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REVIEW

Macrophages as Multifaceted Orchestrators of Tissue Repair: Bridging Inflammation, Regeneration, and Therapeutic Innovation

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Abstract: Macrophages play pivotal roles in tissue repair through remarkable functional plasticity, orchestrated by their developmental origins and local microenvironmental cues. Embryonically derived resident macrophages primarily maintain tissue homeostasis, while monocyte-derived macrophages respond predominantly to inflammation and extracellular matrix remodeling. Effective tissue repair requires precise temporal regulation of macrophage polarization, balancing inflammation resolution, angiogenesis, and scar formation. Metabolic reprogramming further enhances macrophage plasticity, enabling adaptation to fluctuating energy demands at injury sites. Emerging evidence also highlights that macrophages integrate biomechanical forces—such as matrix stiffness and shear stress—with biochemical signals to fine-tune their inflammatory and reparative programs. Recognizing this mechanoregulation broadens therapeutic avenues for precisely modulating macrophage behavior in regenerative medicine. Targeting macrophage subsets, polarization states, or metabolic pathways has emerged as a promising therapeutic strategy to optimize healing outcomes. However, the inherent complexity of macrophage heterogeneity presents considerable challenges to therapeutic precision. This review systematically summarizes the multifaceted roles of macrophages in tissue repair, emphasizing how developmental origins dictate functional specificity, dynamic phenotypic transitions, and metabolic adaptability, aiming to advance macrophage-based precision therapeutics for regenerative medicine.

Keywords: macrophage, tissue repair, macrophage polarization, therapeutic strategy

Introduction

Following tissue injury, necrotic cell debris and invading pathogens release damage-associated molecular patterns and pathogen-associated molecular patterns, triggering an inflammatory response.[1] Immune cells—including macrophages, neutrophils, and natural killer cells—are recruited to the injury site to clear cellular debris and pathogens, while simultaneously collaborating with epithelial cells, endothelial cells, fibroblasts, and stem cells to facilitate tissue repair.[2] During this process, the innate immune response is activated to recruit inflammatory cells that initiate the repair cascade.[3] As the inflammatory phase subsides, macrophages shift from a pro-inflammatory phenotype to a reparative phenotype, eventually departing the injury site or being cleared to restore tissue homeostasis.[4] Disruption of macrophage function during this process can lead to various pathological conditions, including the overproduction of inflammatory mediators and fibroblasts, which may result in chronic wounds and eventually progress to pathological fibrosis.[5]

Macrophages play a dual regulatory role in tissue repair. In the early inflammatory phase, macrophages secrete chemotactic factors that enhance the inflammatory response following injury.[6] Once the inflammatory phase concludes, the macrophage population undergoes a phenotypic transformation into a pro-reparative state.[7] At this stage, these cells secrete large amounts of pro-proliferative factors such as platelet-derived growth factor, which not only accelerates the regeneration of damaged cells but also promotes the formation of new vascular networks.[8] By releasing specific signaling

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molecules, macrophages can also induce fibroblasts to transform into contractile myofibroblasts—a process that is essential for wound closure and extracellular matrix (ECM) remodeling.[9] During the later stages of repair, macrophages gradually adopt an anti-inflammatory phenotype.[10] These cells, by sensing inhibitory signals such as IL-10, secrete their own anti-inflammatory mediators and express immune regulatory molecules like PD-L1.[11] This immunomodulatory function is critical for terminating the inflammatory cascade; however, if dysregulated, it may cause secondary tissue damage and significantly delay the healing process.

By elucidating the interplay between macrophage ontogeny, phenotypic plasticity, and metabolic reprogramming, this review highlights the critical regulatory roles macrophages play in tissue regeneration. Specifically, we discuss their contributions to inflammation resolution, fibrosis attenuation, angiogenesis promotion, and interactions with mesenchymal stem cells and fibroblasts. Furthermore, we examine the mechanisms underlying macrophage phenotype transitions and metabolic reprogramming during tissue repair. These insights may transform current therapeutic paradigms in regenerative medicine by enabling more precise modulation of macrophage functions, thus enhancing tissue integrity and facilitating targeted tissue restoration.

Origins and Phenotypic Heterogeneity of Macrophages

Macrophage Polarization: Beyond the Classical M1/M2 Paradigm

Macrophages exhibit remarkable plasticity, with their phenotypes being profoundly influenced by the local tissue microenvironment, thereby adopting multiple distinct states. The traditional M1/M2 dichotomy is primarily derived from in vitro studies (as shown in Figure 1). Under experimental conditions, macrophages stimulated by lipopolysaccharide (LPS), TNF-α, or IFN-γ typically polarize towards a pro-inflammatory M1 phenotype. These cells highly express TLR-2, TLR-4, CD80, CD86, iNOS, and MHC-II, accompanied by the activation of NF-κB and STAT1 signaling pathways. During wound repair, M1 macrophages promote the inflammatory response by releasing cytokines such as IL-6, IL-12, TNF-α, reactive oxygen species (ROS), and antimicrobial peptides.[12,13] Additionally, M1 macrophages possess a robust phagocytic capacity, facilitating the clearance of debris and bacteria from the wound environment.[14]

As the acute inflammatory phase wanes, macrophages tend to transition into a reparative M2 phenotype, characterized by high expression levels of CD206, CD163, CD209, and FIZZ1. M2 macrophages enhance tissue repair through the

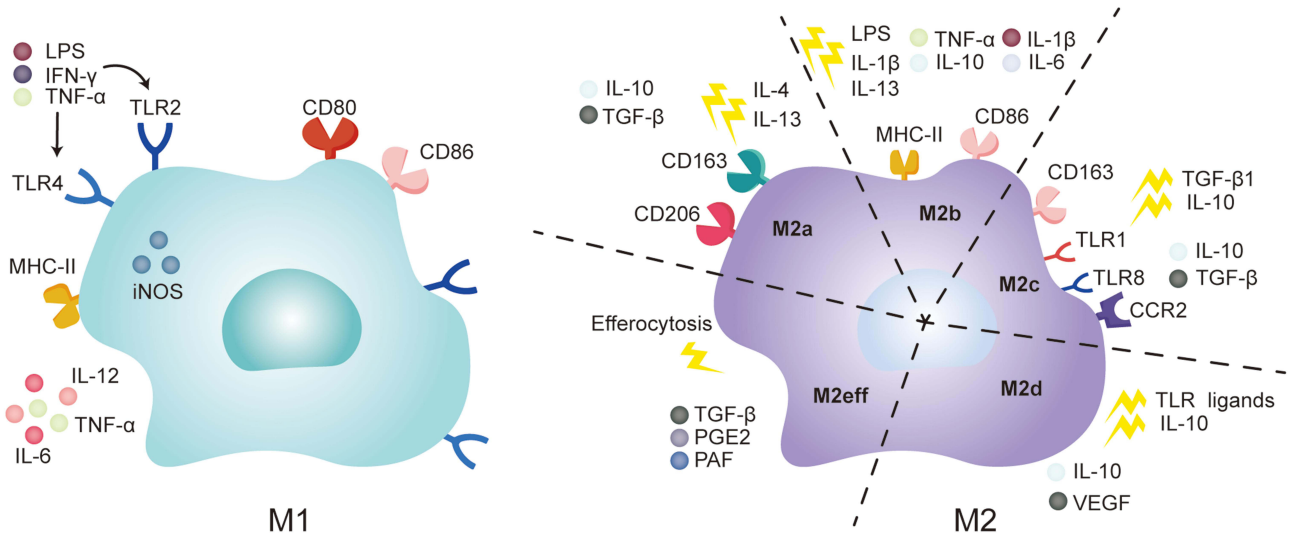

Figure 1 Functional Dynamics of Macrophage Polarization in Inflammatory and Tissue Repair Processes. Upon stimulation with LPS, TNF-α, or IFN-γ, M1 macrophages display pro-inflammatory characteristics, marked by elevated expression of TLR-2, TLR-4, CD80, CD86, iNOS, and MHC-II. Activation of NF-κB and STAT1 signaling pathways promotes the release of IL-6, IL-12, and TNF-α, which in turn intensifies inflammation and aids in pathogen elimination during acute wound healing. During tissue repair, macrophages shift toward anti-inflammatory and pro-repair M2 phenotypes. These M2 subtypes are distinguished by specific activation stimuli, surface markers, and functional roles: M2a: Activated by IL-4 or IL-13, these macrophages express CD206 and CD163 while producing IL-10 and TGF-β. M2b: Triggered by immune complexes, LPS, or IL-1β, they retain MHC-II and CD86 expression and secrete TNF-α, IL-1, IL-6, and IL-10. M2c: Stimulated by IL-10 or TGF-β1, they express CD163, CCR2, TLR1, and TLR8 with elevated IL-10 and TGF-β levels. M2d: Activated via TLR ligands or IL-10, they release IL-10 and VEGF. M2eff: Efferocytosis-induced, these macrophages produce TGF-β, PGE2, and PAF.

secretion of anti-inflammatory cytokines like IL-10 and growth factors such as PDGF and TGF-β.[15,16] Notably, the M2 phenotype can be further subdivided into distinct subtypes (M2a, M2b, M2c, M2d, and M2eff) based on differences in activating factors and surface markers.[17] Specifically, the M2a subtype is predominantly activated by IL-4 or IL-13, exhibiting high expression of CD206 and CD163 alongside the secretion of IL-10 and TGF-β, and is associated with type II inflammation, ECM deposition, fibrosis, and angiogenesis.[18] The M2b subtype is typically induced by immune complexes, LPS, or IL-1β, characterized by the expression of MHC-II and CD86, and the secretion of TNF-α, IL-1, IL-6, and IL-10, thereby participating in immune regulation and TH2 activation.[19] The M2c subtype is mainly induced by IL-10 or TGF-β1, with markers including CD163, CCR2, TLR1, and TLR8, which enhance the expression of IL-10 and TGF-β, contributing to MMP secretion, ECM remodeling, fibrosis, angiogenesis, and apoptotic cell clearance.[20] The M2d subtype emerges following stimulation by TLR ligands or IL-10, accompanied by the secretion of IL-10 and VEGF, thus promoting angiogenesis and eliciting immunosuppression.[21] The M2eff subtype is activated via efferocytosis and participates in the resolution of inflammation and tissue repair by secreting cytokines such as TGF-β, PGE2, and PAF.[22]

It is important to note that this simplified classification has certain limitations in vivo, as macrophages rarely exist in purely M1 or M2 states. Instead, they often adopt a spectrum of intermediate phenotypes in response to dynamic changes in the local microenvironment to meet diverse physiological and pathological demands.[23]

Developmental Origin Dictates Macrophage Function in Tissue Homeostasis and Injury

In addition to the functional variations resulting from different activation states, the developmental origin of macrophages significantly influences their behavior. There are two ontogenic sources for macrophages.[24] The first source arises during embryonic development, where macrophages are initially generated in the yolk sac or fetal liver, subsequently migrating to specific tissues where they differentiate into tissue-resident macrophages (TRMs) with region-specific characteristics. These cells play a critical role in maintaining organ homeostasis.[25] The second stems from the bone marrow hematopoietic system, in which macrophages differentiate from monocytes (moMs), representing the primary source of macrophages postnatally. These cells are capable of homing to sites of injury and, in response to local biological signals, differentiating into specialized functional phenotypes that execute a range of biological roles.[26]

Lineage-tracing studies have demonstrated that most adult cardiac macrophages are derived from the embryonic yolk sac, whereas CCR2-positive monocytes that infiltrate following injury dominate the early inflammatory response.[27] Notably, TRMs of embryonic origin accelerate the repair process by promoting cardiomyocyte proliferation and vascular regeneration. When the migration of monocytes into the injured heart is inhibited, the retention of resident macrophages significantly enhances tissue healing through their anti-inflammatory and reparative functions.[28] Subsequently, monocytes and moMs become the predominant mononuclear phagocyte population at the site of injury, performing functions such as antigen presentation, regulation of inflammation, and replacement of depleted TRMs.[29] Research has revealed that the transition from monocytes to moMs involves a series of continuous phenotypic states—a process referred to as the "monocyte waterfall"—during which monocytes gradually lose their original characteristics and acquire macrophage functions.[30] Recent studies further indicate that once Ly6Chi monocytes enter tissues, they can differentiate into two distinct stromal macrophage subpopulations: one associated with nerve bundles and the other with blood vessels, a binary differentiation observed across multiple tissues.[31] In addition to the phenotypic differences emerging from the gradual maturation of monocytes into moMs, monocytes themselves exist in multiple subsets. For example, in mice, classical Ly6Chi monocytes and non-classical Ly6Clo monocytes (corresponding to human $CD14^{+}CD16^{-}$ and $CD14^{lo}CD16^{+}$, respectively) perform distinct functions under both homeostatic and inflammatory conditions.[32,33]

This suggests that bone marrow-derived monocytes may exacerbate injury by releasing destructive mediators, whereas resident macrophages coordinate the resolution of inflammation and structural remodeling. In a spinal cord injury model, functionally distinct pro-inflammatory and reparative macrophages were observed to migrate to the injury site via specific molecular signals. Pro-inflammatory Ly6ChiCX3CR1lo monocytes depend on the interaction between the CCR2 receptor and the chemokine CCL2 for migration, while reparative Ly6CloCX3CR1hi cells are directed via a molecular pathway involving vascular cell adhesion molecule VCAM-1, integrin receptor VLA-4, and ecto-enzyme

CD73.[34] Lörchner et al demonstrated that following cardiac injury, TNF released by inflammatory monocytes stimulates damaged cardiomyocytes to secrete substantial amounts of regenerating islet-derived protein 3β. This protein recruits specific macrophage subpopulations to clear neutrophils, effectively preventing excessive degradation of the cardiac matrix and structural damage.[35]

Mechanical Cues, Cytoskeletal Dynamics, and Macrophage Phenotype in Tissue Repair

A growing body of evidence indicates that macrophages are mechanosensitive cells capable of perceiving diverse mechanical stresses—such as substrate stiffness and shear stress—present in host tissues.[36] These physical signals are transduced into intracellular biochemical cues through plasma-membrane mechanoreceptors, cytoskeletal force transmission, and nuclear mechanotransduction pathways.[37] Consequently, they modulate infiltrating macrophage behavior, influencing the switch between pro- and anti-inflammatory phenotypes and altering phagocytic activity.[38]

Extracellular Mechanosensing and Phenotypic Polarization

Focal adhesions (FAs) link the extracellular matrix (ECM) to the cytoskeleton and serve as mechanoreceptors. Upon integrin clustering, ECM components engage integrins, which interface with multiple intracellular proteins—including focal-adhesion kinase (FAK). The mechanical activity of integrins is coupled to actin dynamics through FAs.[38] Integrins are heterodimeric receptors composed of non-covalently associated α- and β-subunits;[39] the β-propeller domain of the α-subunit and the βA domain of the β-subunit form the principal ligand-binding site.[40] Mechanical deformation of the ECM exerts tensile forces on bound integrins, inducing conformational extension and activation.[41] In macrophages, expression levels of β2 and β3 integrins correlate positively with adhesion and motility; inhibition of these integrins markedly suppresses both processes.[42] Integrin signalling can also restrain inflammatory activation: macrophages from αM-integrin-deficient mice secrete significantly more TNF-α than wild-type cells after LPS stimulation.[43] Activated integrins recruit and activate downstream mediators such as FAK.[44] FAK is essential for macrophage trafficking; FAK-deficient macrophages exhibit impaired recruitment to inflammatory sites and attenuated chemotaxis toward CSF-1.[45] FAK activation via phosphorylation propagates to downstream molecules such as Rac.[46] Deletion of Rac1 or Rac2 in mice alters macrophage morphology: $Rac1^{-/-}$ bone-marrow-derived macrophages (BMDMs) become elongated with reduced spreading, whereas $Rac2^{-/-}$ cells are likewise elongated but spread to a similar extent. Rac2 deficiency lowers F-actin content and abolishes podosome formation, whereas Rac1 deficiency merely disrupts podosome assembly. Notably, loss of Rac1 does not impair migration, whereas Rac2 deficiency reduces the number of migrating cells without affecting velocity; invasion through matrix substrates is diminished in both Rac1- and Rac2-null macrophages.[47] Integrin-triggered activation of FAK and Src also stimulates ROCK and, via a Rac1/ROCK-dependent mechanism, remodels cell morphology and promotes anti-inflammatory polarization.[48] Under LPS/ATP stimulation, low-stiffness substrates augment mitochondrial ROS production in macrophages; the ROCK inhibitor Y-27632 limits this response and suppresses inflammasome activation and cell migration.[49] Within the 11–88 kPa stiffness range, macrophages up-regulate the anti-inflammatory gene IL-10 in a RhoA/ROCK-dependent manner.[50]

Mechanosensitive ion channels also transduce mechanical cues by altering intracellular ion concentrations and membrane potential.[51] Key channels include the Piezo family and transient receptor potential (TRP) channels. Piezo1 and Piezo2, trimeric propeller-shaped channels, sense mechanical deformation and induce Ca^{2+} influx.[52] Macrophages exhibit Piezo1-dependent mechanosensitivity; periodic hydrostatic pressure drives Ca^{2+} entry, activates AP-1, and induces EDN1 transcription, thereby stabilizing HIF-1α, up-regulating inflammatory genes, and facilitating neutrophil recruitment and pathogen clearance.[53] Piezo1-mediated Ca^{2+} signals also initiate NF-κB-dependent transcriptional programmes that influence macrophage polarization; channel inhibition dampens inflammation and accelerates wound healing.[54] Mechanical stretch suppresses Piezo1 expression and attenuates inflammatory activation, whereas the Piezo1 agonist Yoda1 heightens inflammation, underscoring the channel's mechanosensory role.[55] TRP channels are likewise expressed in macrophages. TRPV4, a mechanosensitive, non-selective Ca^{2+}-permeable cation channel, triggers Ca^{2+}-dependent cytoskeletal remodelling and gene transcription, thereby influencing macrophage phenotype and function.[56]

Increased matrix stiffness drives TRPV4-dependent polarization toward the pro-inflammatory M1 state.[57] TRPV4 also mediates NLRP3 inflammasome activation and IL-1β production, provoking TRPV4-dependent inflammatory responses in vivo.[58]

Cytoskeletal–Nuclear Mechanotransduction of Inflammatory Programs

The nucleus, harbouring the genetic material, acts as a mechanosensitive organelle that directly modulates gene expression. Mechanical signals are relayed from the cytoskeleton to the nuclear envelope and interior via the LINC (linker of nucleoskeleton and cytoskeleton) complex.[59] External forces induce conformational changes in nuclear-membrane proteins, tension the envelope, and open nuclear-pore complexes (NPCs). The same forces stretch, relax, or compact chromatin, initiate DNA and histone modifications, and consequently modulate transcription-factor accessibility.[60] Alterations in actin dynamics orchestrate the nucleocytoplasmic shuttling of transcriptional regulators such as YAP/TAZ and myocardin-related transcription factor A (MRTF-A).[61] On stiff substrates, elevated cytoskeletal tension promotes actin polymerization, dissociating G-actin–MRTF complexes; MRTF subsequently translocates to the nucleus to activate MRTF–SRF target genes. Simultaneously, NF-κB subunits p50 and p65, together with histone deacetylase 3 (HDAC3), are exported to the cytoplasm, down-regulating NF-κB target genes. Conversely, under low-tension conditions, actin depolymerization retains NF-κB and HDAC3 within the nucleus.[62] Reduced actin polymerization also diminishes MRTF-A–SRF activity, thereby attenuating inflammatory responses.[36]

Functional Diversity of Macrophages During Tissue Repair

Temporal Dynamics of Macrophage Polarization: Balancing Inflammation and Regeneration

The timing and duration of M1 and M2 macrophage responses are critical for successful tissue repair, with factors such as injury severity, duration of inflammation, macrophage activation state, tissue type, and the host's overall health all influencing the repair process.[63] In bone repair, depletion of macrophages inhibits the osteoinductive effects of β-tricalcium phosphate.[64] This observation has been confirmed in a mouse tibial injury model, where Alexander et al demonstrated that bone macrophages are essential for type I collagen matrix deposition and bone mineralization. Colony-stimulating factor 1 (CSF-1) significantly increases macrophage numbers at the injury site, concomitantly enhancing type I collagen matrix deposition and promoting mineralization.[65] An initial inflammatory response dominated by M1 macrophages is necessary for bone healing;[66] however, the clearance of macrophages before or during the acute inflammatory phase[67] or the premature suppression of the immune response[68] negatively affects bone repair. Although M1-polarized macrophage-mediated inflammation is generally detrimental to tissue repair, in vitro studies have shown that M1 macrophages can promote the osteogenic differentiation and mineralization of mesenchymal stem cells, suggesting an additional role in bone repair.[69] Nevertheless, sustained chronic inflammation mediated by M1 macrophages is highly deleterious to bone repair; the persistent production of pro-inflammatory cytokines enhances osteoclast activity, leading to bone resorption and inhibition of osteoblast-mediated bone formation.[70] While the reparative functions of M2 macrophages are considered indispensable in tissue healing, their presence during the acute inflammatory phase can be counterproductive.[71] In vitro stimulation of bone marrow-derived macrophages with IL-4 or IL-10 to generate M2a or M2c subsets, followed by injection of these polarized macrophages into full-thickness skin wounds in diabetic db/db mice, revealed that despite exhibiting an anti-inflammatory phenotype in vitro, M2 macrophages did not improve wound healing in wild-type mice and, in fact, delayed wound closure in diabetic mice.[72] Similarly, Dreymueller et al reported that embryonic stem cell-derived macrophages with an M2-like phenotype prolonged the healing time of deep skin wounds created by tail root flaps in mice.[73] Since M0 macrophages in the control group were not driven toward an M1 phenotype by the early pro-inflammatory wound microenvironment, the delayed healing observed with M2 macrophages is more likely attributable to their interference with the early pro-inflammatory phase.[73] These findings suggest that a certain degree of initial pro-inflammatory response is not only benign but necessary to activate subsequent phases of healing, while uncontrolled, prolonged, or excessive inflammatory activation is truly harmful. This conclusion is further supported by the work of Shinozaki et al, which demonstrated that the absence of tumor necrosis factor-α (TNFα) promotes granulation tissue formation yet delays re-epithelialization in mouse skin wounds.[74]

Macrophages also play a vital role in fibrosis regression through the secretion of matrix metalloproteinases (MMPs) that degrade the ECM.[75] In liver injury, MMPs secreted by macrophages are inhibited by TIMPs produced by myofibroblasts and activated hepatic stellate cells, resulting in continuous ECM deposition and scar formation.[76] Once the injurious stimulus subsides, macrophages undergo a phenotypic switch via efferocytosis, transitioning towards an anti-fibrotic, resolution-promoting state.[77] These resolution-phase macrophages not only clear cellular debris but also secrete fibrotic degradation enzymes, including MMP9, MMP12, and MMP13, thereby accelerating the breakdown of fibrotic matrix.[78,79] This indicates that the phenotypic transition of macrophages is crucial in the resolution of fibrosis. Furthermore, studies have shown that the timing of the M2 response directly determines whether soft tissue injury ultimately returns to normal homeostasis or evolves into chronic fibrosis.[80] For example, depleting macrophages during the liver injury phase can reduce the deposition of myofibroblasts and ECM; however, removing them during the fibrosis resolution phase weakens the capacity for ECM degradation,[81] underscoring the critical role of macrophages in orchestrating the temporal regulation of the injury response.

Moreover, the dynamic balance of macrophage phenotypes has been implicated in key aspects of central nervous system repair. During early demyelination, microglia and infiltrating peripheral macrophages exhibit an M(IFN-γ) phenotype, secreting pro-inflammatory cytokines such as IFN-γ. As repair mechanisms are initiated, these cells transition to an M2 phenotype, secreting anti-inflammatory cytokines such as IL-4 and releasing reparative mediators like activin A.[82] Similarly, in liver injury models, IL-4 and IL-10 have been reported to facilitate the conversion of inflammatory monocytes to a reparative phenotype.[83] In a parasitic lung inflammation model, IL-4 binds to IL-4 receptors on macrophages and drives the production of IGF-1 and IL-10, thereby mitigating IL-17-mediated tissue damage.[84] These findings underscore the importance of IL-4R-mediated signaling in promoting the transition of macrophages from a pro-inflammatory to an anti-inflammatory phenotype. In a mouse model with macrophage-specific IL-4R knockout, it was found that the loss of IL-4R in resident macrophages exacerbates liver inflammation without altering fibrosis, whereas the loss of IL-4R in recruited monocytes significantly worsens liver fibrosis without intensifying inflammation.[85] This suggests that the M2 phenotype of resident versus recruited macrophages plays distinct roles in inflammation resolution and fibrosis.

Metabolic Reprogramming in Macrophage Activation and Repair Efficiency

Recent study indicates that the metabolic characteristics of immune cells influence their plasticity and play a role in the tissue repair processes regulated by the immune system.[86] Although macrophages are known to rapidly adapt to the local microenvironment at injury sites—combating infections while promoting repair—they must activate multiple metabolic pathways, including glycolysis, the tricarboxylic acid (TCA) cycle, and fatty acid synthesis, to meet the biosynthetic demands of tissue repair (as shown in Figure 2).[87] The precise impact of these pathways on the repair process remains an active area of investigation.

Activation of hypoxia-inducible factor 1-alpha (HIF-1α) is crucial for the infiltration and activation of myeloid cells in vivo. When HIF-1α is absent, cellular ATP levels dramatically decrease, which impairs myeloid cell aggregation, motility, invasiveness, and bacterial killing. Conversely, loss of HIF-1α's negative regulator, VHL, leads to a markedly increased acute inflammatory response.[88] Under inflammatory conditions, the concentration of the TCA cycle intermediate succinate in macrophages is significantly elevated. This increase in succinate sustains HIF-1α levels and promotes a pro-inflammatory phenotype in macrophages.[89] For instance, upon LPS stimulation, mitochondrial succinate dehydrogenase facilitates succinate oxidation, driving ROS production and inducing the expression of pro-inflammatory genes.[90] In contrast, itaconate can inhibit succinate dehydrogenase, thereby suppressing succinate oxidation and exerting anti-inflammatory effects.[91] Moreover, the phenomenon of trained immunity in myeloid cells is characterized by high glucose consumption and an increased glycolytic rate. This metabolic shift depends on the activation of the HIF-1α pathway; inhibition of HIF-1α markedly reduces the expression of the glucose transporter GLUT1, thereby lowering glycolysis. Consequently, under LPS stimulation, macrophages generate less ATP, which diminishes their bactericidal capacity.[92] In addition, the synthesis of key mediators involved in wound healing, such as IL-1β and vascular endothelial growth factor (VEGF), is significantly reduced in HIF-1α-deficient macrophages.[88] These findings underscore HIF-1α's role in regulating macrophage glycolysis and the TCA cycle, which in turn affects the antibacterial and pro-inflammatory functions of M1 macrophages.

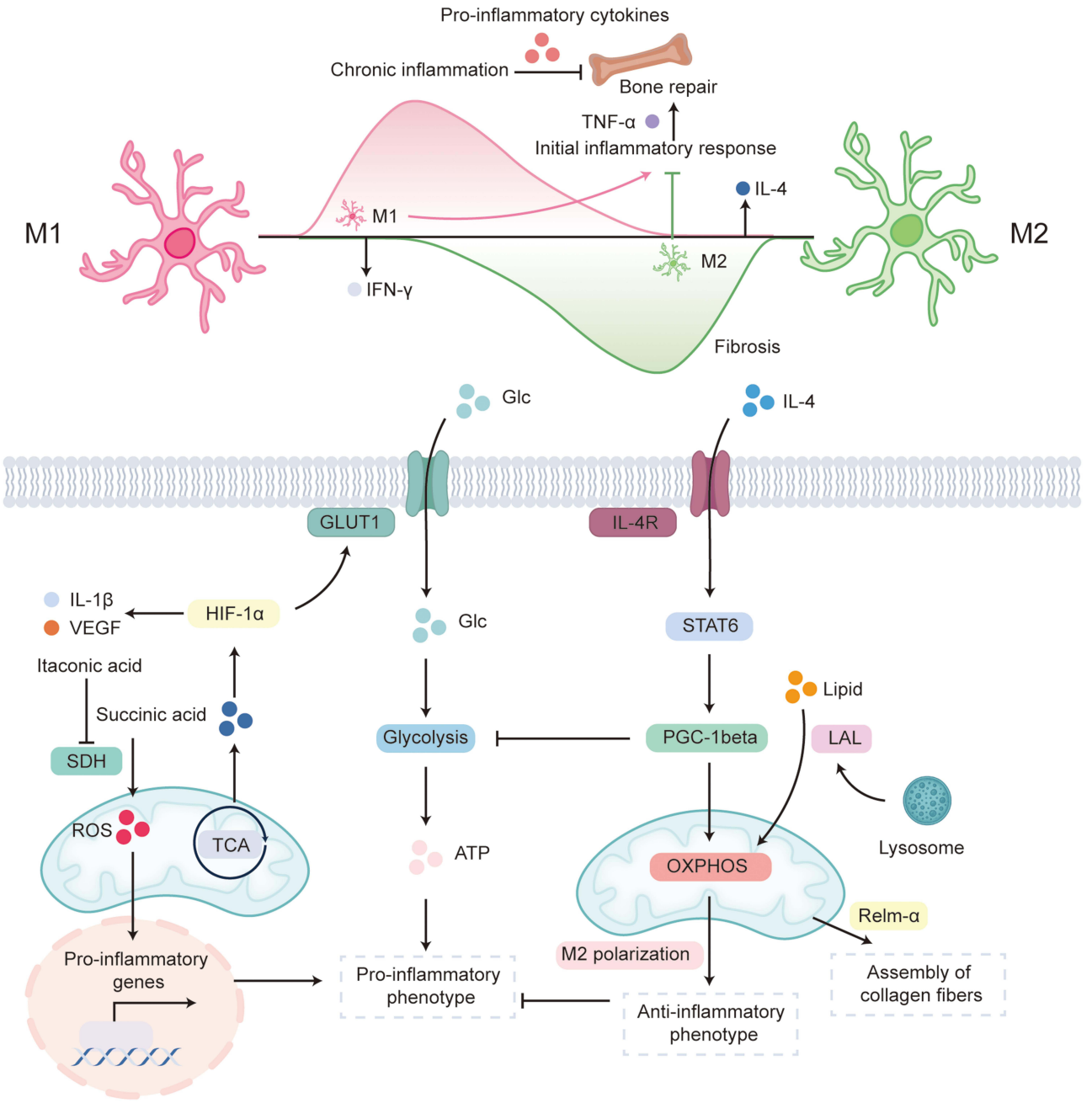

Figure 2 Metabolic reprogramming of macrophages and their role in tissue repair. M1 macrophages secrete inflammatory cytokines such as TNF-α; the acute inflammatory response they drive promotes bone repair, whereas chronic inflammation impairs regeneration. In contrast, M2 macrophages are detrimental during the early repair phase: their anti-inflammatory mediators (eg, IL-4) suppress necessary early inflammation and thereby inhibit the repair process. Glucose is taken up into macrophages via GLUT1 and metabolized through glycolysis to generate ATP, which drives the pro-inflammatory (M1) phenotype. HIF-1α upregulates GLUT1 expression, further reinforcing this phenotype. Under inflammatory conditions, the TCA-cycle intermediate succinate accumulates in macrophages; elevated succinate stabilizes HIF-1α and promotes the M1 phenotype. Succinate can also be oxidized by succinate dehydrogenase to produce ROS, which further enhances pro-inflammatory gene expression. Itaconate counteracts this by inhibiting succinate dehydrogenase, thereby blocking succinate's pro-inflammatory effects. When stimulated with IL-4, macrophages activate the STAT6/PGC-1β pathway to boost mitochondrial oxidative phosphorylation (OXPHOS) and suppress glycolysis; increased OXPHOS favors M2 polarization. Lysosomal acid lipase–mediated lipolysis also supports OXPHOS and M2 differentiation. IL-4–treated macrophages display higher mitochondrial mass, facilitating the release of Relm-α, which signals to fibroblasts to assemble collagen fibers and thereby promotes tissue repair.

Under the influence of Th2 cytokines—including interleukin-4 (IL-4), as well as transcription factors such as STAT6 and PPARγ coactivator-1β (PGC-1β)—macrophages activate pathways of fatty acid oxidation and mitochondrial oxidative phosphorylation.[93] Expression of PGC-1β promotes the M2 polarization of macrophages while strongly inhibiting pro-inflammatory cytokine expression.[93] IL-4-stimulated macrophages exhibit increased rates of fatty acid

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oxidation, improved mitochondrial quality, and enhanced respiratory activity.[93] This metabolic reprogramming from glycolysis toward oxidative phosphorylation is closely associated with the shift from a pro-inflammatory to a reparative (M2) phenotype, suggesting that modulation of macrophage metabolism could be a promising strategy to regulate inflammation. Additionally, lysosomal acid lipase plays a pivotal role in macrophage lipid degradation by promoting fatty acid oxidation. Studies have demonstrated that the lipolytic function of lysosomal acid lipase enhances mitochondrial oxidative phosphorylation and facilitates M2 polarization.[94] Inhibition of lysosomal lipolysis within macrophages has been shown to block IL-4 receptor α-mediated M2 polarization.[94] M2 macrophages activated via IL-4 receptor α further promote tissue repair by facilitating the assembly of collagen fibers. This process involves the transmission of IL-4 receptor α signals from macrophages to fibroblasts, leading to the induction of lysyl hydroxylase 2 expression.[95] Moreover, research indicates that Relm-α participates in this signaling cascade, with its release from macrophages being dependent on proper mitochondrial function.[96]

Anti-Inflammatory and Anti-Fibrotic Roles of Macrophages in Tissue Regeneration

Macrophage anti-inflammatory and anti-fibrotic activities are considered key to the resolution phase of most wound healing responses. As illustrated in Figure 3, De Nardo et al demonstrated that high-density lipoproteins can induce the expression of the transcriptional regulator ATF3 in macrophages, which in turn downregulates the expression of Toll-like receptor (TLR)-induced

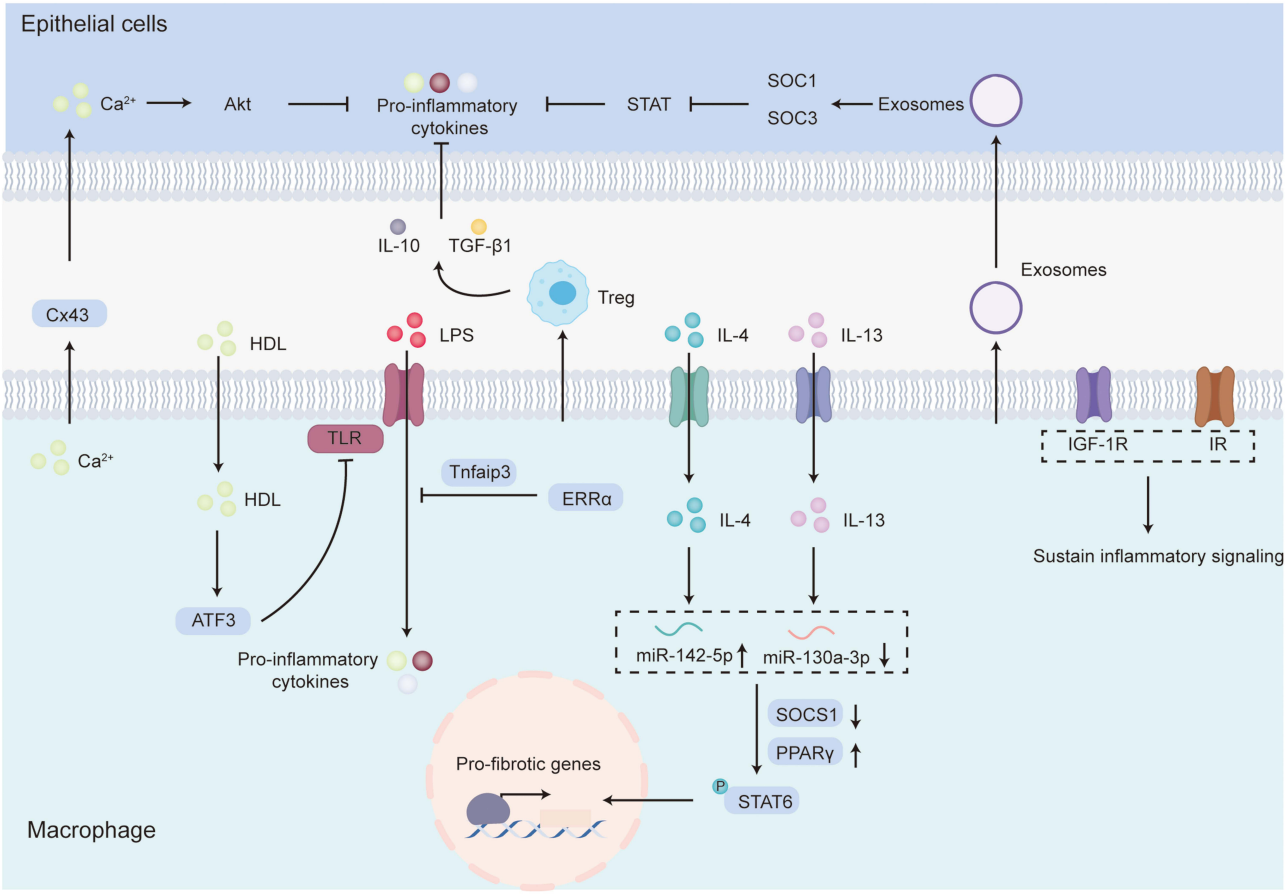

Figure 3 Anti-inflammatory and Antifibrotic Functions of Macrophages. High-density lipoprotein (HDL) induces the transcription factor ATF3 in macrophages; ATF3 downregulates Toll-like receptors (TLRs), thereby suppressing TLR-mediated pro-inflammatory cytokine expression. Estrogen-related receptor α (ERRα) binds to the Tnfaip3 promoter, upregulating Tnfaip3 to inhibit TLR-driven inflammation. IL-4 and IL-13 remodel macrophage microRNA profiles—upregulating miR-142-5p and downregulating miR-130a-3p—to target SOCS1 and relieve PPARγ inhibition, which enhances STAT6 phosphorylation and drives expression of pro-fibrotic genes. Macrophages also assemble Connexin 43 (Cx43) gap junctions that allow direct intercellular Ca^{2+} transfer, activating the Akt pathway in alveolar macrophages (AMs). Via exosomes, macrophages export SOCS1 and SOCS3 to epithelial cells, where they suppress STAT signaling; the combined effect of Akt activation and STAT inhibition alleviates inflammation. Macrophages further promote resolution of inflammation across multiple tissues by regulating regulatory T cells (Tregs) to secrete IL-10 and TGF-β1. Finally, macrophage insulin receptor (IR) and IGF-1 receptor (IGF-1R) signaling play critical roles in controlling interactive inflammatory responses between the epidermis and dermis.

pro-inflammatory cytokines.[97] Yuk et al found that mice deficient in ERRα are more susceptible to endotoxin-induced septic shock, exhibiting a more severe pro-inflammatory response compared to controls. This is because ERRα negatively regulates TLR-induced inflammation by directly binding to the promoter region of the deubiquitinase Tnfaip3 involved in TLR signaling, as well as by controlling metabolic reprogramming.[98] In addition, IL-4 and IL-13 promote the phosphorylation of STAT6 and the expression of pro-fibrotic genes by upregulating miR-142-5p and downregulating miR-130a-3p in macrophages, which leads to the inhibition of SOCS1 and the de-repression of PPARγ.[99] Furthermore, n-3 polyunsaturated fatty acids, which possess anti-inflammatory properties, exert cardioprotective effects by inhibiting macrophage-mediated cardiac fibroblast activation.[100] These findings suggest that multiple mechanisms contribute to the formation of a pro-healing, anti-inflammatory macrophage phenotype. Westphalen et al discovered that a subset of alveolar macrophages (AMs) adherent to the alveolar wall can form gap junction channels with alveolar epithelial cells via connexin 43. These channels permit the direct intercellular transfer of signaling molecules such as Ca^{2+}, which in turn activates the Akt pathway and attenuates the inflammatory response.[101] In addition, AMs have been reported to secrete exosomes and vesicles containing suppressors of cytokine signaling (SOCS) proteins, including SOCS1 and SOCS3, which are then taken up by alveolar epithelial cells. This uptake suppresses the activation of STAT signaling within epithelial cells, thereby limiting the expression of pro-inflammatory cytokines.[102] Macrophages also influence inflammation by modulating intercellular communication among epithelial cells. Knuever et al found that insulin receptor (IR) and IGF-1R signaling in myeloid cells are crucial for regulating the interactive inflammatory response between the epidermis and dermis. When these receptors are absent in myeloid cells, the propagation of inflammatory signals is curtailed, providing a degree of protection against dermatitis.[103] Furthermore, anti-inflammatory macrophages help maintain the resolution of inflammation across multiple tissues by modulating regulatory T cells (Tregs) that secrete IL-10 and TGF-β1.[104]

Recent studies indicate that macrophages activated by type 2 cytokines also exhibit anti-fibrotic activity, particularly during the chronic repair phase. Models of chronic fibrosis and tumors have shown that M(IL-4) polarized macrophages delay fibrosis by inhibiting local $CD4^+$ T cell responses and reducing the ECM production by myofibroblasts.[105,106] In both tumors and granulomas, M(IL-4) macrophages compete with T cells and myofibroblasts in hypoxic regions for arginine and ornithine, thereby creating an immunosuppressive microenvironment.[107] This nutritional competition has been identified as an important immunosuppressive mechanism of regulatory macrophages.[108] Additionally, IL-6, IL-10, and IL-21 have all been shown to enhance the expression of IL-4R on macrophages, thereby promoting their anti-inflammatory and anti-fibrotic functions following IL-4/IL-13 stimulation.[109–111]

Macrophage-Driven Angiogenesis: Mechanisms and Temporal Regulation

Establishing a microvascular network through neovascularization at the wound site is a critical component of tissue repair. However, if this process is not precisely regulated, it may result in either aberrant vascular hyperplasia or insufficient vascular formation/regression—both conditions closely associated with the progression of various diseases.[112] As key modulators of the microenvironment, macrophages are involved throughout vascular regeneration and have been shown to regulate crucial events such as vascular sprouting, elongation, and branching.[113]

Traditionally, M2 macrophages have been regarded as the main promoters of angiogenesis, while M1 macrophages are thought to inhibit vessel formation.[114,115] Yet, recent research has begun to reveal distinct roles for M1 and M2 macrophages at different stages of neovascularization. For example, Willenborg et al demonstrated that during the early phase of repair, a subset of inflammatory CCR2(+)Ly6C(+) macrophages expresses VEGF-A. Macrophage-derived VEGF-A is subsequently converted into epithelial-derived VEGF-A, thereby promoting physiological tissue vascularization and healing.[116] Similarly, other studies indicate that M1 macrophages can release high levels of angiogenic stimulators, including VEGF.[117] Moreover, while a short-term presence (1 day) of M1 macrophages has been shown to promote angiogenesis, their prolonged presence (3 days) leads to vascular regression.[118] This observation aligns with other reports suggesting that M1 macrophages can both enhance[117] and inhibit[16,119] angiogenesis. Notably, vascular regression is an integral part of healthy angiogenesis,[120] implying that M1 macrophages may support vascular formation by modulating their behavior over time. In addition, in vitro studies and in vivo imaging in zebrafish models have shown that $TNFα^+$ M1 macrophages are closely associated with vascular tips, suggesting that these cells not only promote vascular repair through VEGF secretion but also guide endothelial cell migration.[121] The same study further indicated that if pro-inflammatory signals persist or are reactivated in the later stages of repair, proper vascular regression is

impaired, a defect linked to the continued expression of VEGF by pro-inflammatory macrophages.[121] Collectively, these findings suggest that the timely regulation of macrophage function in vascular repair is crucial. An early pro-inflammatory phase to initiate sprouting, followed by a timely transition to an anti-inflammatory phase to permit vascular regression, is essential for successful vascular repair. In addition to M1 macrophages, M2 macrophages also play unique roles during vascular maturation. For instance, M2a macrophages secrete the pericyte chemoattractant PDGF-BB, which stabilizes pericytes and promotes the anastomosis of budding endothelial cells.[117] Meanwhile, M2c macrophages secrete MMPs to degrade the basement membrane, thereby creating space for lumen formation.[122] These data suggest that different M2 phenotypes contribute to various stages of vascular stabilization, remodeling, and maturation, emphasizing the need for further studies to elucidate their functions and dynamic changes in vivo.

Overall, M1 and M2 macrophages cooperate via spatiotemporal regulatory mechanisms to complete angiogenesis: M1 macrophages predominantly drive early vascular sprouting, while M2 macrophages are responsible for later lumen maturation. However, the dynamic regulatory networks governing different macrophage polarization states in complex in vivo environments still require further multidimensional investigation.

Intercellular Crosstalk: Macrophage Interactions with Stromal and Immune Cells During Repair

As core drivers of tissue repair, macrophages interact with mesenchymal stem cells (MSCs) to direct the development of specific cell types.[123] MSCs, which originate from the mesoderm, are multipotent adult stem cells with self-renewal capability that can differentiate into various cell types including chondrocytes, osteoblasts, and adipocytes.[124] The crosstalk between macrophages and MSCs is mediated through paracrine signaling, direct cell–cell contact, and even mitochondrial transfer.[125] MSCs exhibit chemotactic properties, and the initial inflammation and activation of pro-inflammatory macrophages following tissue injury facilitate the recruitment of MSCs to the injury site. Once activated, MSCs secrete a range of chemokines such as CCL2 and CCL4, which further mediate macrophage infiltration.[126]

Direct interactions between macrophages and MSCs via the CD200–CD200R pathway have been shown to enhance the expression of the anti-inflammatory factor TNF-stimulated gene 6 in MSCs.[127] This upregulation, in turn, suppresses the activation of pro-inflammatory macrophages, playing a critical role in protecting tissues from damage induced by excessive inflammation.[128] Moreover, MSCs are capable of forming transient tunneling nanotubes with macrophages, facilitating the transfer of mitochondria.[129] It is reported that the transfer of mitochondria from MSCs to AMs enhances their phagocytic function and promotes their polarization toward a reparative phenotype.[130]

Fibroblasts, which differentiate from MSCs during embryonic development, are responsible for the production of the ECM.[131] Interactions between macrophages and fibroblasts via juxtacrine and paracrine mechanisms promote tissue remodeling.[132] For instance, macrophage-derived TGF-β1 can stimulate fibroblast activation, driving their differentiation into myofibroblasts. These myofibroblasts exhibit high expression of smooth muscle actin and secrete large amounts of collagen, thereby enhancing ECM deposition.[133] Furthermore, as antigen-presenting cells, macrophages interact with T cells to modulate disease outcomes. Within the immune microenvironment, macrophages and T cells play pivotal roles; typically, M1 macrophages are associated with TH1 responses, whereas M2 macrophages are linked with TH2 cells and Tregs. In turn, cytokines secreted by T helper cells also influence macrophage polarization.[134]

Macrophage-Targeted Therapies: Emerging Strategies and Translational Opportunities

Macrophages play complex and essential roles in both disease pathogenesis and tissue repair, and modulation of macrophage functions has become a major focus of preclinical and clinical research.[135] The proliferation, differentiation, and function of monocytes and macrophages are highly dependent on the CSF1/CSF1 receptor (CSF1R) signaling pathway, making this axis an attractive therapeutic target.[136] CSF1 regulates not only macrophage migration, proliferation, and survival, but also their functional heterogeneity and tissue regenerative capacity.[137] Several strategies, including CSF1-Fc fusion proteins, neutralizing antibodies against CSF1 or CSF1R, and CSF1R kinase inhibitors, are currently under extensive evaluation and have begun

clinical testing to modulate macrophage populations within pathological tissues.[138] Anti-CSF1R therapies primarily deplete tissue-resident monocytes and macrophages, impairing their maturation and renewal without substantially affecting pro-inflammatory monocytes, potentially limiting their efficacy in inflammation driven by bone marrow-derived populations.[139] Moreover, activation of the CSF1 pathway notably enhances tissue repair and regeneration. For instance, CSF1-Fc therapy significantly accelerates recovery from acute liver injury and liver regeneration post-hepatectomy by expanding resident macrophage and recruited monocyte populations.[140] Additionally, CSF1-Fc stimulates macrophages to secrete mediators such as urokinase, TNF-α, and IL-6, directly promoting hepatocyte proliferation, although overactivation poses risks of hepatosplenomegaly.[141] Following acute kidney injury, CSF1 similarly accelerates tissue repair by promoting macrophage-derived epithelial regenerative mediators.[142]

Conclusions

Although macrophages are traditionally classified into discrete M1 and M2 states, accumulating evidence indicates that in vivo macrophages predominantly exist in transitional phenotypes, dynamically responding to microenvironmental stimuli. During tissue repair, macrophages undergo sequential transitions from pro-inflammatory to anti-inflammatory and pro-regenerative states, orchestrating processes such as inflammation resolution, fibrosis inhibition, and angiogenesis through precise cytokine-mediated signals. Their intrinsic metabolic reprogramming further underpins this functional plasticity, enabling macrophages to meet the bioenergetic demands of the repair milieu. Interactions between macrophages and stromal cells represent additional critical modulators of macrophage activity, influencing their polarization and regenerative efficacy. Targeting macrophage functions, particularly via the CSF1/CSF1R signaling axis, has emerged as a promising therapeutic approach to enhance tissue healing. Nevertheless, defining macrophage subsets, their dynamic transitional states, and context-specific molecular markers remain critical. Future studies integrating single-cell profiling with functional validation in tissue-specific injury models will be instrumental in refining macrophage-targeted therapeutic strategies, ultimately achieving precise modulation of tissue integrity and regeneration under pathological conditions.

Disclosure

The authors report no conflicts of interest in this work.

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