

Masterful macrophages: understanding and targeting activation dysfunction in diabetic wounds

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Abstract

Diabetes mellitus is a group of chronic metabolic diseases worldwide that seriously threaten human health and increases the social and economic burden; underlying drivers of impaired healing include uncontrolled inflammation, repeated ischemia reperfusion injury, and neuropathy alongside infection risks. Macrophages orchestrate standard repair, exhibit sustained classical pro-inflammatory activation in diabetes, disrupting growth factor secretion, angiogenesis, and matrix regulation. Hyperglycemia mediated advanced glycation end products and reactive oxygen species heighten pattern recognition receptor stimulation, causing reduced alternative macrophage differentiation. Promising immunomodulation approaches redirecting their phenotypes to resolve inflammation and stimulate regeneration provides optimism. We discuss macrophage origination, polarization dynamics, diabetic wounds phenotypic imbalance, and critical microenvironmental disruptions perpetuating pathological function. Elucidating specific regulatory nodes upholding their activation states will inform intelligent targeting opportunities. Overall, infiltrating macrophages constitute indispensable yet amenable diabetic wound healing coordinators.

Keywords: Macrophage; Dysfunction; Diabetic; Wound healing; Mechanism

Highlights

- Wound healing comprises of stages: hemostasis, inflammation, proliferation, maturation, and remodelling. The wound microenvironment includes various cytokines and growth factors, extracellular matrix, oxidative stress, pH, microbiome populations, tissue oxygenation gradient, and other factors.
- The ontogeny and polarization dynamics of macrophages underscore their indispensable roles as master regulators of repair processes, and macrophages orchestrate the wound healing in different phases.
- In diabetic wounds, macrophages exhibit progenitor stage maturation anomalies, recruitment and transmigration impairments, maturation and phenotypic imbalance, substantial deficits in tissue repair function, immunometabolic disruption, and epigenetic rewiring.
- Explore emerging therapies targeting macrophages and microenvironment.

Background

Skin injury elicits an intricately orchestrated series of cellular and molecular events to achieve wound closure and tissue repair [1, 2]. Impaired healing, as manifested prominently in chronic diabetic wounds, remains a significant clinical challenge underscored by poorly understood pathophysiology [1]. Resident and recruited immune cells, especially macrophages, are pivotal in coordinating nearly all phases of wound healing through dynamic activation states and crosstalk with other cell populations [3–6]. Consequently, illuminating macrophage functional regulation in tissue repair processes has important implications for understanding dysfunctional healing.

Wound closure requires the coordinated efforts of various skin resident cells, circulating immune cells, cytokines, growth factors, and extracellular matrix (ECM) components [1]. This process progresses through hemostasis, inflammation, proliferation, and remodeling [2]. Macrophages critically regulate inflammation, clear apoptotic cells (ACs), and stimulate

angiogenesis and matrix deposition, consequently orchestrating the transition between phases [3]. They originate from yolk sac progenitors (YSPs) during embryogenesis and bone marrow-derived monocytes in adults, the latter replenishing tissue macrophage populations during steady state and inflammation [4, 5]. Their versatile functions depend on integrating microenvironmental cues that induce distinct polarization states—pro-inflammatory macrophages (M1) and anti-inflammatory macrophages (M2) subsets. M1 prevail early, releasing tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), IL-6, and IL-12, while M2 dominate later, producing IL-10 and transforming growth factor- β (TGF- β) [1, 2, 6].

Aberrant macrophage phenotype and persistence underpins impaired healing in many chronic wounds [7]. No wounds condition better epitomizes sustained M1 dysfunction than diabetes [8], the leading cause of nontraumatic limb amputations [9]. Diabetic wounds exhibit prolonged inflammation, exacerbated protease activity, reduced angiogenesis and

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ECM deposition, and increased apoptosis [8–10]. These manifestations partly stem from hyperglycemia induced reactive oxygen species (ROS), advanced glycation end products (AGEs), and augmented M1/M2 imbalance [11, 12]. Promising immunotherapeutic developments targeting macrophages and the wounds microenvironment provide impetus to define regulators of macrophage activation for improved healing outcomes.

In this review, we detail the fine coordination of various immune cells and the cytokines they secrete during wound healing in healthy skin, focusing on macrophages [8]. In particular, the polarization mechanism of macrophages has been a hot topic in recent years, and we have described its abnormal manifestations in diabetic wounds [8] providing key molecular nodes to redress wound pathology. Finally, we discuss emerging therapeutic avenues centered on macrophages and their microenvironment of modifiers.

Review

The wound healing process and mechanisms in healthy skin

Tissue injury initiates a finely tuned healing program comprising overlapping phases—hemostasis, inflammation, proliferation, and remodeling [2, 13]. This section describes cellular and molecular events governing each phase and their seamless coordination for skin integrity restoration.

Key phases of wound healing

Hemostasis begins immediately upon injury with vasoconstriction and fibrin clot formation to achieve hemostasis [13, 14]. Thrombin generation activates platelets to release clotting factors, inflammatory mediators like platelet factor 4 (PF4), platelet derived growth factors (PDGFs), and TGF- β . PF4 inhibits angiogenesis. Simultaneously, PDGFs and TGF- β stimulate immune cells chemotaxis [13–16]. The ensuing inflammation phase comprises the early recruitment of neutrophils and later macrophages [7, 17]. Neutrophils release IL-1, IL-6, and TNF- α , followed by AC clearance by M1 [1, 12]. Transitioning to the proliferative phase, alternatively, activated M2 release vascular endothelial growth factors (VEGFs), PDGFs, fibroblast growth factors (FGFs), and TGF- β to stimulate angiogenesis, ECM deposition, and new tissue formation [2, 12, 18–21]. Matrix metalloproteinases (MMPs) mediated ECM remodeling in the final phase enhances the structural integrity of the healed skin [20, 21].

Cellular and molecular events in each phase

Hemostasis. Subendothelial collagen exposure upon injury initiates hemostasis via platelet adhesion through von Willebrand factor (vWF) and glycoprotein Ib α (GPIb α) interaction [21]. Activated platelets release α and dense granules containing adhesion molecules, clotting, chemokines, and mitogenic factors [21, 22]. Released fibrinogen induces thrombocyte aggregation while activating the coagulation cascade [14, 23], forming the platelet plug and fibrin-fibronectin meshwork [21, 24]. Thrombin also elicits inflammatory responses by inducing endothelial cell release of C-C motif ligand 2 (CCL2), IL-6, and IL-8 chemokines [1, 2, 14, 24, 25]. Platelet α particles secrete PF4, a CXC chemokine inhibiting angiogenesis while promoting leukocyte recruitment [15, 22, 26, 27].

Inflammation. Acute inflammation succeeds hemostasis to prevent infection and prepare the wound bed for repair

[1, 27]. Early neutrophils swarming peaks around 24 hours, mediated via complement activation and IL-1 release [17, 28, 29]. Neutrophil extracellular traps (NETs) comprising deoxyribonucleic acid (DNA) and proteins help destroy bacteria [17, 29]. Macrophages dominate later, reaching peak numbers around 48–96 hours post injury. Monocytes recruited by macrophages' chemokines like CCL2 and macrophage colony-stimulating factors (MCSFs) differentiate into M1 [12, 25, 30]. M1 debride cell debris and pathogens through phagocytosis and secrete TNF- α , IL-1 β , IL-6, and IL-12, consequently activating t helper cell type 1 (Th1) immune responses [31]. Around Day 3, macrophages undergo a phenotype transition towards an M2 state, characterized by the release of IL-10, TGF- β , and VEGFs [32–36], M2 initiate inflammation resolution and tissue remodeling while suppressing t helper cell type 2 (Th2) immune responses [33, 36]. Notably, macrophage accumulation precedes the onset of the proliferative phase [34]. Selective macrophage depletion studies underscore their indispensability for the transition from inflammation to proliferation via regulating growth factors balance [7, 35].

Proliferation. M2 growth factors like TGF- β , epidermal growth factors (EGFs), FGFs, and VEGFs stimulate the proliferation and migration of key cell types in this phase—keratinocytes, fibroblasts, and endothelial cells [2, 18, 27, 35, 36], activated keratinocytes at wound edges undergo epithelial-mesenchymal transition (EMT), releasing MMPs like collagenase and gelatinase to promote migration [2, 20, 27, 37]. Fibroblasts proliferate and deposit new ECM enriched in fibronectin and hyaluronan [20, 21, 38, 39].

VEGFs is a mitogen that stimulates the proliferation and migration of endothelial cells, and participates in the formation of neovascularization, followed by the extension of endothelial cells to surrounding tissues, which is highly mediated by integrin $\alpha v \beta 3$ [40]. Pericytes with PDGF- β receptors are then recruited by PDGFs to surround the neovascularization, endowing the vessels with maturation and dormancy [16, 17, 40]. These cellular activities form granulation tissue—a highly vascularized tissue with immune cells and connective tissue elements [17, 27, 41]. Myofibroblasts finally facilitate wounds contraction before undergoing apoptosis, as collagen accumulation provides mechanical integrity [41, 42].

Maturation and remodeling. This phase establishes scar tissue for long-term skin integrity via collagen remodeling to confer tensile strength [27, 38, 41, 42]. The transition from predominant collagen III to collagen I synthesis occurs, although, unlike healthy skin, scar collagen is deposited in parallel bundles [27, 41, 43, 44]. MMPs activity is also crucial—MMP-1 degrades collagen for cells migration, while MMP-9 facilitate angiogenesis by modifying basement membranes [20, 27, 45, 46]. Myofibroblasts contraction and slowed keratinocytes proliferation signify the completion of the maturation phase as collagen production declines [41, 42, 47]. Dynamic ECM turnover continues, but stabilized collagen accumulation reduces wound area without losing strength [20, 41, 48] (Figure 1).

The immune microenvironment in wound healing

The wound microenvironment, comprising infiltrating immune cells, cytokines, growth factors, ECM, and physical factors, is pivotal for repair processes. Perturbations impeding the transition between healing phases manifest as chronic

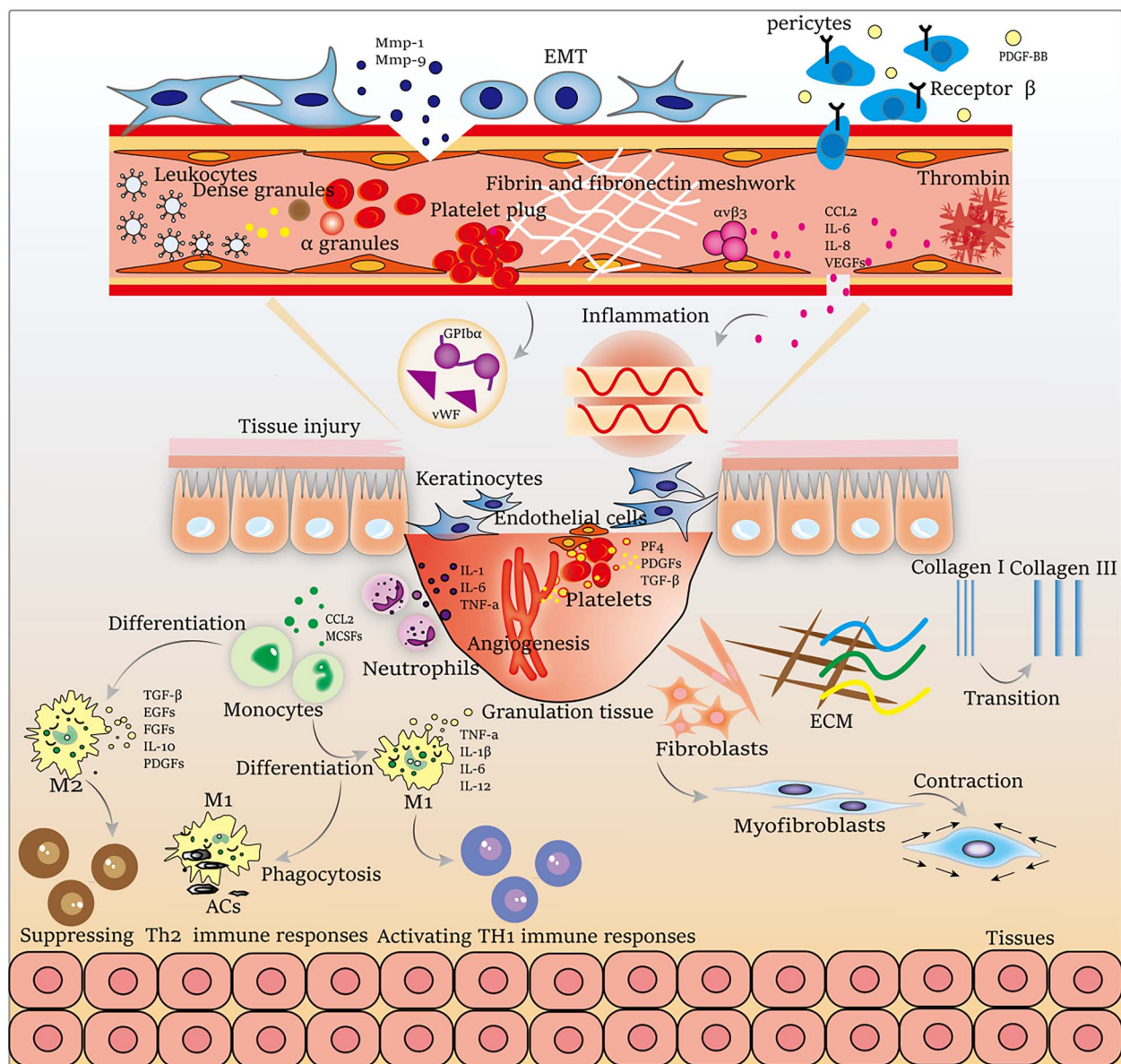


Figure 1. Cells in the normal wound repair process. Tissue injury initiates a finely tuned healing program with overlapping stages—hemostasis, inflammation, proliferation, maturation, and remodeling. During hemostasis, platelets are activated, thrombin is formed and leucocytes are recruited, the production of thrombin activates platelets, leukocytes recruitment. The inflammatory stage includes the recruitment of neutrophils in the early stage and macrophages in the late stage. M1 debride cell debris and pathogens through phagocytosis and secretion, activating Th1 immune responses. Around third day, macrophages transitioned towards an M2 while suppressing Th2 immune responses and initiates inflammation resolution and tissue remodeling. In addition, collagen remodeling gives skin integrity and tensile strength. *Mmp* matrix metalloproteinase, *EMT* epithelial mesenchymal transition, *CCL2* C-C motif ligand 2, *IL* interleukin, *VEGF* vascular endothelial growth factor, *vWF* von Willebrand factor, *PF4* platelet factor 4, *PDGF* platelet derived growth factor, *TGF-β* transforming growth factor-β, *MCSF* macrophage colony stimulating factor, *EGF* epidermal growth factor, *FGF* fibroblast growth factor, *TNF-α* tumor necrosis factor-α, *M2* anti-inflammatory macrophages, *Th2* t helper cell type 2, *M1* pro-inflammatory macrophages, *Th1* t helper cell type 1, *ECM* extracellular matrix, *GPIbα* glycoprotein Ibα, *AC* apoptotic cells

non-healing wounds [1, 7, 19, 27]. This section explores immune cells and soluble mediators critically governing early inflammation and its timely resolution.

Cytokines and growth factors

Inflammation initiates upon IL-1 release from platelets, keratinocytes, and fibroblasts as an early warning signal [1, 49, 50]. The gene sequences of IL-1 family members are highly conserved, which can bind to toll-like receptors (TLRs) to mediate cell signaling and activate the nuclear factor kappa b (NFκB) pathway [1, 12, 13, 18, 27, 49].

IL-1β needs NOD like receptors family pyrin domain containing 3 (NLRP3) inflammasome complex to mediate its cleavage and maturation and further stimulate IL-1 production [13, 17, 49–51]. Other members exhibit dichotomous activities—IL-33 promotes ECM deposition while IL-18 enhances interferon-γ (IFN-γ) generation, and IL-22 significantly accelerates wounds re-epithelialization [12, 18, 49, 50, 52, 53].

As inflammation progresses, infiltrating monocytes differentiate into macrophages [34]. Their predominant early M1 phenotype secretes TNF-α alongside IL-12 and IL-23 to

stimulate Th1 [1, 17, 18, 31, 41, 54–56]. M2 arise later, induced by IL-4 and IL-13 to produce IL-10 and TGF- β [2, 11, 12, 18, 19, 36, 54–56]. These cytokines provide negative feedback to resolve inflammation while enhancing tissue remodeling. Numerous studies highlight that cytokine levels must be precisely regulated across healing phases [17, 19, 27, 57].

The PDGFs family plays indispensable mitogenic roles [1] for mesenchymal stem cells (MSCs) in the proliferative phase [58]. PDGFs receptor ligation stimulates fibroblasts and smooth muscle cell chemotaxis, proliferation, and matrix production [59]. Studies utilizing PDGF injections accelerated granulation tissue formation in rat wound models [16, 17, 27, 60]. PDGF-BB recruits pericytes to stabilize nascent vascular networks by reducing endothelial proliferation [16, 17, 40, 58, 61].

VEGFs are essential in angiogenesis, lymphangiogenesis, and maintaining endothelial homeostasis. The VEGF-A isoform induces tip and stalk cells phenotype in sprouting nascent vessels via vascular endothelial growth factor receptor 2 (VEGFR2), while VEGFR1 modulates its activity [17, 27, 35, 40, 62]. VEGF-C and -D binding VEGFR3 stimulates lymphangiogenesis [41, 63], while placental growth factors (PLGFs) recruit monocytes and promote collateral vessel formation without side effects of abnormal angiogenesis [27, 40, 41, 64].

The TGFs family is indispensable for cutaneous wounds repair by stimulating re-epithelialization, angiogenesis, and ECM synthesis [2, 21, 27, 65–73]. TGF- β 1 accelerates monocytes and fibroblasts infiltration and upregulates collagen production [17, 27, 41, 66, 69]. It also maintains the multipotency of progenitor cells, allowing expansion without differentiation [67]. Potent keratinocyte chemotactic (KC) properties of TGF- β 1 hastens re-epithelialization by upregulating connective tissue growth factor [17, 27, 68, 69]. Counter regulatory roles also exist as TGF- β 3 predominates during scarless fetal repair [65] while TGF- β 2 delays EMT [27, 37, 70].

From the submaxillary gland, EGFs were first isolated and shown to stimulate epidermal proliferation with applications in wound therapy [27, 71]. EGFs accelerates MSCs migration without inducing it to differentiate [27, 72, 73]. In vivo evidence also indicates EGFs enable the transformation of adherent keratinocytes into motile phenotypes—a process sensitive to EGFs gradients rather than absolute concentrations [27, 73]. Related family members like TGF- α , heparin-binding EGFs, and betacellulin exhibit similar activities.

FGFs represent ubiquitous peptides regulating wound angiogenesis and tissue remodeling [27, 74, 75]. Basic FGFs stimulates fibroblast migration by activating rho guanosine triphosphatase (Rho GTPase) and the NF κ B pathway [1, 12, 13, 18, 27, 74–76]. Various FGFs ligands modulate distinct repair phases—FGF7 and FGF10 promote keratinocytes organization [74, 77, 78], while FGF2 induces granulation tissue formation [17, 27, 74, 75, 79]. Unsurprisingly, deficient FGF signaling significantly impairs re-epithelialization and collagen organization [27, 41, 69, 74, 78].

Colony stimulating factors (CSFs) members, including macrophages, granulocytes, and GMs, primarily regulate emergency myelopoiesis. However, the development of macrophages and osteoclasts also depends on their signaling and stimulate multiple tissue proliferation [80–85]. Topical application of GMCSFs, can accelerate re-epithelialization in transgenic murine wounds while deficiency delayed crust

formation [12, 13, 18, 27, 69, 80–82]. Mechanistic studies revealed GMCSFs mediated IRF4 induction in macrophages, causing CCL17 mediated nociception and pain [18, 19, 82–84]. Various immune cell lineages, including T, B, and innate lymphoid cells, secrete GMCSFs, which orchestrates their proliferation and acquisition of effector phenotypes. In addition, GMCSFs can also increase the efficacy of ILs on target cells [81].

The TNFs superfamily member TNF- α exhibits dichotomous wound healing activities [54, 86, 87]. Although TNF- α stimulates TGF- β induced ECM production, its deficiency paradoxically impairs re-epithelialization despite improving other parameters [2, 27, 54, 65, 66, 69, 86–88]. TNF- α can transcriptionally activate divergent cellular outcomes ranging from NF κ B mediated inflammation to ACs or necroptosis via intricate post receptor signaling intermediates [76, 86, 87]. Related family members, TNF- β and lymphotoxin α (LT- α) are likewise involved in keratinocyte proliferation [89, 90] and leukocytes recruitment in skin wounds [87, 90, 91] (Figure 2).

The ECM

The ECM provides structural scaffolding for cells while modulating their adhesion, migration, and communication [20, 48, 92–94]. ECM components like collagen, laminin, and fibronectin accumulate in granulation tissue, functioning through growth factor tethering, immune cells recruitment, and progenitor mobilization [17, 20, 21, 27, 39, 41, 92, 93]. Glycosaminoglycans (GAGs) mediate collagen bundle assembly and crosslinking for skin tensile strength acquisition [21, 41, 42, 93]. In addition, GAGs are a component of the glycocalyx of macrophages and play an essential effect on the function of macrophages. Specific constituents like laminin-332 enable keratinocytes motility by regulating basement membrane MMPs activity [20, 21, 41, 66, 95]. Fibronectin and other provisional ECM components produced early following injury also influence inflammation resolution and fibrosis [20, 21, 39, 61, 94].

Myriad collagen subtypes exist, but type I and III fibrils form skin ECM bulk [2, 20, 21, 41, 96], although type VI collagen regulates macrophage function [41, 42, 97]. Collagen turnover involves concerted MMPs cleavage, while tissue inhibitors of metalloproteinases (TIMPs) provide counterbalance [21, 41, 45, 46, 98]. The intricate chemokine and matrix protein interplay spatiotemporal guides immune cells recruitment and behavior throughout repair phases. Disrupting ECM homeostasis thus compromises critical cell-cell communication pathways fundamental for healing.

Oxidative stress (OS)

Transient oxidative outbursts triggered upon injury activation have physiological immune signaling functions, but sustained stress disrupts healing [99, 100]. Peroxide secretion also regulates macrophage phenotype changes during the transition between healing phases [17, 32, 101]. However, hyperglycemia associated generation of AGEs [102, 103] and sustained ROS eventually cause growth factor and ECM abnormalities, leading to impaired healing [99, 103]. Oxidative stress also perpetuates inflammation by activating NF κ B while suppressing nuclear factor erythroid 2 related factor 2 (NRF2), augmenting protease activity [1, 12, 13, 18, 76, 86, 101, 103–105]. Reinstating redox balance using antioxidant supplements or photobiomodulation helps mitigate pathological damage elicited by unrestrained OS [101, 103, 106, 107].

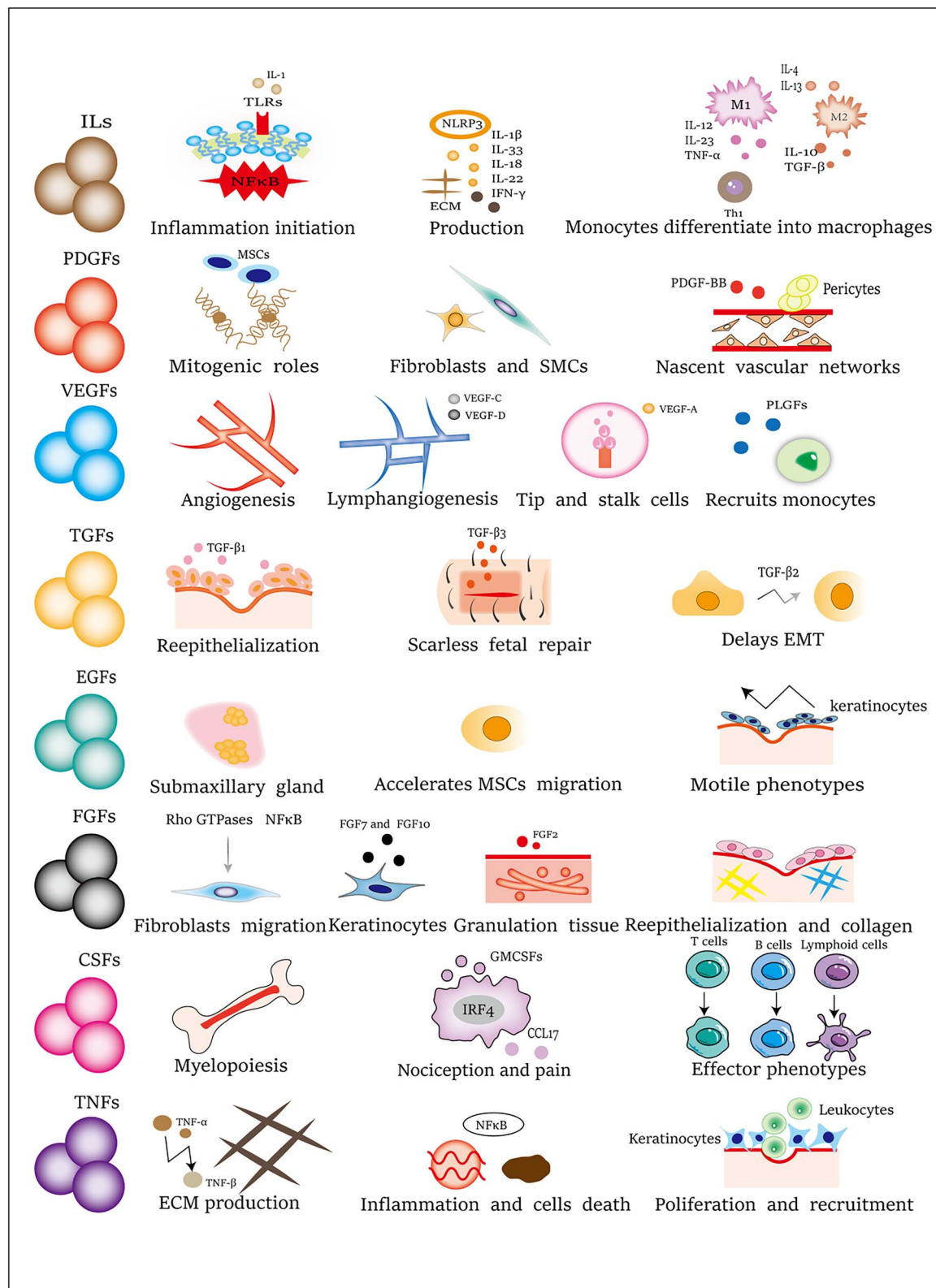


Figure 2. The role of cytokines and growth factors. Eight cytokines families, are part of the wound microenvironment, which play an auxiliary role in wound repair at all stages. Such as re-epithelialization, cell chemotaxis, new granulation tissue, matrix deposition, tissue remodeling, etc. *IL* interleukin, *TLRs* toll-like receptors, *NFκB* nuclear factor kappa b, *NLRP3* NOD like receptors family pyrin domain containing 3, *IFN-γ* interferon-γ, *TNFα* tumor necrosis factor-α, *M1* pro-inflammatory macrophages, *M2* anti-inflammatory macrophages, *TGFs* transforming growth factors, *PDGF* platelet-derived growth factor, *MSCs* mesenchymal stem cells, *VEGF* vascular endothelial growth factor, *PLGF* placental growth factor, *EMT* epithelial mesenchymal transition, *EGFs* epidermal growth factors, *FGFs* fibroblast growth factors, *rho GTPase* triphosphatase guanosine triphosphatase, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *IRF* interferon regulatory factor, *CCL17* C-C motif ligand 17, *TNF* tumor necrosis factor, *ECM* extracellular matrix, *RhoGTPases* rho guanosine triphosphatases

Other local factors

Successfully restoring skin function upon injury necessitates spatiotemporal coordination among diverse cell types and biophysical elements. Multiple studies have explored how biophysical factors like potential of hydrogen (pH), microbiome populations, and tissue oxygenation gradients influence repair programs [1, 13, 17, 108–111]. Low pH causes enzyme inactivation and impairs immune cell viability, while alkaline conditions accelerate re-epithelialization and collagen synthesis [21, 27, 41, 69, 108, 111]. Imbalances in symbiotic microbial populations also delay healing by eliciting inflammatory disturbances [109, 112]. Physiological transitions in oxygen tension promote vascular regression and ECM synthesis, but sustained hypoxia triggers pathological responses [113, 114]. Developing stratified biomaterials replicating native wounds microenvironmental niches can potentially overcome the limitations of traditional wounds therapeutics.

Macrophages orchestrate wound healing

The mononuclear phagocyte system (MPS) exhibits remarkable functional plasticity in orchestrating all wound healing phases [19]. Their ontogeny, polarization dynamics, and multifaceted activities underscore their indispensable roles as master regulators of repair processes. Consequently, illuminating mechanisms governing their activation states provide crucial insights into designing immunotherapies targeting improved healing outcomes.

Origin, subsets and functions

Tissue resident macrophages (TRM) originate from YSP during embryogenesis, while postnatal monocyte-derived subsets replenish local populations [4, 5, 18, 19, 36, 115]. Fate mapping studies reveal YS macrophages give rise to microglia, epidermal langerhans cells (LCs), intestinal macrophages, and heart macrophages while circulating Ly6C^{high} monocytes differentiate into M1 [19, 115–117]. Wound healing requires intricate collaboration between TRM and hematogenous recruited macrophages, although their relative contributions remain undefined [117].

Monocytes recruited towards inflammation sites initially exhibit pro-inflammatory Ly6C^{high} cells surface C-C motif chemokine receptor 2 (CCR2)^{high} chemokine C-X3-C motif receptor 1 (CX3CR1)^{low} phenotype followed by Ly6C^{low} CCR2^{low} CX3CR1^{high} cells [4, 30, 117]. Ly6C subset conversion likely occurs *in situ*, although controversial [30, 118]. Macrophages exhibit significant heterogeneity, with different macrophage subtypes in other tissues, such as alveolar, arterial splenic, and central nervous system (CNS) microglial populations [4, 19, 115, 119]. They express diverse pattern recognition receptors (PRRs) and cytokines receptors facilitating phagocytosis, microbial killing, and antigen presentation [19, 120].

Macrophages dynamically switch activation states in response to microenvironmental signals. Pro-inflammatory cytokines such as lipopolysaccharide (LPS) and IFN- γ polarize M1, while anti-inflammatory cytokines such as IL-4 and IL-13 induce alternative M2 phenotypes involved in tissue remodeling [12, 18, 36, 56, 115, 121–124]. M1 abundantly secrete TNF- α , IL-1 β , IL-6, and reactive nitrogen/oxygens intermediates to combat pathogens [1, 36, 49, 50, 56, 86, 115, 122–124]. Anti-inflammatory, pro-angiogenic M2 release IL-10, TGF- β , and VEGFs, consequently regulating

adaptive immunity and fibrosis [2, 11, 18, 19, 35, 54, 66, 69, 123, 124]. M1/M2 polarization dichotomy nevertheless oversimplifies the spectrum of activation states adoptable by macrophages [18, 56, 115, 121–124].

Dynamic roles of macrophages in different wound healing phases

Hemostasis. Complement and TLRs activation alongside platelets derived TGF- β and thrombin stimulate monocytes recruitment and differentiation before noticeable neutrophils accumulation [2, 14, 29, 34, 115, 125, 126]. Subsequently, endothelial cells, platelets, and fibroblasts release CCL2 and IL-6, which drive monocytes to the vascular site for deformable movement and ultimately to the site of infection [25, 27, 34, 39, 41, 123, 124, 127]. In the early inflammation stage of the wound bed, the release of CCL5 from the α particles of platelet organelles induces the migration of macrophages to the wound bed, and platelets then release other factors to stimulate their differentiation into M1 [17, 25, 124, 127].

Inflammation. Neutrophils and M1 orchestrate the early inflammatory phase [17]. Neutrophils release IL-1 β , IL-6, and TNF- α , consequently stimulating emergency myelopoiesis and M1 differentiation [1, 12, 17, 27, 28, 30, 49, 50, 54, 56, 86, 115, 116]. Dominant M1 activity persists during peak neutrophils clearance by Days 2–5, before declining by Day 7 [27, 29, 34, 124, 128]. They remove pathogens and cell debris via phagocytosis alongside secreting tissue growth factors like EGFs, FGFs, TGF- α , and TGF- β [2, 19, 36, 74, 79, 116, 121, 124, 128, 129].

Around day 3, macrophages adopt anti-inflammatory, pro-repair M2 phenotypes typified by IL-10 and TGF- β secretion [2, 11, 18, 19, 27, 34, 54, 123, 124, 130]. However, M2 manifest even earlier to restrain neutrophils mediated collateral tissue damage [30, 131]. The prevalence of distinct subsets over repair progression suggests that manipulating macrophage activation states rather than specific depletion might provide therapeutic advantages [132].

Proliferation. M2 stimulate angiogenesis, matrix deposition, and cells proliferation in the ensuing proliferative phase [18, 19, 27, 133]. They orchestrate nearly all key reparative events through paracrine signaling. PDGFs, EGFs and FGFs stimulate fibroblasts cells on the proliferation and bulk quantity increases, EGFs like growth factor and keratinocyte growth factors (KGFs) stimulate skin cut in cell DNA synthesis [1, 41, 59, 60, 73, 74, 79, 134]. VEGFs production alongside angiopoietin-2 stimulation culminates in endothelial tip cell guided sprouting angiogenesis [27, 35, 64, 135]. Successful transition to the final phase requires temporally restricted M2 activity and fibroblasts signaling [36, 136].

Maturation and remodeling. Matrix crosslinking into collagen rich scar tissue constitutes the maturation phase [21, 27, 38, 41, 45, 65, 137]. Myofibroblast transdifferentiation and wounds area reduction by concentric collagen bundles provide mechanical strength [21, 41, 42, 138]. Macrophages continue collagen homeostasis maintenance alongside MMPs and their inhibitors [41, 46, 98, 121, 137, 139, 140]. Terminating macrophage influx signals may involve the clearance of ACs [141, 142]. According to research reports, the wound the cause of the formation of pathological scar and

fibrosis contains a disorder of cells apoptosis, angiogenesis, innervation program [27, 41, 65, 143]. Further insights into cellular players and microenvironmental signals involved in inflammation resolution and ECM turnover will pave the way for promising therapeutic developments.

Regulation of macrophage activation and polarization

Two distinct macrophage polarization pathways are recognized. M1 differentiation depends on IFN- γ /LPS activation of interferon regulatory factor (IRF)/signal transducer and activator of transcription (STAT) signaling culminating in transcription of TNF- α , IL-1 β and IL-6 alongside suppressing IL-10 [1, 11, 13, 18, 19, 36, 49, 50, 54, 56, 86, 115, 121, 123, 124, 127, 130, 137, 144]. Anti-inflammatory IL-4 induced M2 polarization utilizes STAT6 and peroxisome proliferator activated receptor (PPAR) nuclear receptors, consequently shutting down NF κ B signaling [1, 12, 13, 18, 19, 36, 56, 86, 89, 115, 121, 123, 124, 130, 144, 146]. M2 is additionally generated through immune complexes acting via Fc receptors (FcRs) and TLRs [27, 115, 121, 147]. Recent studies reveal neuroendocrine signaling via the cholinergic anti-inflammatory pathway also influences activation states [148, 149].

Metabolic reprogramming underpins such functional adaptations [150, 151]. M1 upregulates glycolysis and pentose phosphate pathway (PPP) for increased adenosine triphosphate (ATP) and biosynthesis precursor production [151, 152]. M2 subsets instead rely on fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS) for energetic demands [18, 19, 36, 123, 124, 130, 151–153]. Arginase-1 (ARG-1) induction also distinguishes M2, channeling arginine for collagen production during tissue remodeling [18, 19, 36, 41, 123, 130, 151, 152]. Translation of subset specific surface markers and secreted factors into clinical biomarkers for diagnostic and therapeutic applications remains an area of active investigation [154, 155].

Targeting macrophage activation state transitions and metabolic underpinnings provides exciting immunomodulatory opportunities [151, 156, 157]. In the future, we can use epigenetic and metabolic regulation to explore the phenomenon of macrophage memory, training immunity, and tolerance [115, 151]. Integrating these advances with tissue engineering, biomaterials development, and sensing technologies heralds new horizons for treating pathological wound healing (Figure 3).

Impaired wound healing in diabetes

Overview of diabetic wounds

Diabetes afflicts over 463 million patients globally, exerting profound health and economic burdens [71, 158, 159]. Diabetic foot ulcers (DFU) can lead to disability and death in patients with diabetes [103, 159–161]. Up to 25% of people with diabetes suffer from such recalcitrant wounds despite interventions [161]. Elucidating the underlying impaired healing mechanisms is imperative. Hyperglycemia initiates inflammatory and microvascular cascades, disrupting physiological wound healing choreography, as an example, there is an absolute reduction in the number of pericytes in diabetic wound beds and VEGFR2 on endothelial cells decreased. [137, 162]. Systemic perturbations arise across immune, vascular, and stromal tissues. Aberrant proteolysis, apoptosis, and compromised angiogenesis manifest as signature pathological

hallmarks. Immune cells exhibit dysregulated phenotypes, signaling anomalies, and loss of coordinated functioning [8, 27, 137, 151, 163].

Monocytes and macrophages demonstrate recruitment, polarity, and growth factors secretion deficits [164, 165]. In diabetic wounds, the continuous degradation of microvessels leads to persistent tissue hypoxia, in addition, the accelerated senescence of fibroblasts leads to an imbalance between the deposition and degradation of cellular matrix [103, 130, 166]. Complex pathophysiology interplays forestall transition orchestration between overlapping repair phases [17, 167]. This section elucidates cellular and microenvironmental factors driving the loss of diabetic wound healing control [103, 137, 165]. Hyperglycemia triggers sequelae disrupting the hematopoietic-vascular-mesenchymal axis. Its original role is to regulate skin integrity restoration through interconnected immune, metabolic and trophic signaling pathways [103, 135, 151, 152, 166, 168, 169]. Endogenous myeloid cells dysfunction constitutes the central driver of chronic inflammation, while stromal and endothelial cells establish interdependent pathologies underlying regenerative capacity loss [27, 137, 168, 170, 171]. Abnormal emergency myelopoiesis, lineage divergences, aberrant recruitment, and other factors lead to pathological mononuclear cells within the diabetic wounds [103, 137, 168, 169]. Macrophages demonstrate heightened classical activation alongside impaired phenotype switching from metabolic and epigenetic signaling disruptions [115, 151, 152, 172–174]. Loss of growth factors secretion coordination disrupts MSCs proliferation and migration [175]. Microvascular endothelial dysfunction alongside neural guidance deficiencies drives persistent hypoxia and regenerating matrix instability [137, 168, 176, 177]. Myofibroblasts transdifferentiation impairment from senescent fibroblasts with aberrant integrin signaling further impedes wound contraction [42, 137, 138]. Inhibition of keratinocytes movement leads to inhibition of re-epithelialization [27, 65, 137, 179].

In general, the factors of chronic healing of diabetic wounds include insufficient supply of monocytes and failure of macrophage activation, which lead to chronic inflammation and persistent wound healing. [27, 103, 115, 137, 151, 164, 165, 180, 181]. Hyperglycemia establishes interconnected immune and tissue stromal pathology cascades that uncouple the tightly orchestrated repair schedule. Further insights promise more integrated, systems level therapeutic developments.

Dysregulated macrophages in diabetic wounds

Monocytes and macrophages exhibit altered recruitment, aberrant polarization, and loss of plasticity in diabetic wound healing [1, 103, 122, 137, 151, 182]. Reduced efferocytosis alongside dysregulated growth factors and cytokines secretion hampers their coordination of repair phase transitions. Details on specific facet perturbations have are described below [17, 19, 137].

Progenitor origins and wound recruitment. Monocyte derived macrophages deficits in diabetic wounds manifest from progenitor stage maturation anomalies alongside recruitment and transmigration impairments into injury sites. For example, the researchers found decreased CCR2 expression in monocytes in the circulating blood of patients with type 1 diabetes mellitus (T1DM) [103, 151, 183–185].

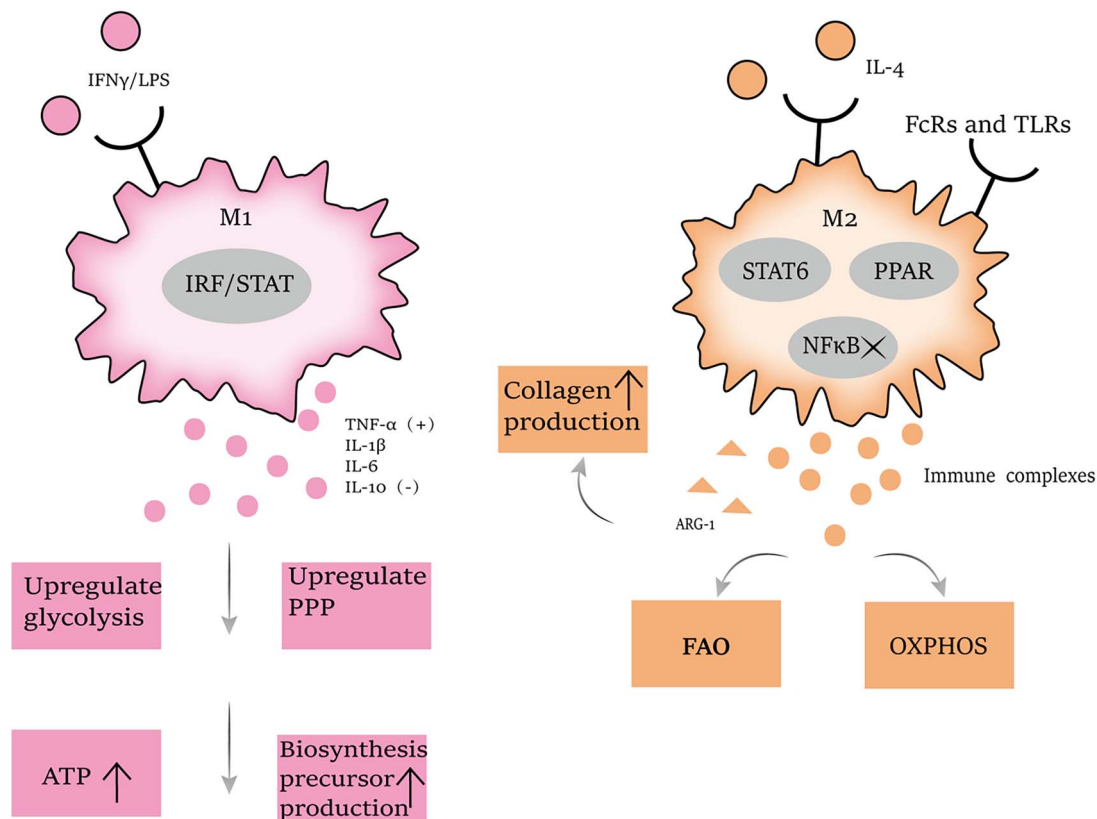


Figure 3. Two polarization pathways of macrophages. M1 differentiation depends on IFN- γ /LPS activation of IRF/STAT signaling. M1 upregulate glycolytic and PPP, thereby increasing ATP and biosynthetic precursors production. M2 polarization utilizes STAT6 and PPAR nuclear receptors. Thus shutting down NF κ B signaling, the M2 subsets rely on FAO and OXPHOS for energetic demands. IFN- γ interferon- γ , LPS lipopolysaccharide, M1 pro-inflammatory macrophages, IRF interferon regulatory factor, STAT signal transducers and activators of transcription, TNF- α tumor necrosis factor- α , IL interleukin, PPP pentose phosphate pathway, ATP adenosine triphosphate, FcRs fc receptors, TLRs toll-like receptors, M2 anti-inflammatory macrophages, PPAR peroxisome proliferator activated receptor, NF κ B nuclear factor kappa b, ARG-1 arginase-1, FAO fatty acid oxidation, OXPHOS oxidative phosphorylation

Emergency myelopoiesis

The number of wound macrophages is realized through the coordinated mobilization, interconversion, and migration of blood monocytes subsets Ly6C^{high} and Ly6C^{low} [161, 184]. These dynamics trace upstream to BM hematopoietic stem and progenitor cells emergency response cascades upholding renewal and lineage specification [185, 186]. External stress such as infection or injury triggers the protective mechanism of the sympathetic nervous system (SNS) and the signaling of inflammatory mediators in the body to accelerate the process of the cell cycle. Chromatin remodeling enables rapid amplification of downstream multipotent, standard myeloid macrophage progenitors (MMPs), and granulocytes macrophage progenitors (GMPs) compartments [115, 187, 188].

In diabetes-induced hyperglycemic stress conditions, bone marrow progenitors (BMPs) instead manifest exacerbated quiescence and cells death from mitochondrial dysfunction [103, 176, 185, 189, 190]. Recent explorations into mechanisms reveal inhibition of rapamycin target protein C1 (mTORC1) signaling disrupts nutrient sensing pathways underlying emergency expansion [150, 151, 191, 192]. Glycotoxicity disrupts the post-transcriptional control of glucose metabolism enzymes, especially pyruvate kinase M2(PKM2), key enzymes that integrate the stress response [157, 173, 192]. Consequently, the robust yet tightly regulated myelopoiesis program that ordinarily restores monocytes pool

homeostatic balance following acute high demand becomes chronically hampered [174].

Recruitment and transmigration

Ly6C^{high} inflammatory monocytes surveilling vascular endothelium (VE) undergo rapid extravasation into damaged sites through diverse chemokine gradients and adhesion molecule pairs [161, 184, 193]. CCR2 recognition of CCL2, produced by platelets, fibroblasts, and endothelial cells, provides indispensable directional migration cues [25, 27, 30, 41, 76, 124, 127, 130, 184, 192–194]. Selectin mediated slow rolling enables integrin activation for arrest and diapedesis through intercellular junctions. Depletion studies underscore near abrogation of wound macrophages accumulation upon CCR2 or CX3CR1 ablation [4, 30, 151, 193, 194, 196].

In diabetes, epithelial glycocalyx degradation alongside endothelial cells dysfunction contributes toward monocytes recruitment anomalies [190, 197]. Reduced CCL2 induction stems from underlying microvascular pathology interfering with perfusion responses [25, 41, 124, 127, 168, 174, 176, 189, 192, 194, 196, 198]. Migration itself suffers impairment from cytoplasm rigidification, affecting motility and cytoskeletal rearrangements necessary for transendothelial passage [199, 200]. Dampened extravasation promotes vascular inflammation from heightened monocytes vessel wall adhesion while depleting wounds bed accumulation rates [201, 202].

Subsets dynamics

Ly6C^{low} subsets arise from local differentiation or precursor conversion rather than Lenovo mobilization. These cells with high levels of human leukocytes antigen dr (HLA-DR) are less dependent on glycolysis [124, 203] and instead use FAO for energy [203, 204]. Phenotypically, they down-regulate inflammatory capacity in favor of angiogenic VEGFs and EGFs production alongside acquiring roles in matrix remodeling [73, 137]. Depletion studies reveal essential contributions toward inflammation resolution and fibrosis regulation over repair progression.

In the wound microenvironment, a clear temporal skew towards early Ly6C^{high} accumulation prevails with profoundly, a phase that is extremely important for health, and delayed appearance of pro-resolving subsets in hyperglycemia [161, 184, 205]. BM exhaustion represents the foremost driver via repressing lineage maturation capacity from metabolic and epigenetic disruptions [115, 148, 152, 170, 186, 190, 205, 206]. Sustained inflammatory stimuli and growth factor imbalances subsequently perpetuate impairments in interconversion [32]. Restoring coordinated cues that temporally switch inflammatory processes toward healing thus constitutes a promising, yet challenging therapeutic avenue requiring further illumination.

Activation states and phenotype imbalance. Macrophages undertake remarkable functional adaptation driven by transcriptional and metabolic remodeling circuits that integrate local microenvironmental cues [130, 151]. The classically activated M1 subsets dominates the early stage of the wound, and M1 extend out of the pseudopodia to remove various debris, while replacing the activated M2 subsets to relieve tissue inflammation and help the wound tissue rebuild [1, 18, 19, 36, 56, 124, 130, 137, 147, 164, 207–209]. Preserving such activation trajectory, balance becomes disrupted in diabetes through several interconnected mechanisms.

Phenotype programming

Macrophages adopt activation states spanning an M1/M2 spectrum according to changing tissue repair requirements [121, 124, 144, 207, 210]. M1 arises from IFN- γ signaling through NF κ B dependent cytokines production [1, 12, 13, 18, 19, 56, 86, 115, 144, 152, 164, 192, 201, 211]. Additionally, they undertake robust phagocytosis, microbial destruction, and antigen presentation following pathogen signature recognition [19, 36, 121, 123, 124, 141, 212]. M2 conversely attenuate inflammation and stimulate matrix deposition, angiogenesis, and remodeling events [19, 27, 130, 205, 209, 213]. They phenotypically express scavenger, mannose, and galactose-type lectin receptors that distinguish their hybridization states [13, 19, 36, 56, 115, 121, 123, 142, 207].

Phenotype acquisition represents a remarkably fluid rather than a terminal process. Early M1 readily adopt alternate activation given appropriate stimuli from ACs or immune complexes. In the later stage, M2 mature in the M2 direction by alternating activation induced by IL-4, upholding tissue growth and homeostasis restoration imperatives [18, 36, 89, 115, 121, 123, 173, 214]. Overall preserving coordinated flux between functional poles of macrophages provides optimal healing outcomes in the wound.

Disrupted equilibrium dynamics

Diabetic wounds environments disrupt such equilibrium trajectories through several interconnected facets [8–10,

32, 103]. LPS, fatty acids, or nucleic acids stimulate macrophages through TLRs, and it exhibits hypersensitivity to this stimulation [12, 27, 56, 115, 121, 151, 152, 210]. Overexpression of downstream enzymes such as protein kinase c (PKC) delays the resolution integration of the signaling pathway [14]. Anti-inflammatory signals like IL-4 and IL-13 demonstrate impaired M2 skewing capacity from IL-1 receptor associated kinase (IRAK) and PPAR γ pathway repression [210, 212, 215–217].

Interestingly, LPS and fatty acids are involved in the glucose metabolic cascade, and they exhibit direct pro-inflammatory signaling effects [152, 209, 218]. Hyperglycemia drives mitochondrial dysfunction and severe OS responses, establishing feedforward loops that interfere with regulatory signal integration [101, 103, 104, 106, 176, 205, 219]. Overall wound macrophages become hyper-responsive to M1 specifies stimuli while resisting subsequent pro-resolution phenotypes which are necessary for timely inflammation cessation.

M1 amplification mechanisms

Diverse signals converge to amplify NF κ B activity under hyperglycemia that locks pathological M1 polarization [1, 12, 13, 18, 56, 86, 115, 144, 164, 192, 220]. AGEs that accumulate on matrix debris act via the receptor of advanced glycation end products (RAGE) and other PRRs to elicit inflammation [27, 102, 103, 137, 164, 174, 201, 212, 221]. PKC pathway enzyme induction downstream of TLRs demonstrates synergy with OS mechanisms [14, 103, 115, 205, 219, 218, 223] in interfering with inhibitor of kappa b kinase (IKK) complex inhibitory regulation [224]. Loss of terminated signals consequently sustains transcriptional outflow.

Interestingly, M1 in diabetic wounds upregulates glycolytic metabolism programmes [103, 157, 225]. Despite negligible gains in ATP production, heightened nutrient uptake capacity enables rapid biosynthetic precursor and cytokines generation that is beneficial for acute antimicrobial responses. However, self-reinforcing hypoxia inducible factor-1 α (HIF-1 α), its stability interferes with subsequent oxidation pathways associated with homeostasis phenotypes [1, 12, 13, 18, 19, 130, 137, 151, 152, 157, 161, 225–227]. Metabolism and signal levels are disrupted, bringing the overall resolution to a standstill [223, 228].

M2 suppression dynamics

M2 skewing signals like IL-4 and IL-13 operate through STAT6 [12, 18, 19, 36, 56, 89, 115, 121, 123, 124, 130, 144, 146, 151, 157, 164, 185, 229], and peroxisome proliferator activated receptor (PPAR) [121, 123, 142, 173, 215, 230] nuclear receptor signaling cascades that temper inflammation via NF κ B repression [1, 12, 13, 18, 86, 103, 115, 144, 152, 164, 192, 201, 222, 224, 231]. However, the diabetic wounds microenvironment interferes with the polarization process by upregulating inhibitory intermediates, including cytokines signaling proteins and inhibitors of protein tyrosine phosphatase (PTP) [19, 103, 116, 163, 167]. TNF- α and IL-1 β also collaboratively suppress PPAR γ activity to reinforce inflammation [12, 13, 18, 49, 54, 115, 121, 124, 142, 151, 164, 173, 210, 212, 215].

Regarding metabolism, the immunomodulatory phenotype shows a dependence on FAO by cellular mitochondria for energy, rather than glycolysis of glucose [204, 223, 232]. However, hyperglycemia disrupts the tricarboxylic acid (TCA) cycle [152, 157], the electron transport chain, and the OXPHOS process, shutting down energy production

Consequently, anti-inflammatory signals fail to manifest maturation while functional properties become compromised even for subsets escaping pathological polarization restraints.

Functional deficits. Macrophages maturation and phenotypic imbalance in diabetic wounds and substantial deficits in maintaining complex tissue repair function [103, 197, 233]. Debris clearance, growth factors production, angiogenesis promotion, and loss of efferocytosis coordination lead to confusion in the repair phase [2, 17, 19, 124, 137, 189, 205, 212, 234–236].

Debris clearing

Myeloid cell lineage effectiveness arises from non-redundant division of labor between neutrophils and macrophages for wound debridement [30]. Following initial swarming activity, macrophages recognize and undertake robust debris phagocytosis [19, 121, 124, 130, 140, 141, 212, 235]. Phagolysosomal trafficking enables the degradation of ECM fragments, spent neutrophils, and foreign particulates for inflammation resolution pre-requisite [236].

In diabetes, by clearing obstacles to the accumulation of by-products such as AGEs, it leads to permanent TLRs stimulation, which can delay diabetic wound healing [103, 137, 164, 190, 216, 222, 233, 237, 238]. Rate limiting measures target lysosomal dysfunction caused by lipid toxicity and oxidative damage, so macrophages swell from residual digestive contents while continuously secreting inflammatory mediators [124, 239]. Restoring phagocytic coordination throughout repair progression stages thus represents an appealing target for ameliorating local disturbances [240].

Growth factors production

All repair phase resident MSCs populations depend upon macrophage paracrine support for driving activities—angiogenesis, cell proliferation, migration, and ECM neosynthesis [27, 93, 200, 205, 241, 242]. The anti-inflammatory subpopulation performed significantly coordinated delivery of VEGFs, EGFs, KGFs, and specific variants produced by endothelial cells, fibroblasts, or keratinocytes, respectively [1, 27].

In diabetic microenvironments, deficient induction of regenerative growth factors blunts nutritive blood vessel (BV) generation, granulation tissue accretion, and epithelial tongue establishment [41, 137, 168, 243]. Molecular studies reveal tendencies toward reduced VEGFs splice variant [244] diversity affecting recruitment and scaffolding roles. TNF- α activation interestingly represses growth factors transcription via divergent post-receptor signaling relative to inflammation evocation [54, 86, 245]. Therefore, if the wound loses the support of macrophages, the biomechanical properties of the wound bed and the perfusion of cellular nutrients are thus hindered [246].

Efferocytosis

Inflammation resolution mandatorily couples ACs death amongst recruited immune cells and tissue debris with efficient clearance mechanisms to avoid secondary necrosis [212]. Macrophages orchestrate the critical process of efferocytosis through redundant surface receptors like cluster of differentiation (CD)36, enabling recognition and engulfment [17, 19, 137, 142, 210, 235, 236, 247]. Subsequent anti-inflammatory signaling allows the adoption of regulatory phenotypes that check exacerbation.

In diabetes, glycoprotein aggregation masks the display of phosphatidylserine (PS) on the cell membrane, which is necessary for early clearance events. OS also causes damage to cytoplasmic proteins and lipids, interfering with phagocytosis [19, 101, 103, 106, 130, 141, 205, 212, 219, 223, 233, 248]. Residual ACs consequently progress toward lytic membrane failure that amplifies inflammasome perpetuation [249, 250]. The discovery of upstream efferocytosis receptors amenable to antibody targeting or scaffold tethering presents an exciting direction for translational developments.

Angiogenesis and remodeling

The proliferative stage depends on macrophage signaling to sustain newly forming vascular networks and ECM development until stability transitions [27, 93, 135, 168, 190, 195, 251]. Subsets secreted MMPs like MMP-9 license angiogenesis through controlled basement membrane degradation for sprout invasion [27, 46, 195, 205, 252, 253]. Subsequently, TGF- β and ARG induce regulation of collagen fiber and elastin fiber arrangement, and give collagen strength and elasticity [2, 41, 42, 65, 66, 173, 254, 255].

In diabetes, dysregulated MMP expression and activity disrupts the delicate balance between stent flexibility. Scaffold flexibility is necessary for cells migration, which avoids bleeding complications as well as vascular degeneration due to unrestricted protease activity [103, 200, 256]. The reduction of TGF- β further leads to uncontrolled proliferation of fibroblasts, eventually leading to pathological contraction of the wound. Overall, the intricate spatial coordination of cues necessary for vessel and matrix maturation suffers impairment from macrophage functional deficits.

Immunometabolic disruption. Macrophages undertake profound metabolic adaptations underlying their remarkable shape shifting capacities, upholding multifaceted tissue repair roles. Inflammatory stimulation signals temporarily upregulate glycolytic flux to meet the needs of rapid innate responses, while restoring oxidative pathways effectively addresses environmental functions [103, 151, 157, 248, 257]. Diabetic wounds environments disrupt such coordinated shifting by instigating maladaptive acceleration.

Metabolic identity and adaptation

Monocytes descendants adopt a spectrum of activated phenotypes characterized by signature bioenergetic and biosynthetic pathways proportional to specialized accessory requirements. Under basic conditions, OXPHOS is centered on the mitochondrial TCA cycle and oxidative catabolism of fatty acids, providing an efficient turnover of cellular energy [103, 151, 152, 157, 173, 232].

Early M1 polarization upregulates aerobic glycolysis, generating energy and biomass precursors for inflammatory mediator generation at the expense of yield [173, 228, 258]. This accelerated Warburg like shift rapidly produces effector molecules before OXPHOS returns to ordered homeostasis, enabling an acute defense response, albeit inefficiently [151, 152, 157, 173]. Preserving innate malleability underpins macrophages' multifunctionality in coordinating wounds repair phase progression.

Hyperglycemic disruption of homeostasis

Attendant glucotoxicity conditions in diabetic wounds subvert otherwise transient glycolytic commitment toward self-reinforcing constitutive acceleration that undermines subsequent efficient OXPHOS utilization [152, 157, 173, 259, 260].

Unrestrained flux consequently culminates in pathological lactate accumulation [157, 261] alongside exacerbated superoxide generation interfering with cytosolic redox homeostasis [103, 262].

TCA enzyme acetylation [157, 173, 258] and fatty acid influx driven mitochondrial membrane dissipation [103, 232, 259] further establish vicious positive feedback loops sustaining catabolite overflow and oxidative damage [248, 262, 263]. Consequently, macrophages become metabolically locked toward detrimental activation modes incapable of resolving phase wise transition orchestration [223].

Loss of activation control

Molecular studies reveal hyperactive HIF-1 α stabilization represents the foremost pivot accelerating glycolytic flux in macrophages while simultaneously diabetic wounds interfering with pyruvate acetyl-coenzyme a (Acetyl-CoA) feed in toward mitochondrial respiration [12, 13, 18, 27, 103, 130, 137, 151, 152, 157, 161, 223, 226, 243, 264–266]. Ordinarily restricted to transient early M1 upregulation, resultant self-reinforcement turn off adoption of subsequent M2 phenotypes dependent on FAO.

Chronic inflammatory drivers such as TNF- α [54, 151, 245, 267] further inhibit regulators such as AMP activated protein kinase (AMPK), which regulates immune metabolic adaptation [151, 191, 257, 268]. Thus, despite adequate upstream cue integration, the overall anti-inflammatory IL-4 induced maturation of macrophages toward M2 is still stalled by insufficient energy. Restoring flux coordination provides an appealing yet challenging target, given the intricacies across levels of metabolic regulation and cell nutrient interaction.

Deficits in microbial activity

Alongside ATP turnover, nicotinamide adenine dinucleotide phosphate b (NADPH) oxidase mediated respiratory burst [152, 269] underpins crucial macrophage microbicidal capacity through ROS generation [100, 103, 151, 270]. Hyperglycemic disruption of mitochondrial electron transport chain (ETC) [103, 260, 271, 272] and glutathione radical quenching turn off regulated production and abets runaway oxidative macromolecular damage [248, 272]. Consequently, debris clearance suffers impairment from lysosomal dysfunction, while protracted inflammation arises from perpetual PRRs triggering [247, 273].

Interestingly, reversing glycolytic irregular polarization can restore the production of NADPH necessary for physiological oxidative respiratory bursts [99, 103, 151, 152, 173, 223, 245, 269]. Nutrient modulation [173, 248, 266, 274] promises to rectify multiple facets of dysregulated metabolism underlying loss of function. Given the limitations of traditional signal targeting methods, we researchers are further investigating the immune metabolic pathway to supplement the treatment of diabetes disease.

Epigenetic rewiring. Beyond signaling and metabolic control layers, evidence reveals diabetic wounds microenvironments extensively remodel macrophage chromatin configurations [130, 151, 187, 188, 192, 212, 223, 233, 264, 275], enforcing fixation toward pathological activation states. Aberrant histone modifications alter key gene promoter and enhancer landscape accessibilities that become perpetuated through atypical cytosine methylation patterns.

Chromatin landscapes

Monocytes progeny integrate extracellular polarization signals through coordinated complex signal transduction and metabolic pathway fluxes, ultimately leading to downstream transcription factor activation, driving monocytes subsets to form specific expression libraries [151, 267, 277]. These bind to the corresponding genomic promoter and distal enhancer modules, with selectivity and output amplitude depending on higher order unpacking dynamics [278].

Thus, chromatin organization represents the functional adaptation of stages from the ancestral stage to lineage maturation and eventual wound healing coordination phenotypes [115, 187, 212, 279–281]. Preserving remodeling fluidity enables responsiveness to evolving microenvironmental contexts. Specialized packing underlies remarkable macrophage shape shifting properties fundamental to repair phase progression orchestration [150, 258, 282].

Dysfunctional consolidation

Hyperglycemia interferes with poised dynamic responsiveness by reconfiguring chromatin structure function, consequently enforcing pathological polarization [115, 187, 188, 233, 264, 283, 284]. Attendant aerobic glycolysis provides increased acetyl-CoA substrate alongside upregulating modifier enzymes that cause widespread hyperacetylation [152, 233, 285, 286]. These alterations interfere with signal integration adaptability by amplifying specific gene subsets while repressing regulators.

Interestingly, self-reinforcement arises epigenetically as well—amplified promoters recruit transcription factors that bring in more modifiers perpetuating accessibility. Abnormal DNA and histone methylation produce effects that lock in harmful chromatin modification patterns by impeding the coordinated decommissioning necessary for normal phenotypes [187, 192, 223, 233, 284, 285]. Overall, chromatin remodeling across hierarchical scales represents pivotal perpetuators underlying chronic inflammation [27, 115, 188, 233, 251, 264, 284, 287].

Functional implications

Epigenomic entrenchment bears profound implications for macrophage capacity, upholding the wide ranging activities necessary for orchestrating repair progression in diabetic wounds [282]. Beyond crippling phenotype transition from dysfunctional signaling pathway wiring, particular facets also come under direct control through genomic packing manipulation [161].

For instance, efferocytosis requires chromatin loosening for surfactant and scavenger receptor induction [13, 17, 19, 137, 164, 235, 236, 247]. Thus the tight accumulation contributes to the accumulation of secondary necrotic debris at the wound site, thus further stimulating TLRs hyperacetylation. Growth factors like VEGFs similarly remain suppressed and refractory to upstream recovery efforts. Overall self-sustaining loops emerge from initial metabolic triggers that undermine function.

Countermeasures

We hold that opinion that rectifying pathological epigenome consolidation represents an attractive but hitherto unexplored avenue to rescue macrophage coordination as well as traditional signal regulation efforts. Directly editing abnormal

methylation or acetylation patterns remains challenging, as the specificity and efficiency of reprogramming *in vivo* face technical limitations [223, 233, 285, 288].

However, some researchers believe that small molecule inhibitors of selective eraser subtype enzymes are expected to progress by restoring dynamic response potential. For instance, blocking readers from activating marks can curb uncontrolled pro-inflammatory perpetuation. Combinatorial treatment alongside biomaterial mediated microenvironment rebalancing and nutrient modulation provides multidimensional opportunities for synergism. We need to be cautiously optimistic about the success of clinical applications, waiting for translational pathways to navigate to generate a new generation of innovative therapeutic technologies.

A comprehensive appreciation of the chromatin topological underpinning that drives diabetic wounds myeloid dysfunction, by focusing on modifiable aspects beyond typical signaling intermediates, these research developments have profound therapeutic implications for patients and readers [187, 188, 233, 283, 284, 290]. We foresee innovation arising from manipulating emergent network properties through hierarchical control layers to rectify the loss of function.

In summary, aberrant macrophage recruitment, activation, and function in diabetic wound healing culminate in the loss of subsets guiding coordination of repair phases [137, 164, 205, 291]. Restoring balance necessitates directing differentiation or reprogramming towards regulatory phenotypes alongside immune metabolic and epigenetic modulation [115, 143, 151, 157, 212, 223, 233, 258, 284, 288] (Figure 4).

Beyond the M1/M2 dichotomy in TRMs. The traditional M1/M2 polarization paradigm, primarily derived from *in vitro* models and animal studies, suggests a binary classification where M1 is pro-inflammatory and M2 is anti-inflammatory [1, 18, 27, 121, 124, 147, 210, 214, 228, 292, 293]. This model has been instrumental in understanding macrophage function in various contexts, including wound healing, cancer, and infection [119, 129]. However, recent advances suggest that the reality is far more complex, especially when considering human TRM. Emerging evidence indicates that the polarization of TRM cannot be fully captured by the M1/M2 dichotomy [210, 294]. Studies have shown that TRM exhibits a remarkable diversity in their phenotypes and functions, shaped by their tissue of residence and the local microenvironment [212, 292–294]. This diversity is further complicated by differences observed between human and animal models, suggesting species specific regulatory mechanisms and functional roles of macrophages, the complexity of macrophage polarization in different tissues and under various pathological conditions, emphasizing the need for a more nuanced understanding of macrophage biology [18, 122, 214].

The regulation of TRM involves a complex interplay of local signals, including cytokines, growth factors, and metabolic cues, which can induce a spectrum of activation states beyond the simplistic M1/M2 classification [151, 210, 212, 214, 294, 297]. For instance, recent research has identified several subsets of macrophages within tissues characterized by distinct surface markers, transcriptional profiles, and functional properties [298–300]. These findings underscore the importance of context in determining macrophage phenotype and function, challenging the applicability of the M1/M2 model to all situations [210,

291–294]. Furthermore, the lack of comprehensive data from human systems represents a significant gap in understanding macrophage polarization in health and disease. Most of our current knowledge is derived from animal models and *in vitro* studies, which, while valuable, may not fully recapitulate the complexity of human TRM biology [301–303]. Therefore, there is a pressing need for more human based studies to elucidate the mechanisms regulating TRM and their roles in various pathological conditions, including diabetic wound healing [3, 294]. TRM have increasingly been recognized as key players in maintaining tissue homeostasis and orchestrating immune responses [121, 130, 151, 300, 304–306]. Their unique transcriptional and functional profiles are shaped by their tissue of residence, allowing them to perform specialized functions tailored to the specific tissue microenvironment [276]. For instance, microglia, the TRM of the CNS, play pivotal roles in neuronal development, synaptic pruning, and neuroinflammatory responses [4, 115, 207, 212, 294, 306–309]. Similarly, alveolar macrophages in the lungs are essential for surfactant homeostasis and defense against respiratory pathogens [36, 121, 124, 297, 300, 306, 310, 311]. The diversity of TRM is further exemplified by their heterogeneity within the same tissue. Recent single-cell transcriptomic studies have revealed the existence of distinct macrophage subpopulations in various tissues, including the brain, heart, and adipose tissue [18, 42, 115, 119, 136, 207, 210, 212, 297, 307, 312–314]. These subpopulations exhibit unique transcriptional profiles and functional attributes, suggesting specialized roles in maintaining tissue integrity and responding to local perturbations [212]. The polarization of TRM is regulated by a complex network of signals from the local microenvironment, including cytokines, growth factors, metabolic cues, and interactions with other cell types [151, 315–317]. For instance, in wound healing, the dynamic interplay between immune cells, fibroblasts, and endothelial cells orchestrates the transition of macrophages from a pro-inflammatory state to a pro-resolving and tissue remodeling state [1, 27, 130, 189, 303, 318, 319]. This transition is mediated by myriad factors, including ILs, growth factors, and lipid mediators, which shape transcriptional and functional profiles throughout the healing process [121, 130, 179, 276].

The recognition of the complexity and context dependency of macrophage polarization has led to the development of more nuanced classification systems [320, 321]. These systems aim to capture the spectrum of activation states and functional diversity, moving beyond the oversimplified M1/M2 dichotomy [18, 124, 137, 164, 210, 214, 314, 316, 319]. For instance, the concept of “functional phenotypes” has been proposed, categorizing macrophages based on their specific roles and functional attributes rather than predefined polarization states [322, 323]. Despite these advances, our understanding of human TRM biology remains limited, as most research has been conducted using animal models or *in vitro* systems [301–303, 305, 313]. While these models have provided valuable insights, they may not fully recapitulate the complexity of human macrophage biology [295]. Human macrophages exhibit unique transcriptional and functional profiles compared to their counterparts in animal models, highlighting the importance of species specific regulatory mechanisms [276, 296, 324, 325]. Researchers have increasingly turned to human based studies to address this limitation, leveraging advanced technologies such as single-cell transcriptomics, proteomics, and functional assays [42, 210, 212, 276,

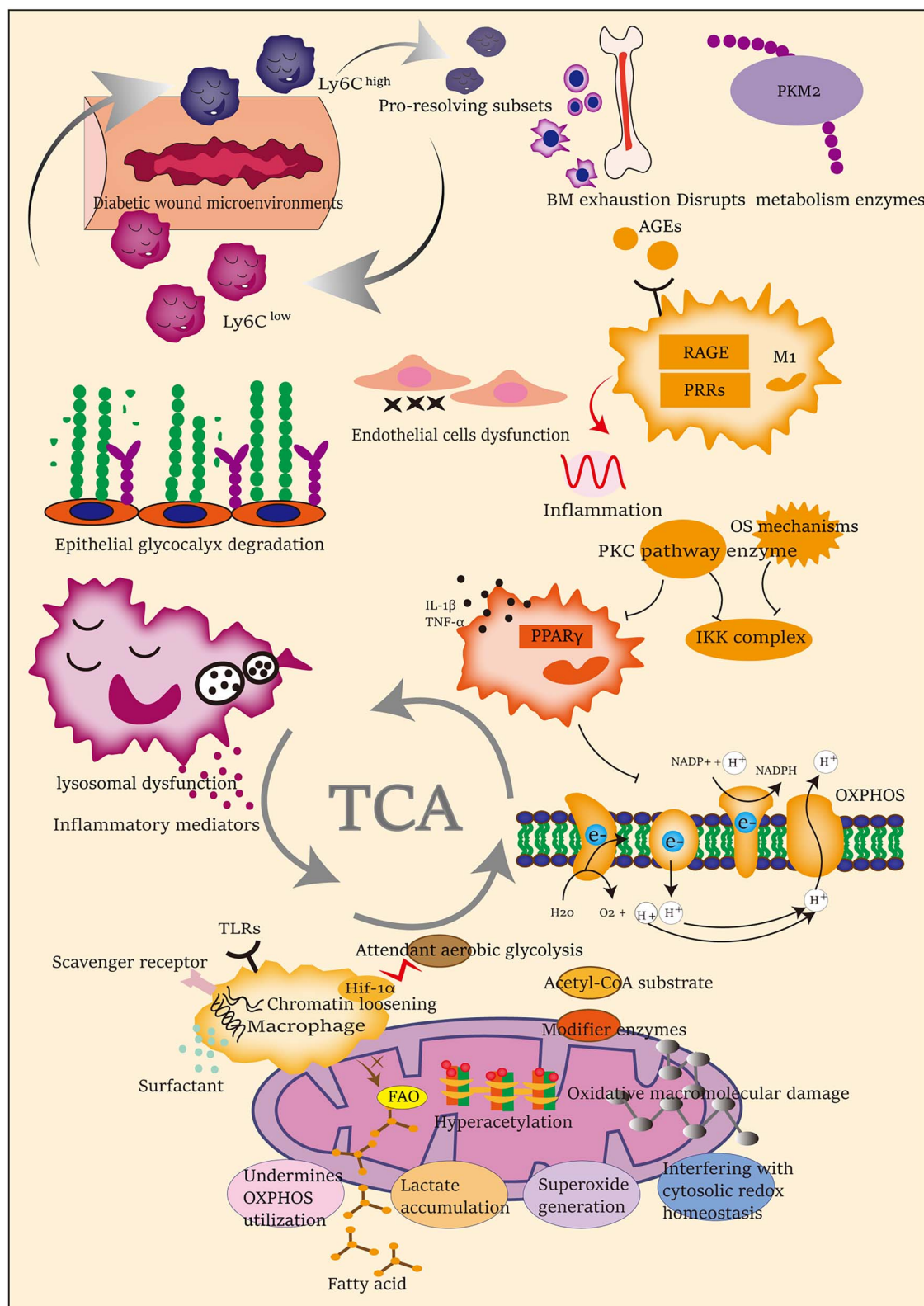


Figure 4. Microenvironment of diabetic wound healing. Monocytes and macrophages exhibit altered recruitment, aberrant polarization, and loss of plasticity in diabetic wound healing. PKM2 pyruvate kinase M2, AGEs advanced glycation end products, RAGE the receptor of advanced glycation end products, PRRs pattern recognition receptors, M1 pro-inflammatory macrophages, PKC protein kinase c, IKK inhibitor of kappa b kinase, IL interleukin, TNF- α tumor necrosis factor- α , PPAR γ peroxisome proliferator activated receptor γ , TCA tricarboxylic acid, NADP $^{+}$ nicotinamide adenine dinucleotide phosphate, NADPH nicotinamide adenine dinucleotide phosphate b, TLRs toll-like receptors, HIF-1 α hypoxia inducible factor-1 α , CoA coenzyme a, FAO fatty acid oxidation, OXPHOS oxidative phosphorylation, BM bone marrow, OS oxidative stress

296, 326, 327]. These approaches have yielded important insights into the diversity of human macrophage subsets, their tissue specific functions, and the regulatory mechanisms governing their polarization and activation states [115, 123, 137, 281, 295, 318].

Furthermore, integrating multi-omics data with computational modeling and machine learning approaches has shown promise in unraveling the complex regulatory networks underlying macrophage polarization and identifying novel therapeutic targets [328, 329]. For instance, network analysis of transcriptomic data from human macrophages have revealed vital transcriptional regulators and signaling pathways associated with specific functional states [210, 276, 306]. This provides a framework for targeted modulation of macrophage phenotypes [330, 331]. In diabetic wounds healing, a better understanding of TRM's roles and regulatory mechanisms is crucial for developing effective therapeutic strategies [172, 317]. Dysregulated macrophage polarization and dysfunction have been implicated in the impaired healing observed in diabetic patients [137, 151, 332, 333]. Targeting the local microenvironment and modulating macrophage activation states through targeted therapies, such as cytokines modulation or metabolic reprogramming [151, 157, 173, 226, 258, 315, 316, 320], may represent promising approaches to promote healing in diabetic wounds [334, 335].

Emerging therapies targeting macrophages and microenvironment

Given the central roles of macrophages in coordinating tissue repair processes [318, 325], targeting their dysregulation in diabetic wound healing offers immense promise. Modulating their activation state and metabolism using pharmacological compounds, functional biomaterials [336], microenvironment alterations, and cellular therapeutics represents emerging approaches that can potentially transform clinical outcomes.

Immunomodulatory biomaterials. Intelligent biomaterials capable of spatiotemporal release of immunomodulatory, pro-angiogenic, and chemotactic factors can potentially rescue dysfunctional diabetic wounds macrophages alongside other repair cell types [336]. For instance, metformin-loaded hydrogels accelerated wounds closure in diabetic mice via macrophage polarization towards regulatory phenotypes [337]. Sustained delivery of microparticle encapsulated IL-4 using injectable carriers similarly enhanced M2, pro-healing macrophage populations [303, 338].

Three dimensional printed scaffolds with spatiotemporal variations in stiffness, alignment, porosity, and adhesion ligand densities provide another promising approach to influencing myeloid cell recruitment and activation [339, 340]. Nanopatterned topographies on bandage materials also beneficially hinder excessive leukocytes infiltration and protease activity, as demonstrated through *in vivo* validations [341]. Further integrating such platforms with cells, nucleic acid therapeutics, or electronic stimuli, responsiveness heralds an exciting Manufacturing 4.0 translational avenue [342, 343].

Microenvironment modulation. Given the profound impact of the physical and biochemical properties of the wound bed on wound healing, our new interventions in correcting pathological abnormalities have the same advantages as

traditional biochemical therapies [344, 345]. For instance, negative pressure wound therapy enhances perfusion and reduces edema while lowering inflammation and infection risks [346]. Oxygen generating biomaterials or hyperbaric oxygen therapy reinstates normoxia necessary for collagen synthesis underlying angiogenesis [205, 347].

Micropatterned dressings spatially regulate hardness, porosity, and ligand density, coordinating cells migration, differentiation, and paracrine signaling [200, 248]. Electric stimuli responsive smart bandages also encourage cell proliferation and microbial clearance [349]. Despite increasing adoption, further mechanistic insights into cell material interactions can potentiate next generation therapies fulfilling unmet needs [336].

Immunometabolic manipulation. The new understanding of the profound influence of *in vivo* metabolism on macrophage activation and wounds healing function makes it an alternative therapeutic node [157, 297, 319, 350]. For instance, inhibiting glycolysis or augmenting OXPHOS can redirect diabetic wound macrophages from pro-inflammatory toward pro-healing phenotypes [1, 173, 303, 315, 316, 351, 352]. Nutrient sensors like the mechanistic target of rapamycin (mTOR) similarly regulate translational pathways supporting subsets skewing amenable for targeting [150, 151, 173, 191, 192, 353].

Metformin and statins, approved by the U.S. Food and Drug Administration (FDA) for the metabolic syndrome indication, have shown sound immunomodulatory effects [151, 285, 354, 355]. Developing targeted delivery systems to achieve wound site bioactive concentrations can thus potentiate their adjunct application alongside conventional standard of care options [73, 356]. Overall, immune metabolic fine tuning through temporal nutrient modulation or pharmacological agents offers flexibility, complementing conventional cytokines signaling targeted immunotherapies [151, 274].

Genome and RNA engineering. The gene editing method allows for correcting disease causing mutations and holds promise for treatments that inhibit the overexpression of pro-healing factors in wounds [357]. Clustered, regularly interspaced short palindromic repeats mediated correction of monogenic diabetes mutations is undergoing rapid clinical translation, exemplifying possibilities [358]. Efficiency, delivery, and regulation remain challenges facing the translation of such nucleic acid therapies toward wound healing applications [359].

Small activating or inhibitory ribonucleic acids (RNAs) similarly allow transient silencing of inflammatory pathways or boosting tissue regeneration mediators dysregulated in diabetes [130, 150, 233, 297, 360]. Identifying optimal molecular targets and engineering tailored delivery vehicles responsive to microenvironmental triggers remains vital for translating preclinical successes into clinically administrable platforms [361].

Cellular therapies. Transplantation of BM or adipose derived MSCs accelerates diabetic wound healing through immunomodulatory and pro-regenerative mechanisms [183, 190, 241, 357, 362]. Cell free derivatives like exosomes and secretomes recapitulate observed therapeutic effects while avoiding concerns about immunogenicity or vascular complications [362, 363]. Synergistic combination strategies

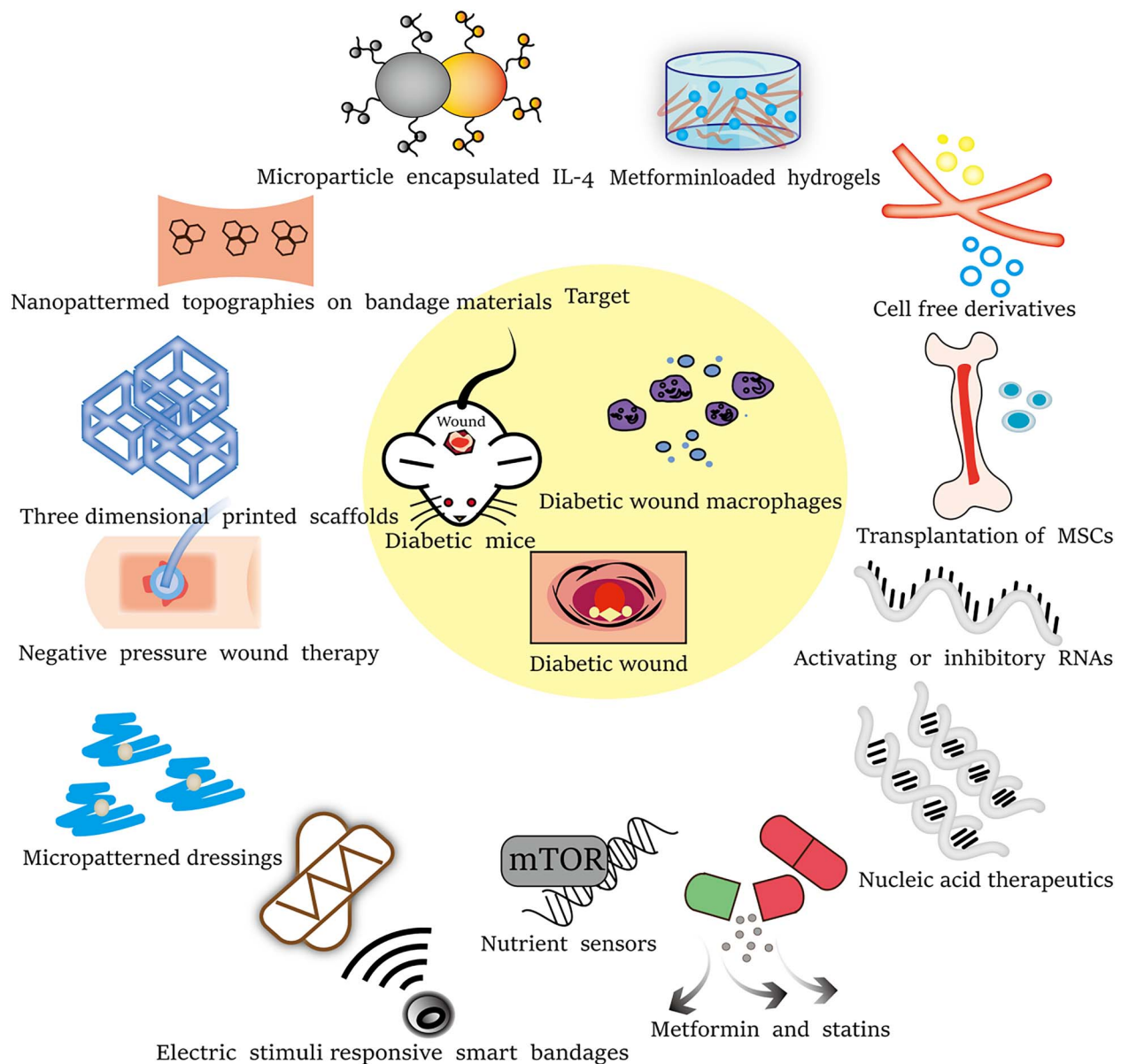


Figure 5. Emerging therapies target macrophages and the microenvironment. Emerging approaches to the clinical treatment of diabetic wounds include pharmacological compounds, functional biomaterials, microenvironment alterations, and cellular therapeutics. *IL* interleukin, *MSCs* mesenchymal stem cells, *mTOR* mechanistic target of rapamycin, *RNAs* ribonucleic acids

also appear promising. For instance, the coordinated delivery of MSCs with regulatory macrophages exerts coupled paracrine activity for inflammation resolution and tissue remodeling [130, 318, 364].

Overall, personalized regenerative medicine approaches simultaneously redressing the interconnected pathologies underlying diabetic wound healing offers flexibility, complementing conventional biomolecular centric interventions [103, 136, 145]. The future of regenerative healing lies in the adoption of such multidimensional tactics.

In summary, biomaterials mediated microenvironmental modulation with immune metabolic and epigenetic reprogramming alongside progenitor cell therapy offers avenues for redressing systemic and local deficits underlying pathological wound healing [67, 115, 151, 157, 170, 173, 212, 241, 288, 294, 336, 347]. Future developments expanding molecular insights on macrophage regulation and clinical translation can

transform outcomes for multitudes of chronic wounds bearers via synergistic, systems level healing augmentation [1, 27, 151, 164, 251] (Figure 5).

Treatment of all types of diabetes. DM have been divided into childhood diabetes also termed as T1DM, and adult onset diabetes is also known as type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM) [106, 137, 159, 165, 168, 174, 178, 180-183, 185, 215, 216, 234, 237, 238, 285, 297, 320, 365-378] and secondary diabetes mellitus (SECDM) [379, 380]. With the understanding of the complexity of the disease, its treatment also faces serious challenges [170, 178]. T1DM, also known as insulin dependent diabetes, is caused by the immune destruction of pancreatic islets. T1DM is not limited to adolescents, but is also common in adults [365]. Current treatments for T1DM are as follows: β cell replacement, detection of anti-islet autoantibodies, use of

Table 1. Several common forms of diabetes mellitus and their corresponding treatments

Treatment of all types of diabetes mellitus	
Name of diabetes mellitus	Therapeutic method
T1DM	β cell replacement Detection of anti-islet autoantibodies Blood glucose detection sensor,vaccine Nutritional therapy,gene therapy Islet transplantation,cell therapy Insulin secretagogues agent,biguanide Incretin analogs,exercise Dietary intervention,acupuncture Euglycemic agent,mental intervention Inhibitor of α -glucosidase Set targets for glycemic control Lifestyle modification
T2DM	Management of hyperlipidemia Management of atherosclerosis Treatment of congestive heart failure Prevention of fall risk,dialysis Examination of eyes,insulin Sliding scale insulin Subcutaneous insulin
GDM	Weight management,insulin Nutritional therapy,glibenclamide Blood sugar monitoring,melbine Blood glucose management during labor Postpartum care
SECDM	Carbohydrate restricted diet treatment Insulin,octreotide Secretagogue hypoglycemic agent Growth hormone receptor antagonists

T1DM type 1 diabetes mellitus,T2DM type 2 diabetes mellitus, GDM gestational diabetes mellitus, SECDM secondary diabetes mellitus

vaccines to stop adverse immune events or environmental factors, development of a series of insulin analogs, continuous glucose monitoring sensors, insulin combined with metformin and pramlintide and glucagon-like peptide-1 receptor agonists (GLP-1RAs), gene therapy and cell therapy, and medical nutrition therapy [254, 365–371, 374]. T2DM is mainly associated with overweight and obesity and is the result of damage to the pancreatic beta cells [181, 228, 234, 259, 373]. Current treatments for T2DM include oral hypoglycemic agents such as, insulin secretants, biguanides, insulin sensitizers, α -glucosidase inhibitors, incretin analogs, pancreatic amylase antagonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors [106, 371–373, 375, 377]. In addition, dietary intervention, psychological intervention, exercise, acupuncture and moxibustion are indispensable non-drug treatment means of T2DM, and also auxiliary targeted therapy means [372, 373]. In T2DM, for patients over 65 years of age, functional aging directly affects the physiological and pathological processes of diabetes, which are usually manifested by weight loss and decreased physical strength [374]. We should screen for pre-diabetes and prevent diabetes, set targets for blood glucose control, intervene in lifestyle, treat hyperglycemia in hospitalized patients, and treat complications of hyperglycemia in gerontal patient [374, 375]. In general, GDM is the most common metabolic disease in pregnancy. The most common complications in women with GDM include large for gestational age, macrosomia, pre-eclampsia, polyhydramnios, stillbirth, etc. It is also a marker of T2DM in the future. Stress management, and glycemic control with insulin and glyburide when necessary [174, 376–378]. Many endocrine diseases are associated with different degrees

of impaired glucose tolerance. Among them, Cushing’s syndrome, acromegaly, and neuroendocrine diseases are characterized by an excess of antisense hormones, leading to varying degrees of insulin resistance and glucose metabolism disorders [380]. This phenomenon is called SECDM and requires endogenous insulin treatment [379, 380] (Table 1). Recently, researchers have found that targeting retinoic acid related orphan receptor alpha (ROR α) in macrophages can promote bone regeneration in diabetes, which has high social value [381].

Conclusions

Chronic wounds represent a vast unmet clinical challenge, with diabetes afflicted patients alone exceeding 463 million currently. Pathological healing arises from perturbations across hematopoietic, vascular, stromal, and cutaneous compartments. Sustained inflammation forms the central mediator resulting from cellular dysfunction alongside hypoxia, acidosis, infection, and loss of coordination. Macrophages play an indispensable role in orchestrating transitions between the overlapping phases of repair. Their remarkable functional plasticity regulating inflammation, debridement, angiogenesis, and matrix remodeling underlies recruitment towards wound beds. Consequently, mechanistic insights into axes upholding macrophage homeostasis are essential for redressing healing impairments. We describe the current understanding of origins, activation states, signaling pathways, and effector functions allowing subsets specialization. Extensive redundancy nevertheless enables the preservation of tissue surveillance, pathogen response,

and wound healing conducting roles despite temporary fluctuations. These are accentuated multifold in disorders like diabetes, where chronic inflammatory stimuli disrupt immune metabolic programming underlying phenotypic stability. Consequently, we elaborate on how hyperglycemia and concomitant OS impact hematopoietic development alongside promoting TLRs overstimulation. Growth factors perturbations also arise from ECM alterations and microbiome changes. Eventual manifestations include recurring ischemia, uncontrolled protease activity, and phenotypic imbalance. Repair phase coordinating abilities become compromised by the loss of angiogenic stimuli production, efferocytosis, and epithelialization routing. Unchecked neutrophils and alternatively activated macrophage persistence propagates self-sustaining chronic inflammation. Encouragingly, recent developments provide an armamentarium for tackling such multifactorial deficits by redressing local microenvironmental perturbations while providing immune recalibration. Biomaterial advances allow customizable cytokine, oxy-redox, and metabolic tuning to push macrophages and other participants toward pro-regenerative roles. Transplantation or endogenous activation of diverse progenitor lineages can simultaneously enhance tissue deposition and remodeling. Wound sites furthermore display heightened amenability for gene and RNA therapeutic administration. Overall, systems approach coopting immune metabolic networks, epigenetic plasticity, and functional biomaterials alongside emerging biotechnologies heralding an exciting era in regenerative medicine. We foresee future innovations arising from cross disciplinary efforts at the tissue material molecular interface. For instance, coupling immunomodulatory platforms with semiconductor sensing or M2 derived exosomes can enable closed loop immunological reprogramming. Machine learning guided cytokines formulations accounting for spatiotemporal nonlinear wound healing dynamics can fast track preclinical developments. Translational efforts would necessitate streamlining regulatory processes to fast track approval of synergistic cell materials combination products with favorable safety profiles. Specifically induced polyenergetic macrophages in patients exhibit enhanced efferocytic and cell matrix remodeling behavior, conditions that can overcome the autologous allogeneic mismatch. Therefore, successful research advances in these areas have far-reaching implications for reducing the healing pain of chronic intractable wounds, not just diabetic wounds.

Author contributions

LNP wrote the manuscript and drew the figures. GXL and WFH evaluated and reviewed the manuscript structure, ideas and science. Author have read and approved the final manuscript.

Conflicts of interest

The authors declare no competing interests.

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