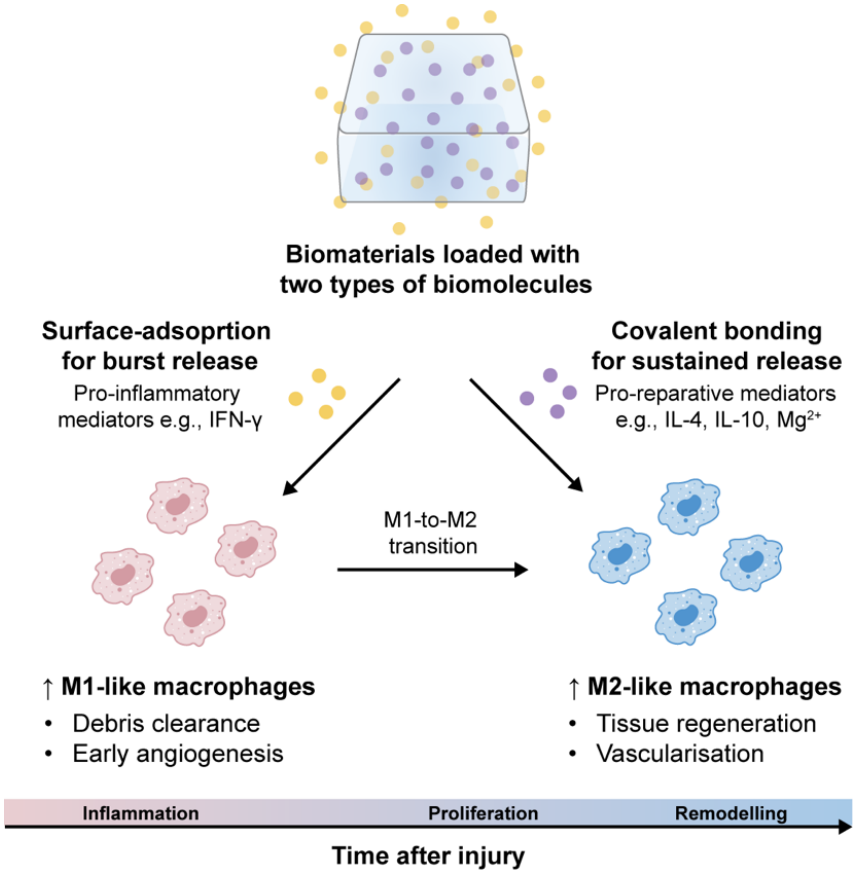

Figure 1. Programmed delivery of immunomodulatory biomolecules for a temporal control of macrophage polarisation.

Overall, these studies demonstrate that effective macrophage modulation requires not only selecting appropriate bioactive signals but also precise control over their spatial and temporal presentation. For these reasons, future strategies should focus on dynamically responsive systems that adapt to the evolving tissue microenvironment, enabling coordinated and context-specific regulation of macrophage function during tissue repair.

3.2. Engineered Matrix with Immunomodulatory Biophysical Cues

In addition to biochemical signals, biomaterials also present a range of inherent biophysical cues, including mechanical properties and topographical features that are sensed by macrophages through an integrated mechanosensing system such as integrin-mediated interactions [85], cytoskeletal remodelling [86,87], mechanosensitive ion channels (e.g., Piezo1) [88], and nuclear sensing pathways [89]. By altering the biophysical

properties of biomaterials, such as stiffness, viscoelasticity, topography, degradability, and architecture, macrophages can be modulated to desired phenotypes to enhance wound healing.

Substrate stiffness is a key regulator of macrophage polarisation. Studies have shown that the stiffness of distinct substrates exhibits contrasting effects on macrophage polarisation. Most *in vitro* studies have shown that soft substrates (typically < 150 kPa) favour anti-inflammatory M2-like macrophage polarisation, characterised by increased expression of markers such as CD206 and Arg1 [44,90,91], even under pro-inflammatory stimulation (e.g., LPS and IFN-γ) [92] (Figure 2a). In contrast, stiffer substrates (>300 kPa) generally promote M1-like polarisation, with elevated expression of TNF-α, IL-1β, IL-6, and inducible nitric oxide synthase (iNOS) [86,92–95]. Consistent with these results, *in vivo* studies demonstrated that softer poly(ethylene glycol)-based hydrogels (e.g., 130 kPa) reduced foreign body reaction and limited macrophage recruitment compared to stiffer counterparts (e.g., 240 kPa or 840 kPa) after 28 days of implantation [93]. Mechanistically, stiff substrates activate mechanosensitive pathways, such as the Piezo1-Yes-associated protein (YAP) signalling axis, thereby promoting M1-like polarisation while suppressing M2-like phenotypes [91,94]. In contrast, soft substrates induce peroxisome proliferators-activated receptor γ (PPAR-γ) expression in activated macrophages [90], which dampens inflammatory signalling pathways by inhibiting activator protein-1 (AP-1), NF-κB, and signal transducers and activators of transcription 3 (STAT-3) [44,96,97]. However, opposing trends have been reported in substrates with stiffness below 100 kPa. For example, very soft polyacrylamide substrates (~2.5 kPa) could promote M1-like polarisation of bone-marrow-derived macrophages, possibly through enhanced NF-κB signalling, while moderately stiff substrates (64 kPa) favoured an M2-like polarisation [98]. In a mouse subcutaneous implantation model after 14 days of implantation, very soft substrates (~2.5 kPa) have been associated with increased infiltration of pro-inflammatory macrophages surrounding the implant, whereas intermediate (35 kPa and 64 kPa) substrates favoured M2-like populations [98]. These discrepancies likely arise from differences in experimental conditions, including macrophage source (e.g., THP-1-derived vs. bone marrow-derived), substrate composition and surface functionalization, dimensionality (2D vs. 3D), study duration, and the *in vivo* model systems. Furthermore, although macrophages initially interact with the surface of implanted biomaterials [99], they are subsequently exposed to a complex 3D mechanical environment complicated by matrix structure, degradation, and cell-matrix interactions, which can substantially influence stiffness-dependent responses. Therefore, future studies should investigate a wider range of substrate stiffness and its effects on temporal changes in macrophage populations across multiple animal models.

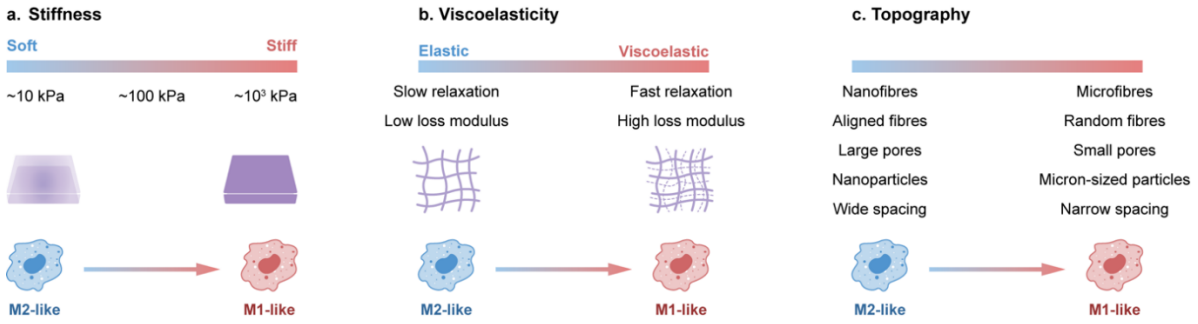

Figure 2. Influence of physical properties of biomaterials (a. Stiffness; b. Viscoelasticity; c. Topography) in macrophage polarisation.

Viscoelasticity refers to the time-dependent, energy-dissipative mechanical behavior in which both elastic and viscous responses are present, and it is an inherent characteristic of biological tissues [100]. Recent studies showed that substrate viscoelasticity is also a key regulator of macrophage behaviour [45]. In particular, more elastic substrates, with slow stress-relaxation and low loss modulus, generally promote a pro-inflammatory M1-like phenotype [101] (Figure 2b). In contrast, more viscoelastic materials, with fast stress-relaxation and high loss modulus, favour a more pro-reparative macrophage phenotype, evidenced by enhanced cell spreading [102], elevated TGF-β1 secretion, increased osteogenesis and a metabolic shift from glycolysis to oxidative phosphorylation via vasodilator-stimulated phosphoprotein (VASP)/hypoxia-inducible factor 1 alpha (HIF1α) signalling [101,103].

Topographical features of biomaterials, including fibre diameter [104,105], fibre alignment [85,106], pore size [105,107–109], particle size [42] and micropatterned substrate's spacing [110,111] as well as pillar size and micropillar density [112], also influence macrophage morphology and elasticity, providing further control over macrophage behavior and repair outcomes [113] (Figure 2c). Nanofibrous scaffolds typically elicit a reduced

inflammatory response compared to microfibrous scaffolds. For instance, a scaffold with a large fiber diameter (11–15 μm) promoted the formation of a thicker fibrous capsule than a scaffold with a small fiber diameter (1–5 μm) in a rat subcutaneous model [104]. Furthermore, fiber alignment also plays a critical role. Aligned fibrous scaffolds favoured M2-like macrophage polarisation *in vitro* [85] and reduced foreign-body responses *in vivo* [106] compared with randomly aligned counterparts.

Pore size of a scaffold is suggested to be a more crucial regulator of M2 macrophage polarisation compared to fibre diameter [105]. Generally, large pores (~360 μm) enhance cell infiltration, vascularisation, and M2-like polarisation, whereas smaller pores restrict cell spreading and are associated with pro-inflammatory responses both *in vitro* and *in vivo* [105,107–109,114]. The exact mechanisms of the scaffold pore size-mediated M1-to-M2 transition remain unclear [108]. It is speculated that large pore size facilitates angiogenesis and neo-vascularisation [115], and the endothelial cells promote macrophage polarisation into an M2-like phenotype [116]. The M2-like macrophages expand and secrete more pro-angiogenic factors, which in turn promote the formation of vascular networks, forming a positive feedback loop. Furthermore, it is important to note that pore size and fibre thickness are closely related, and in most cases, a scaffold with a thicker fibre diameter would exhibit a larger pore size [105,117]. This makes it difficult to discuss the individual effects of pore size and fibre width. While a thicker fibre may elicit a pro-inflammatory response, the larger pore size could dampen this effect [105,117]. For example, a thick fibre graft (5.6 μm) with a large pore size (41 μm) favoured cell infiltration, M2 macrophage polarisation, and vascular tissue regeneration *in vivo* compared to a thin fibre graft (0.7 μm) with a 10-times smaller pore size (4.6 μm) [117]. Therefore, these parameters should be considered collectively when designing an immunomodulatory biomaterial.

In addition, particle size also influences macrophage behaviour. Micron-sized particles tend to induce M1-like phenotypes through phagocytosis, whereas nanoparticles promote M2-like phenotypes with elevated IL-10 production in a STAT3/cellular musculoaponeurotic fibrosarcoma (c-Maf)-dependent manner [42], likely due to differences in cellular uptake mechanisms, such as endocytosis and pinocytosis [118].

Micropatterned substrates further demonstrate that spatial organisation modulates macrophage phenotype by altering cell shape [110]. Wider spacing between surface ridges promotes pro-inflammatory response [110,111]. In contrast, narrow spacing promoted macrophage elongation and M2-like polarisation, with the greatest elongation along the 450–500 nm grooves [119]. This effect is likely due to spatial confinement, which downregulates LPS-stimulated activity of transcription regulators such as histone deacetylase 3 (HDAC3) and of the serum response factor/myocardin-related transcription factor A (SRF/MRTF-A) complex, resulting in reduced pro-inflammatory cytokine expression such as iNOS [120].

While biomaterials are characterised by these physical properties in the laboratory before implantation, these properties change during degradation, creating a dynamic microenvironment. Macrophages also participate in the degradation of biomaterials through phagocytosis, production of reactive oxygen species, and secretion of proteolytic enzymes such as MMPs [99]. Macrophage-driven scaffold degradation has been shown to depend on the scaffold microarchitecture, with a relatively thick (6 μm), anisotropic microfibrous scaffold exhibiting the most pronounced degradation; this mechanism is independent of the canonical M1/M2 polarisation spectrum [121]. However, little is known about how material degradability and degradation by-products affect macrophage behaviour, making it difficult to distinguish the effects of the original material properties from those arising from degradation. Future studies should consider degradation kinetics as an active immunomodulatory parameter rather than solely a determinant of scaffold persistence and assess how degradation-mediated changes in the local microenvironment affect macrophage recruitment, survival, and functional heterogeneity throughout healing.

3.3. Enhanced Macrophage Efferocytosis for Inflammation Resolution

Efferocytosis is the engulfment of apoptotic cells (ACs) by phagocytes, which is a cardinal function of both TRMs and MDMs. The process of efferocytosis entails recruitment, recognition, internalisation, and digestion [122] (Figure 3a). Effective efferocytosis is predominantly performed by alternatively activated, M2-like macrophages [123], resulting in decreased production of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α, as well as increased release of anti-inflammatory cytokines including IL-10, TGF-β, and pro-resolving lipids. As the number of ACs in the wound microenvironment outweighs efferocytes, macrophages display continual efferocytosis for effective clearance of ACs and resolution of inflammation. The process of efferocytosis is initiated with the proliferation of efferocytosing macrophages induced by AC-derived nucleotides [124] and metabolic lactate production [125]. Arginine and ornithine are metabolised from ACs into putrescine, which promotes subsequent rounds of efferocytosis by increasing RAC1 activation for AC engulfment [126], hence expanding the pool of resolving macrophages capable of continual efferocytosis. In addition, AC uptake triggers dynamin-related protein 1 (DRP1)-mediated mitochondrial fission, allowing for endoplasmic reticulum Ca^{2+} release into the cytoplasm that

mediates phagosome formation for continual AC internalisation [127]. For inflammation resolution, macrophages regulate the tryptophan metabolism pathway to release the anti-inflammatory cytokines IL-10 and TGF-β by activating the aryl hydrocarbon receptor (AhR) [128]. Secreted IL-10 further acts as an autocrine-paracrine signal that drives subsequent RAC1-mediated AC engulfment [129]. Furthermore, AC-derived methionine is used to sustain extracellular signal-regulated kinase 1/2 (ERK1/2) activation, thereby promoting prostaglandin E2 (PGE_2) synthesis and PGE_2-mediated induction of TGF-β1for inflammation resolution [130]. Therefore, failed efferocytosis results in the accumulation of ACs, overproduction of pro-inflammatory mediators, and the lack of pro-resolving signals, leading to tissue damage, impaired healing, and the formation of chronic wounds [131]. Bioengineering strategies developed to enhance macrophage efferocytosis have focused on modulating the recognition process, including mimicking apoptotic signals [46–48], bridging-molecule delivery [49,50], and efferocytosis receptor engineering [51–53].

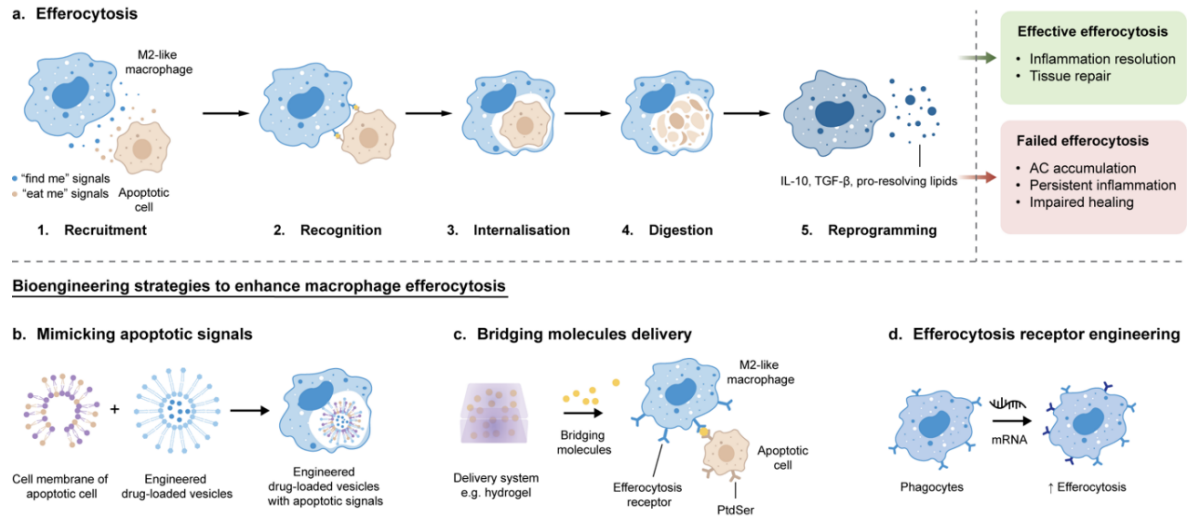

Figure 3. (**a**). Schematic illustration of efferocytosis. (**b–d**). Bioengineering strategies to enhance macrophage efferocytosis: (**b**). Mimicking apoptotic signals; (**c**). Bridging molecule delivery; (**d**). Efferocytosis receptor engineering.

Apoptotic signals can be mimicked by delivering apoptotic vesicles and artificial cell mimics derived from apoptotic cell membranes to the macrophages, thereby enhancing their efferocytosis efficiency (Figure 3b). Phosphatidylserine (PtdSer) is the most widely studied "eat-me" signal displayed by apoptotic cells, and it activates efferocytosis-associated signalling pathways such as mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK), AKT Ser/Thr kinase (AKT), focal adhesion kinase (FAK), or STAT6 pathway [132]. PtdSer-incorporated liposomes have been shown to modulate the cytokine profile of pro-inflammatory MDMs by reducing the secretion of pro-inflammatory cytokines, including IL-1β, IL-6, IL-12, and IL-23 *in vitro*, likely due to the efferocytic nature of PtdSer-liposome internalisation [133]. Furthermore, PtdSer-containing biomaterials have been utilised to achieve macrophage-targeted delivery of therapeutic agents. For example, liposomes incorporating PtdSer-enriched apoptotic red blood cell membranes were used to deliver rosiglitazone (ROSI), a PPAR-γ agonist that induces macrophage polarisation to an anti-inflammatory phenotype in a mouse colitis model, resulting in maintained epithelial mucus integrity, restored crypts, and reduced inflammatory cell infiltration [46]. Tissue repair was accompanied by reprogramming of $CD86^+$ pro-inflammatory macrophages into $CD206^+$ anti-inflammatory macrophages in the repaired colon [46]. Similarly, PtdSer-incorporated lipid nanoparticles were used to deliver tiliroside to macrophages in a diabetic cutaneous wound model and were shown to significantly promote tissue regeneration by promoting efferocytosis and glycolysis-related macrophage reprogramming [44].

Bridging molecule links between apoptotic cells and efferocytosis receptor to initiate efferocytosis. Bridging molecules can be incorporated into delivery systems, such as hydrogels, that enable sustained release to promote continual efferocytosis (Figure 3c). For example, delivering milk fat globulin protein E8 (MFG-E8) through GelMA hydrogel in an anterior cruciate ligament reconstruction model in rats showed reduced terminal deoxynucleotidyl transferase dUTP nick-end labelling-expressing ($TUNEL^+$) AC accumulation and increased M2-associated CD206 and IL10 expression, resulting in more efficient new bone formation at the tendon-bone interface compared to saline injection [49]. To enhance bridging molecule incorporation, a co-assembled polypeptide nanofibres made from amphiphile peptide (PA) with rich polar amino acids, including NNCCCCRRES(p) (PARRES) and NNCCCCS (PAS), was developed [50]. The introduction of PAS into PARRES promoted co-assembly to form β-sheet-rich, negatively charged nanofiber bundles, enabling efficient

adsorption of bridging molecules, such as protein S in human serum, via amino acid hydrogen-bonding. Injection of serum-incubated PARRES-PAS in a mouse periodontitis model reduced the number of $TUNEL^+$ ACs with enhanced M2 macrophage populations, facilitating the resolution of periodontitis and promoting the recovery of bone quality and bone height. Another study enhanced efferocytosis by targeting the bridging molecule C1q using apoptotic stem cell-derived apoptotic vesicles enriched with the complement C1q-binding protein (C1qbp), which anchors soluble C1q on macrophages to engage corresponding efferocytic receptors [134,135]. C1qbp enriched-apoptotic vesicles were embedded in a GelMA hydrogel to treat a full-thickness diabetic wound in mice, which promoted early clearance of apoptotic cells during the inflammatory phase, and subsequently encouraged M1-to-M2 macrophage reprogramming and inhibited NF-κB inflammatory signalling by day 7 after injury, leading to improved epithelialization and functional skin regeneration [135].

Efferocytosis receptor engineering aims to increase the efferocytosis receptor expression by phagocytes and is usually achieved through genetic engineering using gene delivery via lentiviral vectors [51] or chimeric receptor cell therapy [52,53] (Figure 3d). For example, in the immunodeficient NOD scid gamma mouse model of steatohepatitis induced by feeding a high-fat, choline-deficient, amino acid-defined diet, treatment with T-cell immunoglobulin and mucin domain-containing 4 (TIM4)-expressing human MDMs via lentiviral transduction enhanced efferocytosis and reduced liver fibrosis [51]. Development of chimeric receptors for efferocytosis (CHEF) can be achieved by fusing the signalling domain of cytoplasmic adapter protein ELMO1 to truncated PtdSer receptors such as BAI1 (termed BELMO) or TIM4 (termed TELMO) [52]. CHEF-expressing phagocytes were able to significantly increase efferocytosis and dampen inflammation in multiple mouse models of tissue injury. Inspired by TELMO, a synthetic efferocytic receptor (SER) was developed by adding a single-chain variable fragment derived from a monoclonal antibody targeting amyloid-β to a modified TELMO [53]. SER-expressing microglia displayed strong efferocytosis activities, promoted amyloid-β aggregate clearance without inflammation, and substantially reduced neuronal death and synaptic loss, thereby alleviating Alzheimer's disease in a murine model.

4. Opportunities, Limitations and Future Directions

4.1. Biological Limitations and Opportunities

Recent advances underscore the translational potential of macrophage-targeted bioengineering strategies to modulate immune response and promote tissue repair and regeneration. However, the complexity and heterogeneity of macrophage biology present significant challenges for the rational design and evaluation of these immunomodulatory approaches. First, most biomaterial studies remain limited to simplified macrophage classifications (e.g., M1/M2) to characterise the local macrophage population and aim to suppress M1-like macrophages while promoting M2-like macrophages. These characterisation approaches failed to capture the full extent of macrophage heterogeneity *in vivo,* and the reparative M2-like macrophages are also associated with fibrosis after wound repair [136]. Only a few studies have selectively targeted specific subsets of macrophages to promote wound healing and tissue regeneration. For example, an RNA-editing tool, CRISPR-Cas13, was encapsulated in nanoparticles and used to cleave *Spp1* mRNA in SPP1-producing macrophages during tendon injury, thereby reducing fibroblast activation and peritendinous adhesion *in vivo* [137]. Recent studies have revealed new subpopulations of macrophages that are associated with pathological wound healing. For example, C-C motif chemokine ligand 4-like 2-expressing ($CCL4L2^+$) M1-like macrophages promote pro-inflammatory cytokine secretion and impair tendon healing in tendinopathy [138] while galectin-3-expressing ($GAL3^+$) macrophages are key contributors to muscle fibrosis in both acute and chronic injuries [139]. These macrophage subsets are therefore potential therapeutic targets for reducing fibrosis and promoting wound healing.

Changes in the macrophage population following biomaterial implantation may result from monocyte recruitment, local macrophage proliferation, and phenotypic changes of existing macrophages. Among these processes, several studies have focused on regulating monocyte recruitment [140]. For example, recruitment of $Ly6C^{high}$ monocytes can be inhibited with nanoparticle-encapsulated siRNA to silence expression of the monocytic chemokine receptor *Ccr2*, thereby reducing the inflammatory response and enhancing wound-healing outcomes in a myocardial infarction model [141,142]. In contrast, increased recruitment of $Ly6C^{low}$ monocytes via the immunomodulatory small molecule FTY720 promotes the accumulation of M2-like macrophages and vascular network expansion [143]. While these findings demonstrate that monocyte influx can influence tissue repair, they offer limited insight into the subsequent fate of recruited monocytes once they enter the tissue. A recent mouse study revealed that the differentiation of monocytes into TRMs requires deoxyhypusine synthase (DHPS), an essential enzyme of the polyamine–hypusine pathway in steady state [144]. However, it remains unclear to what extent recruited MDMs persist or acquire tissue-resident characteristics during wound healing. Additionally, the

distinct contributions and responses of TRMs and recruited MDMs to implanted biomaterials remain poorly understood. Future biomaterial strategies may therefore benefit from selectively preserving reparative TRMs, or from differentially targeting MDM and TRM populations according to the stage of healing, utilising lineage tracing and/or single-cell techniques [58].

4.2. Translational Challenges

Despite significant advances in macrophage-targeted bioengineering strategies for tissue repair, several challenges continue to impede clinical translation. A major limitation is the lack of cell-type specificity of many immunomodulatory strategies. Numerous signalling pathways that regulate macrophage behaviour are shared among multiple cell types, including fibroblasts, endothelial cells, and other immune cells involved in wound healing. Consequently, it increases the risk of off-target side effects, making it difficult to attribute therapeutic outcomes solely to macrophage modulation. This challenge is particularly relevant for approaches involving the sustained delivery of bioactive molecules, where precise control over target-cell specificity remains difficult to achieve.

Another important challenge is the discrepancy between *in vitro* findings and *in vivo* outcomes. Many bioengineering strategies are initially evaluated using a simplified cell culture system that fails to capture the complexity of the wound environment. The influence of mechanical properties, such as stiffness and viscoelasticity, on macrophage behaviour *in vivo* remains poorly understood due to technical challenges in measuring and controlling these parameters within dynamic tissues. Consequently, biomaterials that successfully modulate macrophage phenotypes *in vitro* do not always produce comparable responses *in vivo*. Developing more physiologically relevant models that better recapitulate the dynamic tissue environment remains an important step toward improving the predictive value of preclinical studies.

The translational feasibility of certain macrophage-engineering approaches also varies considerably. Among the efferocytosis-enhancing strategies, biomaterials designed to mimic apoptotic signals or provide bridging molecules are potentially easier to translate. This is because they utilise biological processes and can be integrated into existing FDA-approved biomaterials. In contrast, more sophisticated approaches, such as receptor engineering or genetic modification of macrophages using transfection vectors, face additional challenges related to safety, delivery efficiency, manufacturing complexity, and regulatory approval. These factors may limit their clinical implementation in the near future, despite their promising experimental results.

Finally, the predictive value of preclinical studies is constrained by differences between experimental models and human patients. Despite the growing number of recent studies testing biomaterials in diabetic wound-healing models, most are still conducted in young, healthy animals, whereas clinical wound-healing disorders frequently occur in elderly individuals and patients with one or more chronic conditions, such as diabetes, cardiovascular disease, or other comorbidities. These discrepancies may not reflect the ageing- and disease-related changes in macrophage plasticity [145,146]. Furthermore, the treatment of chronic wounds may not begin until the later stages of wound healing, whereas most of these macrophage modulation strategies are tested in the early inflammatory phase. Therefore, therapeutic effects observed in animal models may not fully translate to humans. Addressing these challenges will require more clinically relevant disease models, improved human-based experimental systems, and rigorous evaluation of long-term safety and efficacy before macrophage-targeted biomaterials can be successfully translated into clinical practice.

4.3. Future Directions

Future strategies should focus on overcoming current limitations in the precise and dynamic control of macrophage behaviour. In particular, there is a need to develop systems capable of spatiotemporally regulating macrophage phenotypes, enabling coordinated transitions from pro-inflammatory to pro-reparative states that reflect the natural progression of tissue repair. Integrating biochemical and biophysical cues within a single platform is critical, as macrophage responses are not governed by individual signals but by the combined effects of molecular, mechanical, and structural inputs. Achieving this level of control requires an improved understanding of how these cues interact within complex tissue environments. Advancing biomaterial design to better recapitulate the dynamic and heterogeneous *in vivo* microenvironment is essential, as this influences macrophage phenotypes and functions both temporally and spatially. This includes addressing current discrepancies between *in vitro* and *in vivo* findings and developing systems that can adapt to evolving tissue conditions during healing.

Author Contributions

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Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used Grammarly and ChatGPT (version 5.2) for proofreading and language refinement. Following the use of these tools, the authors carefully reviewed and edited the content as needed and take full responsibility for the final published article.

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