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Regenerative potential of immune cells after traumatic muscle injury

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Traumatic muscle injury (TMI) causes significant morbidity and socioeconomic burden. Immune cells are central to the subsequent regenerative response, orchestrating dynamic interactions between innate and adaptive immunity. This review systematically summarizes the current understanding of the roles of key immune cells (neutrophils, macrophages, eosinophils, basophils, T lymphocytes, B lymphocytes) in TMI pathophysiology and repair, based on a comprehensive analysis of recent literature. Their intrinsic mechanisms, contributions to tissue regeneration, and therapeutic implications are discussed. Furthermore, we explore therapeutic strategies targeting immune cells, including biomaterials, pharmacologic interventions, cell therapies, and physical modalities. The aim of this review is to provide a consolidated understanding of immune-mediated repair mechanisms in TMI and to identify critical knowledge gaps and future research directions necessary for developing novel immunomodulatory therapies to optimize muscle regeneration and functional recovery.

KEYWORDS

traumatic muscle injury, immune cell, neutrophil, macrophage, T lymphocytes

Introduction

Traumatic muscle injury comprises a range of skeletal muscle pathologies induced by direct trauma to muscle tissue, characterized by structural disruption and potential loss of function (1, 2). Such injuries have a significant impact on athletes (3), military personnel (4), and the elderly population (5), contributing not only to pain and functional limitations but also to a significant socio-economic burden. In the United States, the annual healthcare expenditure associated with sports-related injuries has been reported to reach up to 55.1 billion USD (6). TMI also reduces productivity and diminishes social participation, further compounding its economic impact (5, 6). Beyond the acute phase, traumatic muscle injuries frequently result in chronic complications such as fibrosis and muscle atrophy, which may predispose individuals to secondary osteoarthritis and significantly reduce long-term quality of life (7).

According to the international consensus classification system outlined in the Munich Declaration, these injuries are systematically categorized into four grades based on severity and pathological progression (8). As shown in Table 1, Grade I injuries involve minimal muscle fiber disruption (<5%) without fascial rupture and are characterized by edema detectable on magnetic resonance imaging (MRI) during the acute inflammatory phase, accompanied by negligible functional impairment (8, 9, 16). Grade II injuries involve muscle fiber tears exceeding 5% and/or partial disruption of the fascia, accompanied by a moderate loss of function, transitioning from the acute to the subacute phase, requiring physical therapy and adjunctive interventions for recovery (11, 12, 17). Grade III injuries are characterized by complete muscle fiber rupture with retraction and a total loss of function, corresponding to the phase from subacute-to-regeneration phase and typically requiring surgical intervention (13, 18). Grade IV injuries involve complete rupture of both muscle fibers and the surrounding fascia, marking entry into the reconstruction phase and necessitating surgical structural repair (8, 14, 15).

The interplay between TMI, therapeutic interventions, and the immune system is governed by an orchestrated network of immune cells and molecular mediators (1). This review focuses on the roles of immune cells in the repair and regeneration of traumatic muscle injuries. Specifically, the functions of each type of immune cell are outlined as follows. This search covered multiple databases, including PubMed, EMBASE, and Cochrane Library. Keywords used included “traumatic muscle injury”, “immune cells”, “muscle regeneration”, “neutrophils”, “macrophages”, “T lymphocytes”, “regulatory T cell”, “B lymphocytes”, “eosinophils”, “basophils”, “inflammation”, “fibrosis”, “satellite cells”, “immunomodulation”, and “biomaterials”. Priority was given to studies published from 2015 to the present. Emphasis was placed on preclinical models and clinical studies involving humans or rodents. Articles focusing on non-traumatic muscle diseases (e.g., genetic myopathies) were excluded. Also excluded were articles lacking original data on immune cell mechanisms.

Neutrophils constitute the first line of immune defense following TMI, rapidly infiltrating the damaged tissue to clear necrotic debris and potential pathogens. They initiate the inflammatory phase through the release of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), and by recruiting circulating monocytes to the

injury site. However, excessive or prolonged neutrophil activity intensifies tissue damage, underscoring the importance of tightly regulated inflammatory responses (19). Following neutrophil infiltration, macrophages transition from pro-inflammatory M1 phenotypes to anti-inflammatory M2 phenotypes. M1 macrophages facilitate the clearance of cellular debris and secrete inflammatory mediators, such as TNF- α and IL-1 β . M2 macrophages promote tissue regeneration through the release of growth factors including transforming growth factor- β (TGF- β) and IL-10, and support neovascular post-traumatic (20). This macrophage polarization is essential for effective muscle fiber regeneration and vascular remodeling. T lymphocytes, particularly cluster of differentiation 8 positive T cells (CD8⁺ T cells) and regulatory T cells (Tregs), further modulate the immune microenvironment (21). CD8⁺ T cells enhance macrophage recruitment by inducing monocyte chemoattractant protein-1 (MCP-1) expression (22–24), while Tregs attenuate excessive inflammation and facilitate satellite cell activation (25). Other immune cell types, such as eosinophils and basophils, contribute indirectly by secreting cytokines such as IL-4 and IL-13, which regulate fibroblast function and extracellular matrix remodeling (26–30). The immune response to TMI entails a highly coordinated interaction among immune cells, mediated by cytokines such as high-mobility group box 1 protein (HMGB1), interleukin-33 (IL-33), and other various damage-associated molecular patterns (31). Disruption of this immunological balance may result in persistent inflammation or immunosuppression, hindering tissue regeneration and functional recovery (32–35). Understanding these mechanisms is significant for developing targeted therapies to optimize muscle repair (36).

Despite recent advances, significant challenges remain in translating immune modulation strategies into clinical applications (37). Firstly, the temporal and spatial dynamics of immune cell phenotypes are not fully elucidated, especially in aging populations where macrophage polarization capacity is reduced (38). Secondly, current surgical treatments for Grades III–IV injuries frequently fail to restore native muscle architecture, highlighting the need for combinatorial approaches involving cytokine-targeted biologics, such as anti-TGF- β antibodies (39) and biomaterials engineered to emulate macrophage-derived Wnt7a signaling (40). Novel interventions, including inhibition of neutrophil extracellular traps (NETs) to mitigate chronic inflammation (41) and chimeric antigen receptor - regulatory T

TABLE 1 The grading system, pathological characteristics, and therapeutic interventions corresponding to the severity of TMI.

Grade	Muscle Fiber Damage	Fascial Tear	Inflammatory Phase	Functional Impairment	References
I	Mild (<5%)	None	Acute (MRI-visible edema)	Minimal	(8–10)
II	>5% or partial	Partial	Acute to subacute	Partial	(8, 11, 12)
III	Complete with muscle retraction	None	Subacute to regeneration	Total	(8, 13)
IV	Complete	Complete	Reconstruction	None	(8, 14, 15)

cells (CAR-Treg cell) therapies aimed at fibrosis suppression, show promise in preclinical models but require thorough validation in clinical trials (42).

Etiology and clinical symptoms of TMI

TMI generally result from either indirect non-contact mechanisms, such as strains and fractures, or direct contact injuries, including contusions and lacerations, often caused by mechanical forces and frequently associated with sports-related trauma (1, 43). These injuries generally occur when a muscle is overexerted or subjected to sudden mechanical shock (44), frequently linked to the overstretching of muscle fibers. Moreover, the deformation and ensuing failure of the cell membrane are key components of mechanical injury. Studies suggest that the cell membrane may experience transient rupture following deformation, a process commonly referred to as mechanical porosity (45).

After TMI, just as shown in Table 2, varied signs may arise, with pain and discomfort being particularly common, especially following unaccustomed or intense physical activity. This response is attributed to the release of pro-inflammatory mediators by immune cells, which sensitize nociceptors and subsequently induce pain (46). The pain may be immediate or delayed for several days and is often associated with microscopic

muscle fiber tears, commonly referred to as delayed onset muscle soreness (46, 50, 51). Muscle stiffness and a temporary reduction in strength are additionally frequent, leading to limited movement after exercise (47). This weakness is primarily caused by structural damage to the muscle and the inflammatory response (52), involving protein degradation, apoptosis, and inflammation-induced ultrastructural damage that impairs muscle function (53). Muscle functionality may be compromised, including a range of motion, coordination, and balance, may be compromised (48). Swelling is another important indicator, visible either locally or systemically, especially after eccentric contraction exercises (54–56). The swelling observed is primarily due to the recruitment of immune cells to the injured site, which increases vascular permeability, facilitating the extravasation of plasma proteins and fluids into the surrounding tissue. These events collectively reflect the interplay between structural damage and immune-mediated repair mechanisms in response to TMI.

TMI leads to significant changes in numerous markers, including increased activity of biochemical indicators such as serum creatine kinase (CK), a key marker for assessing the extent of muscle injury (57). Elevated CK levels indicate cell membrane damage and the release of intracellular components (58, 59). Oxidative stress markers, such as malondialdehyde (MDA) and thiobarbituric acid reactive substances, are elevated following injury, reflecting increased levels of oxidative stress (59–61). The immune system releases inflammatory mediators following TMI and modulates immune cell activity. This is reflected in alterations in the number of white blood cells and lymphocytes, which are likely associated with immune activation (62). Research has demonstrated a strong relationship between changes in biochemical markers and the functional status of the immune system (19). For example, serum adenosine deaminase (ADA) activity is elevated following muscle injury, indicating immune system activation. Furthermore, a post-injury immunosuppressed state may arise due to a subsequent decline in immune function (63).

The onset and progression of these responses are influenced by multiple factors, including the type, intensity, and duration of exercise, as well as the individual’s adaptive capacity to physical activity. Early detection of these responses is essential for timely diagnosis and intervention in traumatic muscle injuries, thus facilitating recovery and reducing the risk of further tissue damage.

Diagnosis and treatment of TMI

Based on these symptoms, a preliminary diagnosis can be made, further supported by diagnostic tools such as ultrasound (64, 65) and MRI (66). These imaging techniques are commonly used to identify the location, extent, and severity of the injury (67, 68). Biomechanical and molecular biological indicators, such as the rate of force development, serve as more sensitive indirect markers for assessing TMI than maximum voluntary isometric contraction peak torque (69).

TABLE 2 Clinical symptoms of TMI.

Symptoms	Causes	A link to the immune system	References
Pain and discomfort	Tearing of muscle fibers	Immune cells release pro-inflammatory mediators that cause sensitization of nociceptors, which triggers pain.	(46)
Muscle stiffness	Pain and limited movement after exercise	Inflammation can lead to muscle stiffness, as well as decreased function, etc., because protein degradation, apoptosis, and local inflammatory response during inflammation can lead to ultrastructural damage of muscle cells, resulting in muscle being unable to perform normal function.	(47, 48)
Muscle dysfunction	Damage to muscle structure and inflammatory response		
Swelling of muscle	Inflammation and increased vascular permeability	Immune cells are recruited to the injury site, resulting in increased local vascular permeability, and the infiltration of proteins and other liquids in plasma into the tissue space causing local edema or swelling.	(49)

Treatment for TMI involves several approaches, including initial management, non-surgical and surgical treatments, rehabilitation, and preventive measures. Initial management typically involves protection, rest, optimal use of the injured limb, and cold therapy, following the RICE principle of “rest, ice, compression, and elevation” (70). For more severe injuries, immobilizing the limb for a few days may be necessary to facilitate scarring. Most muscle injuries recover well with conservative, non-surgical treatments, such as non-steroidal anti-inflammatory drugs (NSAIDs) (71), ultrasound therapy (64, 65), strengthening and stretching training (72), and painless joint mobility exercise (1, 9). Surgical treatment is reserved for cases of complete muscle tears or total loss of function (73, 74). Procedures may include hematoma drainage (75) and muscle-tendon reattachment and reinforcement (76). The recovery phase commences after initial treatment, emphasizing rehabilitation to restore function rather than merely alleviating symptoms (77). Primary rehabilitation objectives encompass accurate diagnosis, mitigating the adverse local effects of acute injury, promoting proper healing, preserving motor function, and restoring normal activity levels (78, 79).

Preventive measures are crucial for reducing the risk of muscle injuries, especially in athletes involved in sports such as football. Key strategies include adequate warm-ups, temperature regulation, and stretching, all of which help lower the risk of strains. Increasing muscle strength, endurance, and flexibility is vital for improving athletic performance and preventing injuries. Although traumatic muscle injuries are prevalent among athletes, successful recovery is attainable through proper classification, prompt diagnosis, and effective treatment.

Immune cells response to TMI repair

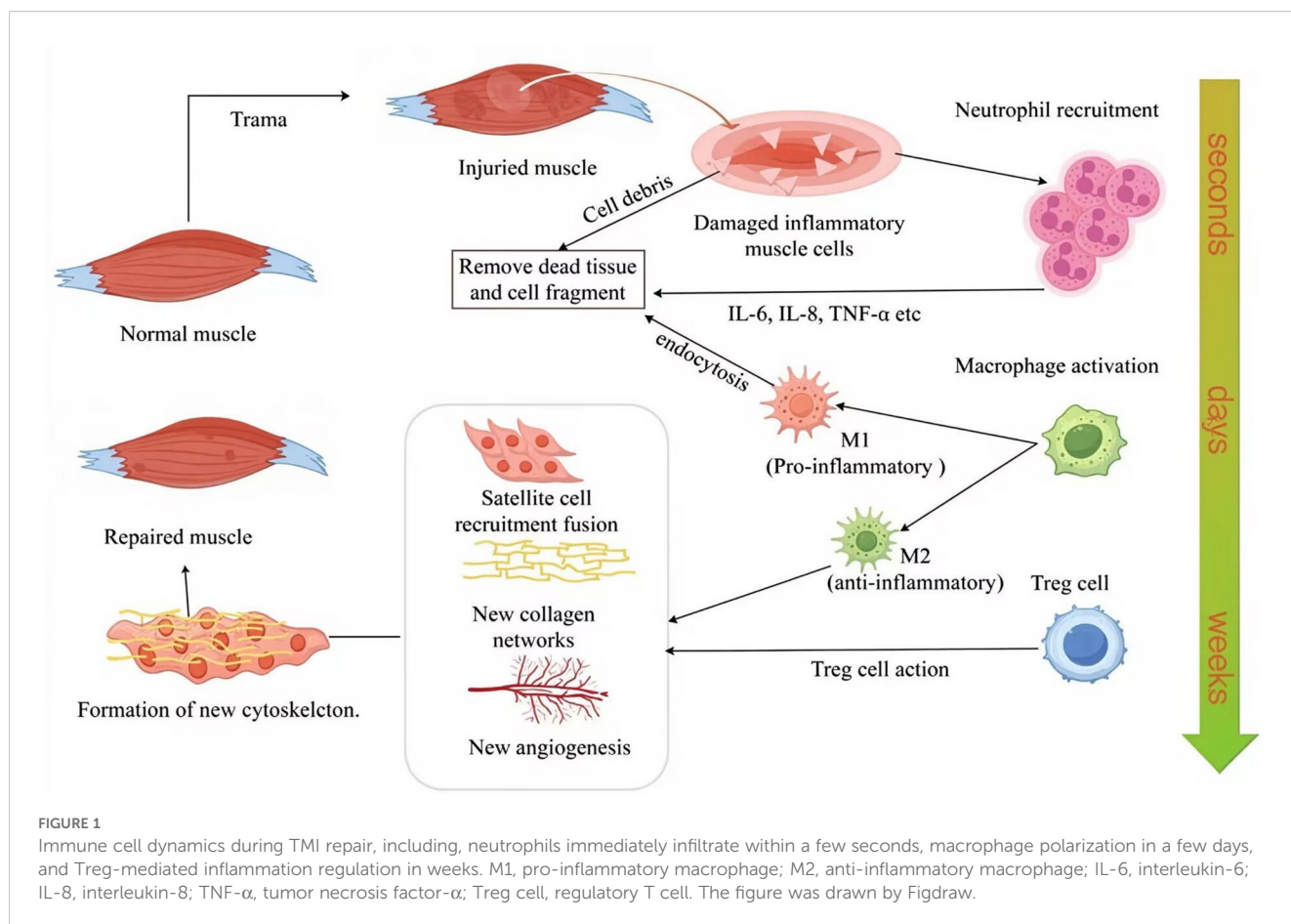
After TMI, the immune system initiates an inflammatory response to remove damaged cells and tissue debris, setting the stage for muscle tissue repair. This process involves vasodilation, cell migration, and the activation of inflammatory cells (80). Simultaneously, the immune system orchestrates and regulates the functions of diverse cellular components, with macrophages playing a central role in driving muscle tissue repair and regeneration following TMI (81). After an injury, the immune system activates muscle stem cells, transitioning them from a quiescent state to active proliferation, which forms the basis for effective muscle tissue repair and regeneration (82). The immune system induces fibroblasts to differentiate into myofibroblasts, which produce collagen and other extracellular matrix components vital for providing structural support to the newly formed muscle tissue (83). It also promotes angiogenesis, ensuring a sufficient nutrient supply and oxygenation for the regenerating muscle tissue.

Moreover, the immune system orchestrates the activities of immunocompetent cells such as macrophages, lymphocytes, and dendritic cells, which secrete multiple cytokines to enhance muscle repair and regeneration (80). The interaction between the immune

system and muscle repair is highly coordinated, involving the recruitment and functional transformation of immune cells and other key processes. Continued research in this area improves our understanding of muscle repair mechanisms and may provide novel strategies for treating related disorders.

TMI triggers an intricate host response that disrupts immune homeostasis, increasing susceptibility to opportunistic infections and inflammatory complications such as infections, multiple organ dysfunction syndrome (MODS) (84), immunosuppression (85), and associated inflammatory responses. Following trauma, the body initiates a cascade of immune reactions to control inflammation at the injury site and support tissue repair (86). However, excessive production of pro-inflammatory cytokines can drive the immune response into an immunosuppressive state (86), significantly contributing to complications like nosocomial pneumonia, systemic inflammatory response syndrome, and MODS (86). Severe trauma often leads to increased activation of innate immune cells and overproduction of inflammatory mediators (87). This over-activation can result in systemic pro-inflammatory circulation and cytokine storms (88) that provoke strong non-infectious systemic inflammatory responses (89). MODS can arise from an orchestrated inflammatory response (90). These observations underscore a crucial point: the complications are closely linked to the immune system, and the regeneration of TMI relies heavily on the inflammatory processes during this phase (91). Furthermore, immune cells are essential in coordinating the inflammatory response, initiating transient inflammation following various types of injury (92). The development and function of these cells are modulated by proteins whose expression is influenced by the surrounding inflammatory environment (93–95). In summary, most complications from traumatic muscle injuries are closely associated with inflammation, primarily driven by immune responses, including activating pro-inflammatory factors and immune cell participation.

As shown in [Figure 1](#), the healing process following TMI progresses through distinct phases, beginning with an inflammatory response. Upon muscle damage, resident cells within the affected tissue release a spectrum of cytokines, including pro-inflammatory mediators such as TNF- α and IL-1 β , as well as anti-inflammatory cytokines such as IL-6, interleukin-8 (IL-8), and interferon- γ (IFN- γ). These cytokines upregulate adhesion molecule expression, facilitating the recruitment of leukocytes from the circulation to the injury site. Neutrophils are the first immune cells to infiltrate the damaged tissue, where they play a pivotal role in removing necrotic material and cellular debris, initiating the repair process (96, 97). As the process advances, macrophage activation shifts significantly, with pro-inflammatory macrophages dominating the local microenvironment. These macrophages secrete pro-inflammatory cytokines, further promoting myogenic cell proliferation and expanding the satellite cell population. Depending on their activation phenotype, macrophages can adopt various roles throughout TMI repair (98). Tregs also play a significant role. Studies have shown that these cells can accelerate healing processes when directly injected into



damaged bone, muscle, or skin (99). Tregs regulate immune responses while creating a microenvironment conducive to effective tissue repair (100, 101). Following debris clearance, satellite cell recruitment and fusion occur: quiescent satellite cells become activated and proliferate, then migrate to the site of injury, where they fuse with adjacent muscle fibers to form new myofibers, ultimately restoring muscle function (102). Finally, new vascular networks form during the fibrosis and maturation phases, and collagen deposition occurs, driven by factors released from macrophages as healing advances. The process culminates in the maturation stage, where damaged tissues are either fully replaced or remodeled to restore functional normalcy (103).

The immune system's response to TMI involves a multifaceted interplay of mechanisms mediated by immune cells, which are crucial for post-injury muscle repair. Following trauma, these cells play pivotal roles, including the activation and differentiation of muscle stem cells, the regulation of inflammation, the clearance of damaged tissues, and active participation in tissue regeneration.

Neutrophils

Neutrophils play an important role in both the initial injury and repair of TMI, serving as a necessary component of the innate

immune system that combats infections through pathogen engulfment and the release of antibacterial enzymes (104). In both murine and human studies, an inflammatory response is triggered upon TMI, producing diverse inflammatory cytokines and chemokines (105). These substances, such as IL-6, IL-8, C-X-C motif chemokine ligand (CXCL) neutrophil chemokines, and TNF- α , act on endothelial cells adjacent to blood vessels, attracting and recruiting neutrophils to the site of injury (106, 107). Many members of the CXCL family, as potent neutrophil chemokines, are secreted by various cell types such as endothelial cells, fibroblasts, and macrophages (108). They induce neutrophil polarization and migration by activating CXCR1 and CXCR2 receptors on neutrophils (109). Moreover, they form a concentration gradient near the injury site, guiding neutrophils to migrate from the intravascular space to the damaged area. Endothelial cells play a crucial role in this process. They not only secrete chemokines but also upregulate the expression of adhesion molecules (e.g., selectins) to promote neutrophil rolling and attachment (110). Additionally, upon treatment with IL-1 or TNF- α , endothelial cells can synthesize and secrete chemokines structurally similar to the neutrophil-activating factor (NAF) derived from human monocytes, further enhancing neutrophil activation and migration (111). Cytokines such as IL-6 and TNF- α also play important roles in the inflammatory response; they can stimulate endothelial cells to produce more chemokines, thereby

strengthening neutrophil recruitment (112). At the very beginning of TMI, neutrophils rapidly migrate to the injured area to eliminate necrotic tissue and cellular debris, creating favorable conditions for reparative processes. Although the core mechanisms of neutrophil recruitment and function are conserved between mice and humans, species-specific differences in cytokine kinetics or receptor expression may affect the magnitude and duration of their response (113).

During the early stages of TMI, neutrophils contribute to the inflammatory response by releasing reactive oxygen species (ROS) and proteases, which facilitate the initial repair of the injured site (114, 115). NETosis (Neutrophil Extracellular Trap formation), a mechanism by which neutrophils release NETs during infection or inflammation to capture and kill pathogens through reticular structures, also contributes here (116, 117). Removing cell and fiber debris facilitates muscle regeneration and connective tissue deposition and triggers a strong inflammatory response (105). As a result, the over-activation of neutrophils may lead to further tissue damage, highlighting the need to precisely regulate their function (118). However, recent studies highlight the functional plasticity of neutrophils, with pro-inflammatory N1 and anti-inflammatory N2 phenotypes mirroring the M1/M2 macrophage dichotomy (119). In the acute inflammatory stage, N1 neutrophils are dominant and release reactive oxygen species and proteases, such as matrix metalloproteinase-8 (MMP-8) and MMP-9, which are involved in the killing of pathogens (120). During the inflammation resolution phase, N2 neutrophils emerge and express anti-inflammatory molecules including CD206, Arg1, and IL-10, thereby participating in tissue repair and scar formation (121). Furthermore, N2 neutrophils, which appear during the resolution phase of inflammation, secrete anti-inflammatory mediators such as IL-10 (122, 123). Notably, under the influence of cytokines such as CXCL1, neutrophils undergo reverse migration from damaged muscle tissue (116). This process rapidly depletes local neutrophil populations, promoting inflammation resolution and creating a favorable microenvironment for tissue regeneration and repair (116). Reverse-migrated neutrophils re-enter the vasculature, transit through the lungs, and return to the bone marrow for clearance (116). This clearance pathway represents the most favorable outcome for effective tissue repair. However, aging significantly impacts this process. The N3 ageing signatures impacts muscle function, including changes in muscle mass, fiber type, and reduced regenerative capacity of muscle stem cells (124). Additionally, age alters immune dynamics post-traumatic muscle injury (TMI). Compared to young mice, older mice exhibit delayed neutrophil clearance after peak infiltration and show age-specific changes in monocyte/macrophage subpopulation abundance (125).

As the inflammatory response at the injury site gradually subsides, IL-10 from N2 neutrophils promotes macrophage polarization toward a regenerative phenotype, enhancing myoblast proliferation and satellite cell activation in murine models (126–128). However, human studies suggest additional complexity, with neutrophil-derived extracellular vesicles (EVs) playing a role in satellite cell regulation (129). Moreover, anti-inflammatory macrophages release pro-inflammatory cytokines

such as IL-6 and TNF- α , which stimulate myoblast proliferation and satellite cell recruitment. These cells then fuse with surrounding muscle fibers, forming new myonuclei, enhancing protein synthesis, and promoting muscle regeneration (73, 130, 131). It is important to note that cytokines and chemical signals finely regulate neutrophil function following muscle injury. IL-8 facilitates neutrophil recruitment and function, while TNF- α is crucial in initiating early inflammatory responses (119, 132). During muscle repair, these cytokines not only influence neutrophil migration and function but exert downstream effects on other immune cells, including macrophages and lymphocytes, during muscle repair.

In summary, neutrophils show dual functions in TMI repair. They facilitate initial repair by eliminating necrotic tissue and pathogens, while promoting muscle regeneration through the release of pro-inflammatory factors and participation in the inflammatory response (104, 115, 133). However, their over-activation can exacerbate tissue damage, necessitating precise regulation of their function for optimal repair (115).

Studies in murine and human models underscore neutrophils' pivotal yet complex role of neutrophils in muscle regeneration (41, 134). In studies on physical therapy for damaged muscles using mouse models, David J. Mooney's team conducted a series of experiments demonstrating that massage therapy can facilitate the removal of neutrophils from injured muscles. This reduction minimizes the negative impact of neutrophil-associated secretions on muscle progenitor cell differentiation, promoting myogenesis by influencing muscle fiber maturation and supporting muscle regeneration (135). Furthermore, studies in CCR2-deficient mice have shown that the peak number of neutrophils coincides with the activation of muscle satellite cells, suggesting that neutrophils may play a role in satellite cell activation (136). This is critical because satellite cells are necessary for maintaining uninjured muscle and rapidly responding to growth or regeneration signals to re-enter the cell cycle (137, 138). Neutrophils influence the dynamics of satellite cells by releasing paracrine factors, further supporting their involvement in muscle regeneration (139). The heterogeneity and plasticity of neutrophils contribute to tissue repair. They clear damaged tissue, and form NETs, which aid in regulating cell proliferation (140, 141). Finally, neutrophil depletion studies, such as those involving mice injected with snake venom toxin, have demonstrated that the absence of neutrophils leads to significant tissue necrosis and impaired regenerative responses (1, 142).

Other studies have suggested that neutrophils may not significantly impact muscle recovery. In one study, mice underwent a 10-day offloading of their hind limbs, followed by reloading after neutrophil depletion. The results indicated that neutrophil depletion did not affect strength loss or the recovery of atrophied muscle fibers (143). The potential for neutrophils to exacerbate muscle injury has been extensively explored, as summarized in Table 3. Besides the previously reported reduction of neutrophils through massage therapy to promote muscle repair (135), and hyperactive neutrophils contribute to severe inflammation. Neutrophil-derived mediators such as superoxide dismutase 2 (SOD-2), glutathione peroxidase (GPX), catalase (CAT), and thioredoxin (TRX) induce muscle fiber damage,

TABLE 3 Overview of the role of neutrophils in TMI repair.

Reference	Research model/ platform	Research mechanism	Conclusions related to immune cells
(136)	Dual laser Multimode nonlinear optical microscope platform	The peak number of neutrophils coincided with the activation of muscle satellite cells.	Neutrophils may be involved in the activation of satellite cells in favor of muscle repair.
(142)	Male Swiss mice were pretreated with anti-mouse granulocyte immunoglobulin G (IgG) or control antibody.	Likely through phagocytosis of necrotic debris and the recruitment of other inflammatory cells, both of which are critical for effective muscle repair.	Neutrophils play a key role in skeletal muscle regeneration following Bothrops asper.
(144)	A peptidyl arginine deiminase 4 (PAD4) deficient mouse model	Neutrophils induce secondary immune thrombosis through PAD-dependent mechanisms, thereby promoting the healing of injured tissues.	Insufficient immune thrombosis caused by neutrophils may cause damaged tissue to bleed and be difficult to heal.
(143)	Mice underwent 10 days of hindlimb unloading and neutrophil depletion before reloading.	LPS alters the activation state of neutrophils, otherwise, neutrophilic infiltration is highly regulated and effectively eliminated during regulated mechanical loading without significant muscle fiber damage	Neutrophil consumption does not affect loss of strength or restoration of atrophied fibers.
(135)	Real-time force control compatible with ultrasound for tissue strain analysis.	In addition to neutrophils in the injured muscle, the inhibitory effect of neutrophil-related secretion factors on the differentiation of muscle progenitor cells was reduced.	Massage to clarify that neutrophils promote myogenesis by changing the type of muscle fiber maturation, thus promoting muscle regeneration.
(145)	Humans normally heal open damage and pressure ulcers.	MPO deficiency leads to an intensification of the inflammatory response and affects neutrophil function, including cytokine production.	MPO, as a key enzyme in neutrophils, produces reactive oxygen intermediates such as hypochlorous acid that help kill microorganisms, but may also cause tissue damage.

(Continued)

TABLE 3 Continued

Reference	Research model/ platform	Research mechanism	Conclusions related to immune cells
(146)	Nanoparticles were used to label bone marrow-derived mesenchymal stem cells (BM-MSCs)	Neutrophil-derived mediators are made by SOD. When hydrogen peroxide accumulates, it is toxic to cells, causing membrane lipid peroxidation and membrane fission, leading to cell damage and death.	When the medium produced by neutrophils is less superoxide, the cytotoxicity and the influence on cell proliferation activity are less, which is conducive to tissue repair.

membrane disruption, and oxidative lipid degradation (146–148). For instance, myeloperoxidase (MPO), a key enzyme in neutrophils, generates ROS such as hypochlorous acid, which plays a crucial role in microbial killing but can also contribute to tissue damage (145).

The presence and activity of neutrophils may be associated with the pathogenesis of TMI. Animal studies have shown that neutrophil depletion can enhance muscle regeneration, supporting the hypothesis that neutrophils contribute to muscle damage. Researchers found the depletion of neutrophils in young mdx mice reduced muscle degradation (149). Furthermore, in the mdx animal models of muscular dystrophy, elevated levels of neutrophil elastase and ROS have been shown to impair myoblast survival and differentiation (150). Overstimulation of neutrophils in these contexts leads to excessive NETs formation, which is cytotoxic and can hinder muscle tissue regeneration; studies have shown that the components of NETs, namely purified histone type-IIA, can inhibit cell growth in a concentration-dependent manner and induce cytotoxicity. This thereby hinders the repair of various tissues (151).

Neutrophils play diverse roles in TMI repair, including initiating the inflammatory response, facilitating muscle regeneration, modulation of the inflammatory environment, and contributing to dual functions. In the pathophysiological process of TMI, neutrophils play a complex and bidirectional regulatory role (115). Their functions exhibit significant duality - they not only provide necessary support for early inflammation initiation and tissue regeneration, but also may exacerbate secondary damage due to excessive activation (104). From a positive perspective, after injury occurs, neutrophils rapidly migrate through the vascular endothelium to the damaged muscle tissue, using phagocytosis to clear local necrotic muscle fiber fragments and invading pathogens, creating a microenvironment for subsequent repair (109, 116). At the same time, the proteins and ROS secreted by them can activate satellite cells through signal transduction pathways, promoting the proliferation and differentiation of myogenic precursor cells; the released chemokines (such as CXCL8) can recruit monocytes and macrophages to infiltrate the injury site, initiating the regeneration cascade reaction. Moreover, NETs play a key role in limiting the

expansion of the injury range by capturing pathogens and degrading cell debris, thereby restricting oxidative stress damage to healthy muscle fibers and degradation of extracellular matrix. However, excessive activation and continuous infiltration of neutrophils may lead to amplification of the injury effect (117). Excessive ROS and proteins can exceed the physiological regulatory threshold, directly causing oxidative damage to healthy muscle fibers and degradation of the extracellular matrix. This inhibits the regenerative potential of muscle satellite cells; moreover, the pro-inflammatory mediators these cells secrete delay the phenotypic transformation of macrophages from M1 to M2, hinder the establishment of an anti-inflammatory microenvironment, and thereby promote fibrosis and ectopic ossification (116). In the future, through precise regulation of their temporal and spatial dynamics, while retaining their early clearance function, and avoiding excessive damage, it will be possible to maximize their promoting effect on muscle repair (152).

Monocytes/macrophages

Macrophages are critical to TMI, which is pivotal in initiating and resolving inflammatory responses (153, 154). Their functions are regulated through distinct phenotypic polarization—M1 and M2—which either promote or inhibit muscle regeneration (155, 156). Herein, there are three main approaches to macrophage differentiation: 1) each monocyte subpopulation differentiates into a specific macrophage phenotype; 2) the macrophage phenotype is determined by microenvironmental signals and cytokines, primarily in the context of inflammation; 3) mature macrophages can shift between pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes in response to changes in their tissue environment (157, 158).

M1 macrophages, primarily pro-inflammatory, contribute to clearing damaged tissue by engulfing apoptotic or necrotic muscle fibers, releasing inflammatory mediators such as TNF- α and IL-1 β (159, 160), and activating other immune system components. These pro-inflammatory actions facilitate tissue cleaning and fibrous debris (139). However, as clearly illustrated in Figure 2, M1 macrophages may also intensify muscle damage by generating ROS and nitric oxide (NO) (161). NO concentration critically determines its effect: high levels induce apoptosis, while low levels protect against oxidative stress and even promote muscle cell proliferation/growth in early repair (162, 163), suggesting NO modulates the regeneration-fibrosis balance. Furthermore, prolonged M1 activation promotes excessive fibrosis (164, 165) and can inhibit axon (166, 167) and potentially muscle fiber regeneration (168) impairing long-term recovery. In summary, while M1 macrophages are essential for initial inflammation and clearance, their overactivation or persistence negatively impacts repair through fibrosis and inhibition of regeneration (169, 170). Meanwhile, studies have shown that by synthesizing PLGA (poly (lactic-co-glycolic acid)) nanoparticles that encapsulate magnesium and delivering them to macrophages to reduce the M1 phenotype, the macrophage phenotype can be resolved in the context of muscle repair to alleviate inflammation and improve tissue regeneration

(171). In summary, M1 macrophages release pro-inflammatory factors that serve a dual function in muscle repair.

In contrast, M2 macrophages transition from an initial anti-inflammatory role to become central mediators of tissue regeneration. This functional adaptation is facilitated by distinct M2 subtypes (M2a, M2b, M2c, M2d), classified based on activating stimuli and transcriptional profiles, each with specific functions (172). M2a is activated by IL-4 or IL-13 and is primarily involved in immune regulation and tissue repair. M2b is activated by LPS or IL-1 β and has immune regulatory and inhibitory functions. M2c is activated by IL-10, TGF- β , or glucocorticoids and exhibits anti-inflammatory and immunosuppressive properties. M2d is activated by stimuli such as IL-10, IL-12, TNF- α , TGF- β , Vascular endothelial growth factor (VEGF), and MMPs, and its main functions are immunosuppression and angiogenesis.

As regeneration progresses into later stages, M2a macrophages, also referred to as alternatively activated macrophages, predominantly function during the early stages of immune responses. They suppress inflammatory reactions and stimulate the proliferation of non-myeloid cells through the secretion of regulatory cytokines such as IL-4 and IL-13. Additionally, M2a macrophages play a role in fibrosis by regulating fibroblast activities via the secretion of factors like TGF- β (173). M2b macrophages show increased activity during the later stages of muscle regeneration. They facilitate the proliferation and differentiation of muscle cells while simultaneously reducing apoptosis, and improving enhancing muscle repair capacity. Evidence suggests that M2b macrophages promote muscle cell differentiation and muscle fiber formation through the secretion of anti-inflammatory factors such as TGF- β 1 (91). Furthermore, M2b macrophages suppress the activity of M1 macrophages and mitigate inflammatory responses, thus fostering an environment conducive to muscle regeneration. M2c macrophages inhibit the pro-inflammatory function of M1 macrophages by secreting anti-inflammatory factors such as IL-10 and TGF- β , facilitating tissue repair and fibrosis processes. They can inhibit the phenotype of M1 macrophages and promote the proliferation of non-myeloid cells. M2c macrophages are likewise involved in the fibrosis process and promote tissue remodeling by regulating the differentiation of fibroblast precursors (11).

Following skeletal muscle injury, macrophage subsets. Spatially and Temporally form multi-layered regenerative inflammatory zones (RIZs). Spatially resolved transcriptomic analyses reveal that the dynamic changes in macrophage subtypes and the ordered structure of RIZs are fundamental to efficient skeletal muscle regeneration (174). Within these zones, subsets such as Growth Factor expressing macrophages (GFEMs) promote regeneration by secreting factors like growth differentiation factor (GDF-15), a process transcriptionally controlled by the PPAR γ /RXR axis. GDF-15 deficiency results in delayed muscle regeneration, highlighting GFEMs and GDF-15 as key regulatory factors in regenerative repair (175).

Exploring the specific mechanism of macrophages in TMI, we know macrophages are modulated by multiple signaling pathways during their polarization and functional transformation. Following

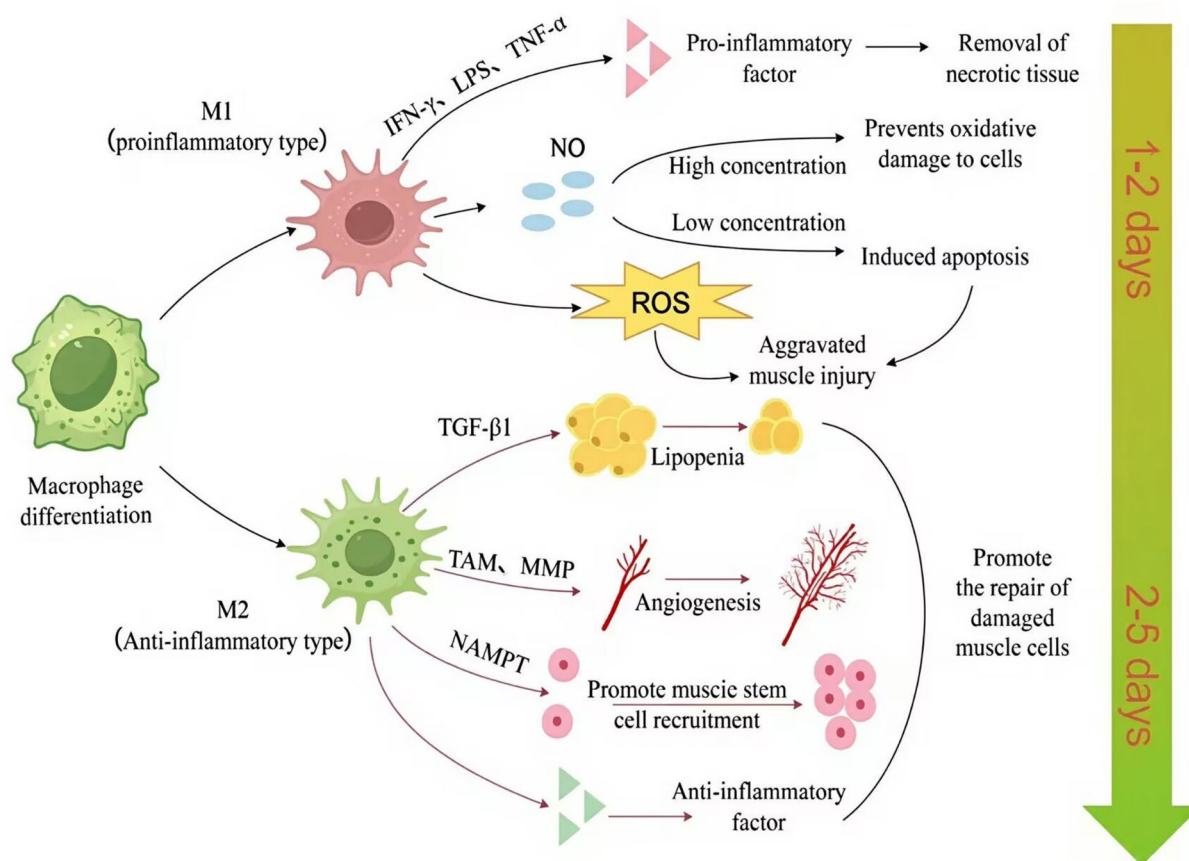


FIGURE 2

Macrophages shift from a pro-inflammatory (M1) phenotype (peaking at 0.5–2 days post-injury) to an anti-inflammatory (M2) phenotype (maximal at 3.5–10 days), dynamically coordinating tissue debridement, stem cell activation, and regenerative remodeling (2). The figure was drawn by Figdraw. ROS, reactive oxygen species; TAM, tamoxifen; MMP, matrix metalloproteinase; NO, nitric oxide; NAMPT, nicotinamide phosphoribosyl transferase. TGF- β 1, transforming growth factor- β 1; LPS, lipopolysaccharide; TNF- α , tumor necrosis factor- α ; IFN- γ , interferon- γ ; M1, pro-inflammatory macrophage; M2, anti-inflammatory macrophage.

tissue injury, the nuclear factor- κ B (NF- κ B) pathway is activated by Toll-like receptors (TLRs) (176), ROS, or damage-associated molecular patterns (DAMPs) (177). This activation dominates the pro-inflammatory response and regulates the release of inflammatory cytokines such as TNF- α . While this process facilitates the clearance of necrotic tissues during the acute phase, persistent activation may lead to chronic inflammation. The p38 branch of the mitogen-activated protein kinase (MAPK) pathway enhances the secretion of pro-inflammatory factors, including TNF- α , and augments phagocytic activity (178). In comparison, the extracellular signal-regulated kinase (ERK) branch is associated with the production of the anti-inflammatory cytokine IL-10 and may play a role in the repair phase. The c-Jun N-terminal kinase (JNK) branch mediates apoptotic signals and amplifies inflammatory responses (179). Within the signal transducer and activator of the transcription (STAT) family, STAT1 promotes the expression of pro-inflammatory genes upon activation by IFN- γ , whereas STAT3 attenuates inflammation by inhibiting NF- κ B under the influence of IL-10 signaling. Additionally, STAT6 induces the expression of anti-inflammatory and repair-related genes in response to IL-4/IL-13 stimulation (180). The TGF- β /

Smad pathway regulates collagen synthesis and myofibroblast differentiation by suppressing inflammation and promoting fibrosis (181). In the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway, protein kinase B activation inhibits NF- κ B activity and stimulates the secretion of anti-inflammatory factors, while target of rapamycin complex 1 (mTORC1) influences macrophage function through metabolic reprogramming, thereby maintaining a balance between inflammation and repair (179).

Recent studies have shown the effect of macrophages on the behavior of myoblasts and muscle stem cells by releasing paracrine factors. For example, real-time imaging with genetically modified zebrafish has allowed scientists to observe interactions between muscle stem cells and the innate immune system, underscoring the critical role of macrophages in muscle regeneration (136). Studies have further demonstrated that macrophages are rapidly activated by the complement system during muscle injury, particularly through the complement activation molecule complement component 3a (C3a). This molecule recruits macrophages via its receptor, C3a receptor, and plays a pivotal role in regeneration following skeletal muscle damage (182). The metabolic state of

macrophages is another key factor influencing muscle regeneration. Sterol regulatory element binding protein 1 has been identified as a regulator of macrophage lipid metabolism, which affects their ability to facilitate tissue repair. Macrophages aid in the activation and proliferation of muscle stem cells by secreting specific factors that promote differentiation and fusion of these cells, improving muscle regeneration (183). Research has also identified that muscle stem cell subpopulations labeled with glioma-associated oncogene 1 positive (Gli1⁺) remain in an “alert” state in uninjured muscle, allowing for a rapid and efficient response to injury, thus accelerating muscle repair.

Macrophage activation and function are highly versatile, with distinct roles at different muscle injury and repair stages. In both stable and injured skeletal muscle, their functional diversity encompasses phagocytosis, regulation of inflammation, and tissue remodeling (184).

Eosinophils and basophils

Both eosinophils and basophils play vital roles in TMI repair. Eosinophils contribute significantly to muscle tissue repair and epithelial remodeling by interacting with the clotting system to promote hemostasis and tissue repair. Moreover, eosinophils are recruited to damaged organs such as the liver and muscles, where they secrete IL-4 and IL-13. These cytokines activate IL-4 receptor α Chain-expressing hepatocytes and progenitors in both liver and muscle tissues, supporting tissue regeneration. IL-4 activates the IL-4R α /STAT6 signaling pathway on (Fibro adipogenic progenitors) FAPs, thereby promoting the proliferation of FAPs (185–189). Although initially implicated in muscle fat degeneration, heterotopic ossification, and fibrosis, FAPs are now recognized as essential for skeletal muscle homeostasis (190). Takahashi et al. demonstrated that autocrine IL-33-suppression of tumorigenicity 2 (ST2) signaling in FAPs protects against immobilization-induced atrophy (190). Furthermore, recombinant IL-33 administration counteracted this atrophy in aging murine models (190). Notably, creatine supplementation elevates macrophage ATP levels, which promotes eosinophil recruitment and consequently enhances their antigen presentation, inflammatory responses, and critically, their muscle repair capacity (191).

On the other hand, basophils also play a significant role in immune surveillance and damages repair. Although they constitute only a small fraction of circulating white blood cells, basophils release histamine and other mediators necessary for initiating allergic reactions (192). While the exact mechanisms of basophil action remain incompletely understood, they are believed to be important for maintaining normal physiological functions and responding to trauma. Recent studies suggest that basophils contribute to traumatic muscle repair by releasing multiple mediators. These mediators include some anti-inflammatory substances, such as IL-4 and IL-13; as well as pro-inflammatory substances, such as IL-6, IL-9, CCL8 and granulocyte-macrophage colony-stimulating factor (GM-CSF), all of which play roles in inflammatory responses and tissue repair (193). IL-4, a key

mediator released by basophils, can promote the polarization of macrophages toward the M2 phenotype (194). Additionally, IL-4 can indirectly influence the muscle repair process by activating mast cells and eosinophils (194). IL-6 plays a significant role in the inflammatory response; it not only participates in the early inflammatory reaction but also promotes muscle repair by regulating the proliferation and differentiation of satellite cells. Meanwhile, IL-6 may bind to receptors on the surface of muscle cells to enhance their repair and regeneration (165). Similar to IL-4, IL-13 has anti-inflammatory and reparative effects, which can promote the polarization of macrophages toward the M2 phenotype and enhance their phagocytic capacity, thereby clearing damaged tissue debris and creating conditions for muscle repair (195). CCL8, as a chemokine, can attract neutrophils and macrophages to migrate to the injury site, thus accelerating the inflammatory response and tissue repair (196). Granulocyte-macrophage colony-stimulating factor (GM-CSF) can promote the activation and proliferation of macrophages, enhance their phagocytic function, and at the same time stimulate the activity of fibroblasts and promote the synthesis of collagen, thereby supporting the repair of muscle tissue (165). Overall, these mediators promote inflammation by recruiting more immune cells to the injury site, thereby accelerating muscle regeneration. Basophil activation is triggered through type I hypersensitivity reactions and immunoglobulin E (IgE)-mediated type 2 inflammation. When allergens bind to IgE-sensitized mast cells and basophils, these cells degranulate, releasing histamine and further amplifying the inflammatory response. Furthermore, basophils facilitate macrophage activation and migration, and recruit other immune cells by secreting additional pro-inflammatory mediators such as IL-6 and IL-9. This activity aids in clearing damaged tissue and promoting new tissue formation (193). Eosinophilic and basophilic granulocytes repair traumatic muscle through diverse mechanisms, including promoting hemostasis, tissue regeneration, and inflammation regulation.

T lymphocytes

T lymphocytes, or T cells, are crucial components of the immune system, maturing primarily in the thymus before migrating to various immune organs and tissues to carry out their immune functions. They are derived from pluripotent stem cells in the bone marrow and, during embryonic development, from the yolk sac and liver (197, 198). Studies have shown that T lymphocytes are essential in repairing and regenerating severely injured muscle tissue in mice (100). T lymphocytes accumulate in human muscle tissue following injury and contribute to the “repetitive practice effect”, enhancing muscle resilience against recurrent damage (199). They play a vital regulatory role post-injury. For instance, increased $\alpha\beta$ T cells may help suppress inflammation, and activated $\gamma\delta$ T cells (expressing CD4/CD69) modulate the inflammatory response (200).

Investigations into T lymphocytes have highlighted the significant role of Tregs in muscle recovery. Numerous studies

have demonstrated that Tregs are essential for maintaining muscle tissue's homeostasis, integrity, and functionality. They regulate skeletal muscle function and regeneration through IL6 receptor α signaling (201). One study revealed that exercise enhances Treg stability, improving muscle retention and increasing the expression of molecules such as calmodulin, epidermal growth factor receptor (EGFR), and ST2. The functional capabilities of Tregs were shown to restore muscle repair in IL6 receptor α triple knockout (TKO) mice (201). Further research suggests that Tregs produced in the gut can contribute to repairing injured muscles and damaged livers, underscoring the significant influence of gut microbiota on Treg function and their role in muscle healing. The beneficial effects of Tregs on muscle repair can be categorized in several ways. In terms of inflammation regulation, Tregs inhibit the IFN- γ signaling pathway (202), as illustrated in Figure 3. This inhibition reduces the expression of associated genes on macrophage cell membranes and promotes the transition from pro-inflammatory M1 to anti-inflammatory M2 macrophages, thereby facilitating muscle repair (203). The regulation of Tregs is crucial for the effective transformation and repair of skeletal muscle inflammation, directly influencing the reparative outcomes of damaged skeletal muscle (204). Therefore, given that Tregs already have a repairing effect in traumatic muscles, and the CAR-Tregs technology enhances the specificity and function of Tregs, enabling them to target specific antigens more precisely and further improving the immune regulatory effect, it thus demonstrates significant clinical application prospects in the treatment of traumatic muscle injuries (42).

Other T cell subsets, such as CD8⁺ T cells, also influence muscle repair processes. It is suggested that the releasing of pro-inflammatory molecules from damaged muscle fibers may exacerbate muscle damage induced by CD8⁺ T lymphocytes (205). Studies have shown that in patients with active juvenile

dermatomyositis, a reduction in peripheral circulating CD8⁺ T cells may be linked to specific muscle injury phenotypes (206). Although CD8⁺ T cells do not directly participate in muscle repair, they can regulate the balance between T cell subsets, including Th1, Th2, Th17, and Treg cells, through immune modulation. This regulation affects the differentiation and function of CD4⁺ T cells, ultimately influencing the repair process following TMI (207).

B lymphocytes

B lymphocytes are key components of the immune system, playing essential roles in antibody production and the establishment of immune memory (208, 209). Studies have highlighted their direct involvement in diseases related to muscle injury-related diseases, particularly inflammatory myositis, whereas their role in traumatic muscle injuries appears more indirect (210). Although B lymphocytes are primarily associated with the humoral immune response, they may indirectly influence cellular immune responses through cytokine secretion and immune regulation. Following trauma, the immune system regulates a multifaceted interplay of inflammatory and regulatory responses. Evidence suggests that trauma can impair B lymphocyte function. For instance, a study found that B cells from trauma patients exhibited significantly reduced immunoglobulin synthesis and secretion *in vitro*, a defect attributed to the trauma itself rather than the surgical procedures. This suggested that trauma may directly impact B lymphocyte activity, potentially modulating the immune response (31).

The role of B lymphocytes in TMI has been less extensively studied. However, their immune regulatory functions suggest they may indirectly support repair processes by modulating macrophage activity or secreting specific cytokines. B lymphocytes can influence

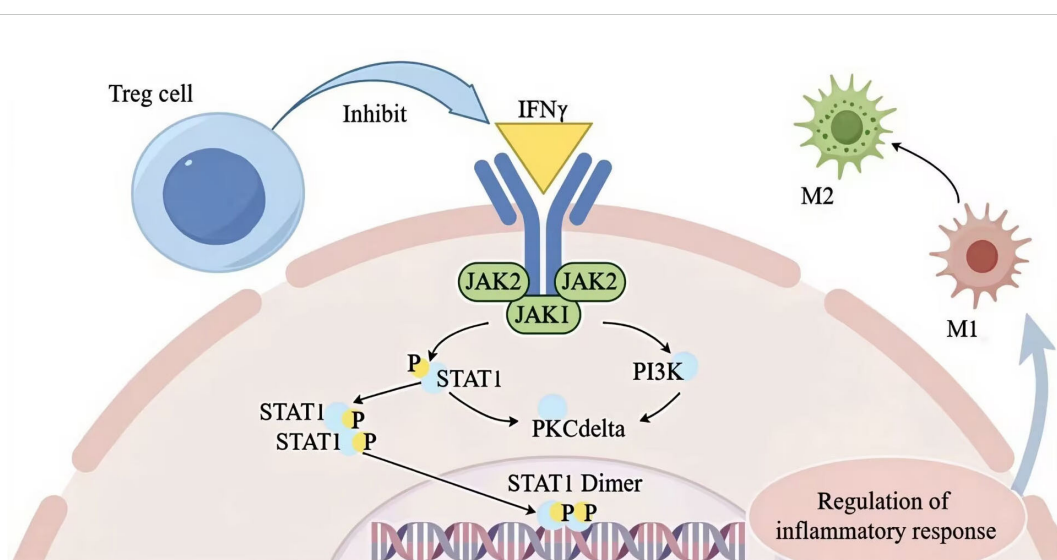


FIGURE 3

Treg cell modulation of IFN- γ signaling to promote M1-to-M2 macrophage transition and resolve inflammation during muscle repair. The figure was drawn by Figdraw. STAT1, signal transducer and activator of transcription 1; JAK1, janus kinase 1; PKC delta, protein kinase C delta; PI3K phosphatidylinositol 3-kinase; M1, pro-inflammatory macrophage; M2, anti-inflammatory macrophage; IFN- γ , interferon- γ ; P, phospholipid.

macrophage phenotypes by releasing cytokines such as IL-10 (211, 212), which may impact the healing trajectory following muscle injury. During the phases of skeletal muscle injury and repair, inflammatory cytokines like IFN- γ , IL-6 (213), and TNF- α (214) facilitate phagocytosis and play crucial roles in muscle repair. These cytokines, produced by various cell types, including B lymphocytes, contribute to the cytokine network and may coordinate muscle injury and repair processes.

The functions of B lymphocytes in muscle injury and repair may mirror their roles in other tissue injuries. In liver disease, B cell activity not only aids in controlling infections but may also exacerbate tissue damage and fibrosis by amplifying chronic inflammation (215). This suggests that B cells play a multifaceted role in tissue repair, promoting inflammatory responses and potentially hindering recovery by exacerbating inflammation. Moreover, disruptions in immune function following surgery or trauma may impair cell-mediated immunity, increasing susceptibility to infections. In the context of muscle injury, B lymphocytes may influence the repair process by modulating the immune response, regulating T cell activation and inhibition, and affecting the intensity and duration of inflammation (216, 217).

B lymphocytes contribute to TMI repair by directly participating in tissue repair through cytokine secretion and regulating inflammatory responses. These insights provide a valuable foundation for understanding the mechanisms by which B lymphocytes influence TMI repair.

Therapeutic strategies targeting immune cells for TMI repair

In addition to conventional surgical management for advanced stages (Grade III and IV), current therapeutic strategies for TMI include the use of biomaterials, pharmacological agents, cell-based therapies, and physical rehabilitation approaches.

Biomaterials effectively regulate the behavior of immune cells

As clearly illustrated in Table 4, biomaterial-based therapies for TMI improve the inflammatory microenvironment and support tissue regeneration by modulating immune cell activity. Cell delivery and tissue engineering strategies use cell carriers, such as stem cells, to establish biomimetic microenvironments, induce macrophage polarization for immune microenvironment optimization, and improve the healing in chronic injuries (220). Natural polymers include collagen and gelatin. They possess an inherent scaffold structure. This structure supports cell adhesion and proliferation (221). Natural polymers promote macrophage polarization. Specifically, they drive polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory and reparative M2 phenotype. Additionally, they contribute to enhanced mechanical strength during muscle regeneration. They also aid in improving structural organization during muscle

regeneration (218, 225). Immunomodulatory biomaterials, when combined with immunomodulators, modulate immune responses, attenuate inflammation, and immune rejection, and improve the immune microenvironment following muscle injury through the regulation of macrophage polarization (218). Bioprinted scaffolds offer precise three-dimensional structural support, facilitating cell distribution and proliferation, improving the local microenvironment, and modulating immune responses to enable *in situ* tissue regeneration and functional integration. Nanofiber scaffolds, characterized by their high specific surface area and porosity, provide attachment sites for cells, promote a favorable immune microenvironment, and induce macrophage polarization, improving the efficiency of tendon regeneration and enhancing mechanical properties (223). These therapies collectively target macrophages as central regulators, using the interplay between biomaterials and immune cells to resolve inflammation, support angiogenesis, and neurogenesis, and restore mechanical function following muscle injury. This represents a multi-technology-integrated immuno-regulatory biomaterial strategy for clinical tissue repair (224).

Drug intervention balances immune cells in the inflammatory response

Pharmacological interventions for TMI primarily aim to modulate inflammatory responses to preserve immune homeostasis and prevent excessive immune activation, which can hinder muscle regeneration (226). NSAIDs, such as aspirin, inhibit cyclooxygenase (COX) activity, reducing prostaglandin synthesis, directly suppressing neutrophil function, and effectively controlling acute inflammation, although concerns about their safety persist (227). β -adrenergic receptor antagonists promote the shift from Th1 to Th2 cell polarization, lowering the risk of post-traumatic infection and indirectly fostering a pro-regenerative immune microenvironment (228). Corticosteroids suppress the activity of various immune cells, including T cells (229) and macrophages (230), alleviating inflammation during the early injury phase and increasing cellular responsiveness to growth factors. This facilitates cell proliferation, migration, and differentiation, ultimately promoting muscle tissue repair (231).

Cell therapy activates the regenerative potential of immune cells

Cellular therapies promote muscle regeneration by modulating specific immune cell populations. Tregs are key mediators in this process, secreting anti-inflammatory cytokines such as IL-10 and TGF- β to suppress pro-inflammatory signaling and establish a microenvironment conducive to tissue repair (232). Additionally, Tregs release IL-33, which directly stimulates myocyte regeneration, and facilitates the polarization of M1 macrophages toward the anti-inflammatory M2 phenotype, therefore reestablishing immune homeostasis (233). Treg

TABLE 4 Biomaterial-based therapies for TMI and immune cell involvement.

Classification Application	Biomaterial Technology	Specific Mechanism	Immune Cell Effect	Specific Efficacy	References
Acellular Scaffold Technology	Natural polymers (e.g., collagen and gelatin)	Exhibits excellent biocompatibility, biodegradability, and mechanical properties; alleviates inflammatory response; promotes stem cell proliferation and differentiation	Reduces inflammatory response; accelerates tissue regeneration	Mitigates post-tendon-injury inflammation and enhances regenerative capacity	(218)
Cell Delivery and Tissue Engineering	Cellular Carriers (e.g., Stem Cells)	Provides biomimetic microenvironment; facilitates cell migration and proliferation	Promotes macrophage polarization; improves immune microenvironment	Enhances healing quality and repair efficiency of chronic injuries	(219)
Bioactive Polymers and Electrical Stimulation	Bioactive Polymers (e.g., Hydrogels)	Modifies material surface properties; provides mechanical support and growth factor release	Promotes angiogenesis and neural precursor cell migration	Enhances tendon regenerative apacity and mechanical properties	(220)
Natural and Synthetic Materials	Natural Polymers (e.g., Collagen, Gelatin)	Provides native scaffold architecture; supports cell adhesion and proliferation	Promotes M1-to-M2 macrophage polarization	Improves mechanical properties and tissue architecture of tendon regeneration	(218, 221)
Mechanical Stimulation and Biomechanics	Dynamic Mechanical Stimulation Devices	Simulates biological environment; promotes tenocyte differentiation	Enhances cell adhesion and proliferation capacity	Improves mechanical properties and regenerative outcomes of tendon tissue	(222)
Immunomodulation	Biomaterials Combined with Immunomodulators	Regulates immune response; reduces inflammation and rejection	Promotes muscle tissue repair via macrophage polarization modulation	Improves post-muscle-injury immune microenvironment and accelerates tissue regeneration	(218)
Bioprinting Technology	Bioprinted Scaffolds	Provides precise three-dimensional structural support; facilitates cell distribution and proliferation	Improves local microenvironment; promotes immunomodulation	Achieves <i>in-situ</i> tissue regeneration and functional integration	(223)
Nanomaterials	Nanofibrous Scaffolds	Features high specific surface area and porosity; provides cellular adhesion sites	Improves immune microenvironment; promotes macrophage polarization	Enhances tendon regeneration efficiency and mechanical properties	(224)

infiltration peaks within four days post-injury, rapidly shifting the inflammatory landscape toward a reparative state (234). In parallel, stem cell therapies contribute to immune regulation by secreting immunomodulatory factors or replacing damaged immune cells, acting synergistically with other cell populations to support tissue regeneration (235).

Physical intervention non-invasively regulates the function of immune cells

Physical interventions provide non-pharmacological strategies for immunomodulation in TMI. Massage therapy directly reduces neutrophil infiltration, disrupting inflammatory barriers that hinder muscle regeneration and exerting anti-inflammatory effects (136). Extremely low-frequency electromagnetic fields (ELF-EMF) modulate immune cell activity indirectly by regulating oxidative stress in muscle cells and increasing the expression of genes associated with myogenesis,

establishing an immune microenvironment favorable for tissue repair (236). Both approaches support TMI recovery through non-invasive mechanisms.

In Summary, diverse immunotherapeutic strategies for TMI show translational promise across varying clinical readiness stages. Biomaterial-based therapies, such as decellularized scaffolds and hydrogels, modulate immune cell behavior to improve inflammatory microenvironments and support tissue regeneration, with preclinical validation demonstrating biocompatibility and efficacy, laying the groundwork for early-phase trials (237, 238). Pharmacological interventions, including NSAIDs and corticosteroids, are clinically used to regulate immune responses, though safety concerns (e.g., gastrointestinal risks with NSAIDs and delayed repair with long-term corticosteroid use) necessitate cautious dosing (239). Cell therapy can promote muscle regeneration by regulating the immune cell population. Particularly, Tregs secrete anti-inflammatory cytokines to establish a repair microenvironment, release IL-33 to stimulate muscle cell regeneration and M2-type phenotypic polarization (234). Although

Tregs have been subject to clinical research in various diseases, their application in TMI is still in the stage of clinical research and early application (101). Physical interventions like massage therapy and ELF-EMF, which non-invasively regulate neutrophil infiltration and immune cell activity, are clinically established with favorable safety profiles (240). Emerging combined strategies (e.g., biomaterial-loaded CAR-Tregs, macrophage-targeted nanoparticles) represent promising preclinical approaches (241, 242). Ongoing trials aim to enhance specificity and safety by optimizing biomaterial scalability, refining cell delivery systems, and mitigating drug-related adverse effects. These advances collectively highlight the immune system's fascinating yet complex role in TMI repair.

Conclusions and future perspectives

Immune cells infiltrate the site of muscle damage. Following this infiltration, signaling molecules such as cytokines and growth factors are released into the microenvironment. These molecules regulate muscle repair and regeneration by directly interacting with satellite cells, as illustrated in Figure 1. Although previous studies have highlighted the crucial roles of neutrophils, macrophages, and Treg in skeletal muscle inflammation and tissue repair, significant gaps remain.

In recent years, the rapid development of single-cell (243) and spatially-resolved multiomics technologies has profoundly reshaping our understanding of the complexity of the immune response after traumatic injury (244). These technologies have revealed, with unprecedented resolution, the astonishing heterogeneity of immune cells during the injury repair process (245, 246). The trajectories of dynamic state transitions, and their precise localization and interaction relationships within the tissue space (247). For instance, single-cell transcriptomics has identified unique functional programs of macrophages and T cell subsets. These programs go beyond the traditional binary or simple classifications, such as M1/M2 for macrophages or Th1/Th2/Th17/Treg for T cells. Spatial multi-omics has illustrated how these immune subpopulations form specific spatial niches. These niches involve interactions with muscle stem cells, fibroblast/adipocyte progenitor cells, vascular cells, and other cell types (247). Through paracrine signals or direct contact, these immune subpopulations precisely regulate the regeneration process. Integrating these high-dimensional data with live dynamic imaging and computational biology is enabling systematic depiction. This integration is constructing a complete “cell map” and “interaction network” of the TMI immune microenvironment. Ultimately, it provides a powerful engine for deciphering the molecular logic underlying regeneration regulation (248).

Future research should focus on several critical aspects. The specific contributions and functional heterogeneity of immune cells in TMI repair remain unclear (249). By using single-cell transcriptomics and proteomics analysis, the subpopulation composition, activation status, and key secreted factors of these cells at different stages of injury can be systematically identified, and their unique roles in fibrosis regulation, angiogenesis, and extracellular

matrix interactions can be clarified (250, 251). Targeted immunotherapy strategies may include modulating neutrophil-macrophage crosstalk to optimize inflammation-regeneration balance. This approach precisely regulates interactions between neutrophil subsets like N1/N2 and macrophage subpopulations using transformation patterns identified through single-cell analysis (252, 253). Another strategy involves genetic engineering of repair-promoting Treg subpopulations to overexpress immunomodulatory cytokines. Key Treg subsets or their signature molecules should be selected based on single-cell profiling (254, 255). Additionally, combining intelligent biomaterials with cell therapy can direct immune cell recruitment. Such biomaterials leverage tuned stiffness, topological features, and sustained-release capabilities to deliver specific ligands. These engineered systems recruit functionally validated pro-repair immune cells, including multiomics-identified macrophages or Tregs, to injury sites for enhanced regeneration (256, 257). In clinical translation, several promising approaches include: combined targeted therapy of immune cells and stem cells to treat refractory muscle injuries, implementing short-term anti-inflammatory intervention measures in sports medicine, and applying gene editing technology to enhance repair capabilities (257–259). Integrating systems biology with artificial intelligence to construct an immune map for muscle injury repair may help predict individualized treatment responses (256, 257).

Looking toward the future, the development of drug delivery systems with spatiotemporal specificity for fine-tuning the inflammation-regeneration balance, the investigation of immune crosstalk between organs, and the design of biomimetic materials that replicate the native extracellular matrix are imperative (13). Meanwhile, given the established close interaction between immune cells and traumatized muscles, the clinical translation of immunotherapy, based on current research findings, will offer a scientifically grounded approach to the management of injured muscles. A deeper understanding of immune-mediated repair mechanisms, combined with emerging technologies, will enable muscle regenerative medicine to move beyond symptom relief and achieve true functional recovery (260).

Author contributions

SP: Writing – original draft. GH: Writing – original draft. YC: Writing – original draft. GS: Writing – review & editing, Conceptualization, Supervision. YW: Supervision, Writing – review & editing, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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Glossary

TMI	traumatic muscle injury	TKO	triple knockout
MRI	magnetic resonance imaging	EGFR	epidermal growth factor receptor
IL	interleukin	GDF-15	growth differentiation factor
TNF- α	tumor necrosis factor- α	FAPs	fibro adipogenic progenitors
TGF- β	transforming growth factor- β	RIZs	regenerative inflammatory regions
CD8+ T cells	cluster of differentiation 8 positive T cells	ST	suppression of tumorigenicity
IFN- γ	interferon- γ	MMP-8	matrix metalloproteinase-8
MCP	monocyte chemoattractant protein	SOD-2	superoxide dismutase 2
Tregs	regulatory T cells	GPX	glutathione peroxidase
M1	pro-inflammatory macrophage	CAT	catalase
M2	anti-inflammatory macrophage	TRX	thioredoxin
CXCL	C-X-C motif chemokine ligand	TLRs	toll-like receptors
NETs	neutrophil extracellular traps	DAMPs	damage-associated molecular patterns
ROS	reactive oxygen species	ERK	extracellular signal-regulated kinase
NAF	neutrophil-activating factor	c-Jun N-terminal kinase JNK	
HMGB1	high-mobility group box 1 protein	MPO	myeloperoxidase
ADA	adenosine deaminase	PI3K	phosphoinositide 3-kinase
CK	creatine kinase	Akt	protein kinase B
MDA	malondialdehyde	mTOR	mammalian target of rapamycin
NF- κ B	nuclear factor kappa-light-chain-enhancer of activated B cells	STAT1	signal transducer and activator of transcription 1
MAPK	mitogen-activated protein kinase	JAK1	janus kinase 1
STAT	signal transducer and activator of transcription	NO	nitric oxide
VEGF	vascular endothelial growth factor	PKC	protein kinase C
NSAIDs	non-steroidal anti-inflammatory drugs	NAMPT	nicotinamide phosphoribosyl transferase
CAR-Tregs	chimeric antigen receptor-r T cells	GM-CSF	granulocyte-macrophage colony-stimulating factor
EMBASE	excerpta medica database	IgE	immunoglobulin E
GFEMs	glycoprotein 130-expressing macrophages	COX	cyclooxygenase
PPAR γ /RXR	peroxisome proliferator-activated receptor gamma/retinoid X receptor	ELF-EMF	extremely low-frequency electromagnetic fields.