Review

Skeletal Muscle Regeneration in Cardiotoxin-Induced Muscle Injury Models

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Abstract: Skeletal muscle injuries occur frequently in daily life and exercise. Understanding the mechanisms of regeneration is critical for accelerating the repair and regeneration of muscle. Therefore, this article reviews knowledge on the mechanisms of skeletal muscle regeneration after cardiotoxin-induced injury. The process of regeneration is similar in different mouse strains and is inhibited by aging, obesity, and diabetes. Exercise, microcurrent electrical neuromuscular stimulation, and mechanical loading improve regeneration. The mechanisms of regeneration are complex and strain-dependent, and changes in functional proteins involved in the processes of necrotic fiber debris clearance, M1 to M2 macrophage conversion, SC activation, myoblast proliferation, differentiation and fusion, and fibrosis and calcification influence the final outcome of the regenerative activity.

Keywords: cardiotoxin injury; mice; skeletal muscle; regeneration; mechanism

1. Introduction

Skeletal muscle, the main organ of systemic metabolism in the body, is composed of differentiated fibers and displays a strong ability to regenerate after injury. Skeletal muscle injuries occur frequently in daily life and exercise, and the capacity of regeneration is critical for the repair and functional maintenance of skeletal muscle. The regeneration of adult muscle is based on the activation of satellite cells (SCs), which are mononuclear progenitors of skeletal muscle and are located between the sarcolemma and basal lamina [1]. After injury, the regeneration of muscle occurs in three overlapping stages: in the first stage, inflammatory cells infiltrate into damaged sites, and necrotic fiber fragments are removed; in the second stage, SCs are activated and proliferate into myoblasts, thereafter differentiating and fusing to form new muscle cells and replace damaged fibers; the last stage involves the maturation of newly formed fibers and the remodeling of damaged muscle [2,3]. The processes of regeneration are highly coordinated, and the expression of genes involved in regeneration are spatially and temporally regulated [4,5]. Numerous studies have been conducted to investigate the molecular mechanisms underlying muscle regeneration. A comprehensive understanding of the events involved in muscle regeneration will facilitate the treatment of skeletal muscle diseases.

In order to achieve a better understanding of muscle regeneration following physiological injury, the innervation, tendons, vascularization, and SCs should not be injured in mouse models because they contribute to myogenesis following injury. Cardiotoxin (CTX), derived from Naja pallida, induces a transient and reproducible acute injury without affecting the vasculature or nerves, and then produces a consistent injury in the whole muscle followed by synchronized regeneration [6–8]. Its application also has the advantages of allowing molecular and biochemical analyses to be performed on the whole muscle in contrast to physiological injury models induced by exercise [9,10]. Additionally, CTX injury models have relatively low harmfulness for animals compared with other non-physiological models such as crushing models [11]. Due to these characteristics, the CTX-induced skeletal muscle injury model is a suitable model for exploring the mechanisms of skeletal muscle regeneration.
In this review, we summarize the effects and mechanisms of different mouse models for obesity, diabetes, exercise training, and nutrition on regeneration after CTX-induced muscle injuries. The results may provide therapeutic targets for the repair of damaged muscle in addition to new ideas for further studies.

2. The Characteristics and Positions of Injury in CTX-Induced Skeletal Muscle Injury Models

CTX, a natural amphiphilic peptide derived from *Naja pallida*, can affect membrane calcium binding sites, and lower the threshold of calcium-modulated calcium ion release from the sarcoplasmic reticulum, thereafter inducing the destruction of skeletal muscle [12,13]. Muscle injury occurs at days 1 to 2 after CTX injection, where inflammatory cells infiltrate and SCs are activated to proliferate; at days 3–5, the myoblasts are induced to differentiate; at days 5–7, the new fibers with a central nucleus begin to form; and at days 10–14, the major muscle structures are restored; at day 28, the damaged muscles have almost completely recovered [14–16]. Due to its characteristics of transience and reproducibility, the CTX-induced injury model has been widely used to explore the mechanisms of skeletal muscle regeneration.

In CTX-induced injury models, the damaged sites are hindlimb muscles, where injuries also often occur in humans. In the related literature, the tibialis anterior is the most widely studied site in CTX-induced injury models. This is because of its obvious location and the characteristics of having a mixture of fiber types. Additionally, as a highly heterogenous muscle, tibialis anterior has only one belly, which results in uniform injury. Gastrocnemius consists mainly of fast-twitch fibers and is a bicep muscle, which may result in nonuniform injury despite the obvious location. Furthermore, other hindlimb muscles were also used in the studies such as the extensor digitorum longus, soleus, and quadriceps. The characteristics of only one type of muscle fiber and the muscle group may lead to a preference for position.

Notably, there are still some limitations in CTX-induced skeletal muscle injury models. First, the skeletal muscles include antigravity (e.g., gastrocnemius, quadriceps) and non-antigravity muscles (e.g., tibialis anterior, biceps brachii) [17]. The mechanisms identified in CTX-induced non-antigravity muscle injury models may not apply directly to the CTX-induced antigravity muscles. Second, in CTX-induced injury models, it always does not affect the vasculature or nerves in muscles [8]. In contrast, the vasculature or nerve damage often occurs during the pathogenesis of human muscle injuries [18]. This discrepancy limits the exploration of the contribution of vasculature or nerves in muscle regeneration using CTX-induced muscle injury models. Third, CTX may induce a complete necrosis of the small muscles such as EDL when examined in cross-section 48 h after injection [19]. This may make it impossible to explore the mechanisms involved in the early stages of these muscles.

3. Skeletal Muscle Regeneration in Different Mouse Models after CTX-Induced Skeletal Muscle Injury

CTX has been used to induce skeletal muscle injury in many mouse models (Table 1) including that of diabetes, obesity, aging, exercise training, mechanical loading, and nutrition intervention, among others. Studies have shown that streptozocin and gene mutation-induced diabetes [20–23], high fat diet-induced obesity and ob/ob mice [22,24,25], cancer cachexia [26], aging [27,28], irradiation [29], elevated carbon dioxide (CO₂) level [30], and hindlimb suspension [31,32] lead to impaired regeneration, whereas exercise training [33,34], microcurrent electrical neuromuscular stimulation [35], microelement zinc [36], and overloading [37,38] improve the regeneration of CTX-induced damaged muscle. The accumulation of mitochondrial DNA alterations activates muscle regeneration in myofibers during aging, but leads to reduced muscle mass [39].
| Author, Year | Injury Portions | Mouse Models | Targets | Regeneration (Impair/Improve) | Ref. |
|-------------|-----------------|--------------|---------|-------------------------------|------|
| Moussel E, 2010 | Right tibialis anterior | Male and female C57BL/6J mice, young 4-6 months, middle 12-19 months, old 25-30 months and very old 32-33 months | Different ages | Impair | [28] |
| Fearing CM, 2016 | Right hind limb anterior and post compartments | 22 weeks C57BL/6- WT, C57BL/6-Akita, KK/Ta-WT, and KK/Ta-Akita male mice | Ages and sex | Impair; —— | [40] |
| Takahashi Y, 2021 | Left tibialis anterior | 3-4 months STZ-treated Swiss and Akita male mice | Diabetes | Impair | [20] |
| Vignaud A, 2007 | Right tibialis anterior | 12 weeks ovarioectomized and normal C5BL/6Jcl female mice | Diabetes | Impair | [21] |
| Chaiyasing R, 2021 | Tibialis anterior | 10-12W STZ-treated and normal male C57BL/6J mice | Estrogen | Impair | [41] |
| Rebalka IA, 2017 | Tibialis anterior | 14-16 weeks leptin-deficient, leptin receptor-mutant mice and a group of C57BL/6J mice fed a high-fat diet | Fluvastatin | Impair | [42] |
| Nguyen MH, 2011 | Extensor digitorum longus | 16 weeks male C57BL/6J mice fed a high-fat diet | Diet-induced obesity | Impair | [22] |
| D’Souza DM, 2015 | Left gastrocnemius-planatris, tibialis anterior, quadriceps | 8 weeks male C57BL/6J mice: a marginally zinc-deficient diet-fed group, a zinc-adequate diet-fed group and a zinc-high diet-fed group | Zinc | Impair | [36] |
| Jinno N, 2014 | Right gastrocnemius | 2-4 months C57BL/6J male mice treated with STZ, 20-24 months C57BL/6J male mice and C57BL/6J-lm2Akita mice | Gravitational unloading | Impair | [32] |
| Matsuoka Y, 2009 | Soleus muscle | 4-6 months ovarioectomized, castrated and normal male and female C57BL/6J mice | Cancer cachexia | Impair | [26] |
| Jeong J, 2013 | Tibialis anterior and gastrocnemius | 2-6 months BoyJ, C57BL/6J male mice with or without irradiation and Pax7 Cre-Rosa26 DTA mice | Sex hormones | —— | [44] |
| Inaba S, 2018 | Tibialis anterior | 10 weeks myasthenia gravis and normal female C57BL/6J mice | Myasthenia gravis | Impair | [46] |
| McHale MJ, 2012 | Right hind limb anterior and posterior compartment | 9 weeks normal and NAFLD male CD-1 mice | NAFLD | Impair | [47] |
| Patsalos A, 2017 | Tibialis anterior | 6-8 weeks C3H/HeJ (TLR4 defective), C3H/HeN (TLR4 WT), C57BL/6 (WT) and TLR-4 knockout male mice | Different strains | —— | [49] |
| Ikeda Y, 2019 | Gastrocnemius | 8 weeks male C57BL/6J mice with or without iron overload | Iron | Impair | [45] |
| Attila, 2017 | Right tibialis anterior | 10 weeks myasthenia gravis and normal female C57BL/6J mice | Myasthenia gravis | Impair | [46] |
| Salihu TP, 2022 | Left tibialis anterior and gastrocnemius | Both male and female K320E<sup>ski</sup> and K320E<sup>hmd</sup> transgenic mice | Mitochondrial DNA alterations | Impair | [39] |
| Rahman FA, 2020 | Left tibialis anterior | Isogenic 6-8 weeks C3H/HeJ (TLR4 defective), C3H/HeN (TLR4 WT), C57BL/6J (WT) and TLR-4 knockout male mice | Different strains | —— | [49] |
| Kohno S, 2012 | Soleus | 24 months old male C57BL/6J mice and mdx mice | Exercise and age | Improve; impair | [35] |
| Kimoloi S, 2022 | Tibialis anterior | 8 weeks C57BL/6J mice with ultrasound exposure | Ultrasound | Improve | [51] |
| Paiva-Oliveira EL, 2017 | Right gastrocnemius | 10 weeks male C57BL/6J mice with or without functional overloading | Functional overloading | Improve | [37] |
| Yoshioka K, 2021 | Tibialis anterior and masseter | 7 weeks male C57BL/6J mice with or without microcurrent electrical neuromuscular stimulation (MENS) | MENS | Improve | [35] |
Gender and sex hormone levels also influence the regeneration processes in CTX-induced muscle injuries. Males exhibit larger newly formed fibers than females at the same age after injury, whereas females show higher fat deposition than males during regeneration [40,44] and also remove necrotic tissue more rapidly [44]. Castration of males increases the cross-sectional areas (CSAs) of the newly formed fibers and fat accumulation, whereas ovariectomized mice exhibit inhibited regeneration and decreased adipocyte accumulation, and estrogen supplementation rescues regeneration in ovariectomized mice [41,44]. Lack of estrogen-related receptor \( \alpha \) also impairs the recovery of mitochondrial energetic capacity and decreases the activity of adenosine 5'-moophosphosphate (AMP)-activated protein kinase (AMPK), which then also leads to delayed regeneration [52].

Additionally, the studies also revealed that different mouse strains have similar regeneration processes with no significant morphological and functional differences. However, the mechanisms of skeletal muscle regeneration may be strain-dependent. For instance, toll-like receptor 4 (TLR4) plays distinct roles in the injured muscle of C57BL/6 and C3H/HeJ [49,53].

It was also reported that the regeneration of skeletal muscle is position-specific: after CTX injury in tibialis anterior and the masseter, head muscles recover slowly and eventually return to the base level, whereas limb muscles show quicker recovery and eventually excessive growth [50].

4. Mechanisms of Regeneration in CTX-Induced Injury Models

It has reported that the trajectories of skeletal muscle regeneration vary considerably despite achieving complete regeneration in different injury models [54], wherein the mechanisms of regeneration in damaged skeletal muscle depend on the injury models [54]. In the following section, we summarize the mechanisms of regeneration based on CTX-induced skeletal muscle injury.

4.1. Inflammatory Response in CTX-Induced Injury Models

Inflammatory response could play an important role in timely skeletal muscle regeneration after CTX-induced injury. In this section, we summarize the mechanisms of this process and its three stages: immune cell infiltration, M1 to M2 macrophage polarization, and the clearance of necrotic fiber debris.

4.1.1. The Mechanisms of Inflammatory Response in CTX-Induced Skeletal Muscle Injury

Upon injury, immune cells residing in the skeletal muscle are rapidly activated and then release tissue destruction factors to accelerate muscle injury [55]. Additionally, the immune cells also secrete cytokines such as tumor necrosis factor alpha (TNF\( \alpha \)) and interleukin 6 (IL-6), recruiting neutrophils into damaged areas, which in turn stimulates the secretion of chemokines including monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1 alpha (MIP-1\( \alpha \)), MIP-1\( \beta \), and promotes the invasion of circulating monocytes [56]. Studies have shown that the mechanisms of inflammatory response involved in CTX-induced skeletal muscle regeneration are complex (Figure 1, Table 2).
Table 2. The mechanism of inflammatory infiltration, conversion of macrophages, and elimination of the necrotic debris.

| Author, Year | Injury Portions | Target Molecule/Drug | Target Process | Expression | Effects (Positive/Negative) | Regeneration (Impair/Improve) | Ref. |
|--------------|-----------------|----------------------|----------------|------------|-----------------------------|-----------------------------|------|
| Shi D, 2018  | Tibialis anterior | CaMKIV               | Infiltration of macrophages | Up/Down   | Positive/Negative           | Impair/improve              | [57] |
| Neves Jde C, 2015 | Right tibialis anterior | Neuraminidase-1 | Inflammatory response; myofiber maturation | Down | Positive; Negative | Impair | [38] |
| Liao ZH, 2019 | Tibialis anterior | Estrogen signaling | Inflammation infiltration; conversion of macrophages from M1 to M2 | Down | Positive; Negative | Impair | [59] |
| Kohno S, 2011 | Tibialis anterior | Cbl-b                | Cytotoxic T-cell infiltration | Down | Positive | Impair | [60] |
| Wang H, 2014  | Right tibialis anterior and hindlimb posterior compartment | Monocyte/macrophage | Monocyte and macrophages recruitment; conversion of macrophages from M1 to M2 | —— | Positive; Negative | Impair | [61] |
| Park CY, 2010 | Gastrocnemius and soleus | skNAC | Inflammation infiltration and myonecrosis | Down | Positive | Impair | [62] |
| Shi H, 2010  | Right tibialis anterior | MKP-1               | Inflammation; myoblast proliferation; differentiation | Down | Positive; Negative; Positive | Improve | [63] |
| Manoharan P, 2019 | Gastrocnemius | CaM signaling | Inflammatory response | Up | Positive | Improve | [64] |
| Gao Y, 2012  | Unilateral tibialis anterior | STAT1               | Inflammatory response | Down | Positive | Improve | [65] |
| Kozakowska M, 2018 | Gastrocnemius | Hmx1                | Inflammation and SC proliferation | Down | Positive | Improve | [67] |
| Koh, 2005    | Extensor digitorum longus | PAI-1               | Macrophage and SC migration | Down | Positive | Improve | [2] |
| Zhang, 2020  | Tibialis anterior and gastrocnemius | IFN-γ/CXCL10/CXCR3 | Macrophages and myoblast proliferation | —— | Positive | Improve | [68] |
| Yaden BC, 2014 | Right Gastrocnemius | Activin A          | Macrophage infiltration | Up | Positive | Improve | [69] |
| Mothe-Satney I, 2017 | Left Tibialis Anterior | PPARβ              | Macrophage recruitment | Up | Positive | Improve | [70] |
| Tanaka Y, 2019 | Tibialis Anterior | APN                | Elimination of the necrotic fibers | Up | Positive | Improve | [71] |
| Dinulovic I, 2016 | Tibialis Anterior | PGC-1x              | Conversion of macrophages from M1 to M2 | Up/Down | Positive; Negative | Improve/Impair | [56] |
| Sugihara H, 2018 | Tibialis Anterior | PGRN               | Prolonged Persistence of M2 Macrophages | Down | Positive | Improve | [72] |
| Lo Sicco, 2017 | Tibialis Anterior | Extracellular vesicles released by human adipose derived-MSCs | Conversion of macrophages from M1 to M2 | Up | Positive | Improve | [73] |
| Yang M, 2022  | Tibialis anterior | Balenine            | Phagocytosis ability of macrophages | —— | Positive | improve | [74] |
| Cardoso ES, 2016 | Gastrocnemius | Thymol              | Inflammatory response | —— | Negative | Improve | [75] |
| Wang ZG, 2021 | Gastrocnemius | Conversion of n-6 to n-3 PUFAs | Inflammatory response; SC activation | Up | Negative; Positive | Improve | [76] |
| Chawweewannakom C, 2018 | Unilaterally tibialis anterior | IL-1α/β | Inflammatory response | Down | Negative | Impair | [77] |
| Senf SM, 2013 | Tibialis anterior | Hsp70              | Inflammatory response | Down | Negative | Impair | [78] |
| Mojumdar K, 2016 | Tibialis anterior | TLR2               | Macrophage accumulation; elimination of the necrotic fibers | Down | Negative; Negative | Impair | [79] |
| Varga T, 2013 | Tibialis anterior | NUR77              | Macrophage development | Down | —— | Impair | [80] |
| Author, Year      | Injury Portions                                                                 | Target Molecule/Drug | Target Process                                                       | Expression | Effects (Positive/Negative) | Regeneration (Impair/Improve) | Ref. |
|------------------|---------------------------------------------------------------------------------|----------------------|---------------------------------------------------------------------|------------|-----------------------------|-------------------------------|------|
| Ochoa O, 2007    | Right anterior and posterior compartment                                        | CCR2                 | Macrophage recruitment and angiogenesis and VEGF production        | Down       | Negative                     | Impair                         | [81] |
| Zhang C, 2013    | Tibialis anterior and gastrocnemius                                              | IL-6/STAT3           | Infiltration of macrophages and myoblast proliferation              | Down       | Negative                     | Impair                         | [82] |
| Zhang J, 2014    | Tibialis anterior                                                                | CD8                  | Macrophage recruitment                                              | Down       | Negative                     | Impair                         | [83] |
| Martinez CO, 2010| Right tibialis anterior and hindlimb posterior compartment                        | CCR-2/MCP-1          | Macrophage recruitment                                              | Down       | Negative                     | Impair                         | [84] |
| Krause MP, 2013  | Left tibialis anterior and gastrocnemius-plantaris-soleus                        | Diabetes             | Macrophages infiltration                                            | ——         | ——                          | Impair                         | [23] |
| Cheng M, 2008    | Extensor digitorum longus and tibialis anterior                                  | IFN-γ                | Macrophages infiltration; myoblast proliferation                   | Down       | Negative                     | Impair                         | [85] |
| Zhang, 2017      | Tibialis anterior and gastrocnemius                                              | C3a                  | Monocyte/macrophage infiltration                                   | Down       | Negative                     | Impair                         | [86] |
| Sun D, 2009      | Right hind limb anterior and posterior compartment                               | CCR2                 | Recruitment of macrophages and neutrophils                         | Down       | Negative                     | Impair                         | [87] |
| Nishimura D, 2015| Tibialis anterior and gastrocnemius                                               | ADAM8                | Elimination of the necrotic fibers                                  | Down       | Negative                     | Impair                         | [88] |
| AI-Zaeed N, 2021 | Tibialis anterior and gastrocnemius                                             | TAM kinase receptor   | Elimination of the necrotic fibers and conversion of macrophage from M1 to M2 | Down       | Negative                     | Impair                         | [89] |
| Zhang J, 2019    | Tibialis anterior                                                               | SRB1                 | Elimination of the necrotic fibers and conversion of macrophage from M1 to M2 | Down       | Negative                     | Impair                         | [90] |
| Jin R M, 2018    | One or more hindlimb muscles                                                     | Preexisting inflammatory environment | Conversion of macrophage from M1 to M2                                | ——         | Negative                     | Impair                         | [91] |
| Bronisz-Budzynska I, 2020 | Gastrocnemius                                                  | Nrf2                 | Inflammatory response                                              | Down       | Positive                     | No effects                     | [92] |
| Tarban N, 2022   | Tibialis anterior                                                               | Retinol saturase     | Phagocytosis ability of macrophages                                 | Down       | Negative                     | No effects                     | [93] |
| Dalle S, 2020    | Tibialis anterior                                                               | Ibuprofen            | Inflammatory response                                              | ——         | Negative                     | No effects                     | [94] |
| Shen W, 2008     | Gastrocnemius                                                                  | Macrophage, TGF-β1 and COX-2 | Inflammatory response                                    | ——         | ——                          | ——                            | [95] |
| Rousseau AS, 2021| Left tibialis anterior                                                          | PPARβ/δ              | T cell dynamic                                                     | Down       | ——                          | ——                            | [96] |
It is reported that the lack of interleukin (IL-1) [77], CC chemokine receptor 2 (CCR2) [81], toll-like receptor 2 (TLR2) [79], and heat shock protein (Hsp70) [78] and the inactivation of IL-6/signal transducer and activator of transcription 3 (STAT3) signaling [82] and complement C3a-C3a receptor (C3aR)/CCL5 signaling [86] lead to reduced/delayed monocyte/macrophage infiltration, which then reduces the clearance of necrotic fiber debris and impairs myoblast proliferation, attenuating/delaying muscle regeneration. The endogenous conversion of n-6 to n-3 polyunsaturated fatty acids [76] and pretreatment with thymol [75] reduce macrophage infiltration and cell apoptosis, leading to increased SC migration and proliferation and improved muscle regeneration. Loss of Kruppel-like factor 2 (KLF2) [65], and the lack of plasminogen activator inhibitor (PAI-1) [2,23] and signal transducer and activator of transcription 1 (STAT1) in bone marrow-derived cells [66] and the inhibition of activin A [69] stimulate monocyte/macrophage recruitment, accelerate damaged muscle degradation, and promote myoblast proliferation, thereby improving muscle regeneration. Additionally, the accumulation of interleukin 17A (IL-17A)-producing T cells can also promote muscle regeneration in a microbiota-dependent way [97]. Lack of neuraminidase-1 (Neu1) [38] and estrogen signaling [39] and increased activation of calcium/calmodulin-dependent protein kinase IV (CaMKIV) [57] increase the inflammatory response but inhibit muscle regeneration. This may be because the lack of Neu1 leads to delayed myoblast differentiation and myofiber maturation [58]; however, the activation of CaMKIV and the lack of estrogen signaling increase the infiltration of pro-

**Figure 1.** The inflammatory response in CTX-induced skeletal muscle injury. (I) Infiltration of the immune cells. Upon injury, the immune cells are recruited into the damaged area, then induce inflammatory response in the damaged muscle. In this process, the lack of Klf2, STAT1, Hmox1, MKP-1 and upregulation of adiponectin (APN), activin A, and calmodulin (CaM) signaling increase, while the lack of IL-1α/β, Hsp70, CCR2, and IL-6/STAT3 and so on, inhibits the inflammatory infiltration. (II) Elimination of necrotic muscle fibers. The monocyte infiltrated into the damaged site, and become pro-inflammatory macrophages (M1 macrophages). M1 macrophages could secrete proinflammatory cytokines, maintain the inflammatory environment, then clean the necrotic debris. In this process, RetSat/MFG-E8 is required in the regulation of efferocytosis. ADAM8/PSGL-1 signaling, the TAM kinase signaling pathway, and the expression of SRB1 facilitate the elimination of necrotic fibers. Additionally, supplementation of balenine also increases the phagocytosis ability of macrophages. (III) Polarization of the macrophages. As the clearance of the muscle debris, the pro-inflammatory macrophages switch to anti-inflammatory macrophages (M2 macrophages), then secrete anti-inflammatory factors and stimulate regeneration. TG2 deficiency and the excessive calmodulin-dependent signaling delay/impair, while PGC-1α, SRB1, and so on, stimulate the polarization of the macrophages.
inflammatory macrophages, impair the transition of macrophages from M1 to M2, reduce the phagocytosis of macrophages, resulting in impaired muscle regeneration [57].

In addition, muscle cells are also involved in the immune response. Studies have shown that the inflammatory environment induced by interferon gamma (IFN-γ) stimulates the expression of major histocompatibility complex (MHC) and some co-stimulatory molecules from regenerated myofibers or cultured myoblasts and myotubes, which then contribute to the immune response [98]. Myofibers also mediate the inflammatory response through the activation of transforming growth factor beta (TGF-β)/IL-6 signaling, and direct Th17 and Treg cell responses [99]. Moreover, oxidative stress during the inflammatory response can also change the structure and function of proteins, which then regulates muscle regeneration in CTX-induced injury [100].

4.1.2. The Mechanism of Macrophage Polarization in CTX-Induced Skeletal Muscle Injury

Macrophages are the main inflammatory cells, and macrophage polarization is involved in the regulation of regeneration [79]. Infiltrated monocytes differentiate into pro-inflammatory M1 macrophages, secreting proinflammatory cytokines, cleaning up necrotic fiber debris, and maintaining an inflammatory environment. Upon the removal of necrotic fiber debris, M1 macrophages switch to M2 macrophages, secreting anti-inflammatory factors and stimulating regeneration [101]. Research shows that (Figure 1, Table 2) a preexisting inflammatory environment [91], irradiation [29], transglutaminase 2 (TG2) deficiency [102], and the excessive activation of calmodulin-dependent signaling [64] delay or impair the M1 to M2 macrophage conversion, which then delays or impairs muscle regeneration. On the other hand, estrogen signaling [59], extracellular vesicles (EVs) derived from mesenchymal stem cells (MSCs) [73], peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) [56], and scavenger receptor class B1 (SRB1) [90] stimulate macrophage polarization, eliminate necrotic fibers, reduce fibrosis, and then induce muscle regeneration. In addition, the lack of progranulin prolongs the existence of M2 macrophages and increases the size of newly formed fibers [72]. Increased activation of peroxisome proliferator-activated receptor beta (PPARβ) promotes the recruitment of M2 macrophages and accelerates the regeneration processes [70].

4.1.3. The Mechanism of Necrotic Fiber Debris Clearance in CTX-Induced Skeletal Muscle Injury

The phagocytic ability of macrophages plays an important role in the elimination of necrotic fiber debris (Figure 1). The lack of retinol saturase (RetSat) in macrophages results in less milk fat globule-epidermal growth factor-factor-8 (MFG-E8) produced and impaired efferocytosis [103]. However, skeletal muscle regeneration in RetSat-null mice is normal following CTX-injury. This is because other cell types participating in muscle regeneration such as myoblasts compensate for the impaired macrophage function, which leads to normal muscle regeneration in RetSat-null mice [93]. Supplementation with balenine promotes the infiltration of immune cells into damaged muscle, and increases the phagocytic ability of macrophages, leading to improved regeneration [74].

Additionally, the genes involved in the clearance of necrotic muscle fiber debris are highly expressed in immune cells (Table 2). Disintergrin and metalloprotease (ADAM) 8 expression in neutrophils reduces the expression of P-selectin glycoprotein ligand-1 (PSGL-1) on the surface of neutrophils, which then increases the ability of neutrophils to infiltrate into damaged areas and contribute to the removal of fiber debris [88]. Tyro3/Axl/Mer (TAM) kinase signaling mediated by Axl/Mer (AM) receptor Mer expressed in CD45+ cells and SRB1 expressed in macrophages could also facilitate the elimination of necrotic fibers and stimulate macrophage transition from M1 to M2 [89,90].
4.2. SC Activation and Myoblast Proliferation, Differentiation, and Fusion in CTX-Induced Injury Models

Upon injury, the regeneration capacity of the skeletal muscle is due to the SCs, and the critical steps such as SC activation and myoblast proliferation, differentiation, and fusion determine the extent of regeneration. Additionally, myotube maturation and the self-renewal of SCs also influence regeneration.

4.2.1. Mechanisms of SCs Activation and Myoblast Proliferation in CTX-Induced Injury Models

In normal adult muscle, SCs are in a quiescent state (Figure 2) and express paired box 7 (Pax7); once injury occurs, SCs begin to express myogenic differentiation 1 (MyoD) and myogenic factor 5 (Myf5) and are activated and then enter the cell cycle [104–106]. During this process, the basement membrane plays an important role in triggering the activation of SCs. After injury, the components of the basement membrane that mediate the contacts of the basal lamina to SCs and myofibers are degraded, and key components of the basement membrane (collagen IV alpha 1, laminin gamma-1, nidogen-2, and heparan sulfate proteoglycan-2) are downregulated, which further leads to a release of growth factors from the dismantling basement membrane and increased the elasticity of the SC niche, thus providing a suitable environment for SC proliferation [107]. As shown in Table 3, Xin and insulin-like 6 (Insl6) are involved in the activation of SCs. Insl6 over-expression in muscle facilitates SC activation and proliferation through the reduction in cell apoptosis upon CTX injury [108]. Xin, which increased in SCs within 12 h following the CTX-induced injury, maintains the activation of SCs, and the downregulation of endogenous Xin leads to the increased proliferation and migration of myoblasts [109]. Other research has shown that Xin deficiency reduces the activation and proliferation of SCs, and muscle regeneration is then impaired through the reduction in primary myoblasts and increased apoptosis of SCs [110,111]. Additionally, studies have also reported that the over-activation of myostatin/TGF-β receptor/pSmad3 signaling in diabetic mice [43] inhibits the activation of SCs. Nevertheless, the inhibition of TGF-β signaling by simultaneous knockout of TGF-β type I receptor (Tgfbr1) and activin receptor type 2B (Acvr1b) accelerates the myogenic process and improves skeletal muscle regeneration [112], whereas knockout of TGF-β receptor II (TGF-βr2) increases the inflammatory response by affecting T-cell function and the withdrawal at the later stage of muscle regeneration. The lack of nuclear factor (erythroid-derived) like 2 (Nrf2) [113] and lipocalin-2 (LCN2) [114] also inhibits the activation of SCs. These may be associated with the pro-oxidation state, reactive oxygen species (ROS) accumulation, and reduced matrix metalloproteinase-9 (MMP-9) expression, which then lead to delayed or impaired regeneration [113,114].
| Author, Year | Injury Portions | Target Molecule/ Drug | Target Process | Expression | Effects (Positive/Negative) | Regeneration (Impair/Improve) | Ref. |
|-------------|-----------------|-----------------------|---------------|------------|--------------------------|-----------------------------|-----|
| Schaaf G J, 2018 | Quadriceps femoris and gastrocnemius | Acid alpha glucosidase | SC activation | Down | Negative | Impair | [115] |
| Serra C, 2013 | Left tibialis anterior | Testosterone | SC activation | Up | Positive | Improve | [116] |
| Liu Q, 2021 | Left tibialis anterior | Salvador | SC activation and angiogenesis | Down | Positive | Improve | [117] |
| Zeng L, 2010 | Tibialis anterior or gastrocnemius | Ins6 | SC activation and proliferation | Up/Down | Positive/Negative | Improve/impair | [108] |
| Sheler SB, 2016 | Tibialis anterior | Nrf2 | SC activation and proliferation | Down | Negative | Impair | [113] |
| Rebalka IA, 2018 | Left tibialis anterior or left gastrocnemius | Lcn2 | SC activation and fibrosis | Down | Negative | Impair | [114] |
| Zeng P, 2016 | Right tibialis anterior | Mir-378/IGF1R | SC activation and differentiation | Up | Negative | Impair | [118] |
| Nissar AA, 2011 | Tibialis anterior | Xin | SC activation | Down | Negative | Impair | [111] |
| Lagalice L, 2018 | Tibialis anterior | Acid alpha glucosidase | SC activation | Down | Negative | Impair | [119] |
| Mizbani A, 2016 | Tibialis anterior | Mira-501 | SC activation | Down | Negative | Impair | [120] |
| Fiore PF, 2020 | Tibialis anterior | Pckδ | SC self-renewal | Down | Positive | Improve | [121] |
| Fortier M, 2013 | Tibialis anterior | S1pr3 | SC proliferation | Down | Positive | Improve | [122] |
| Cai S, 2020 | Tibialis anterior | Mill/myf5 | SC proliferation | Up | Positive | Improve | [123] |
| Sincennes MC, 2021 | Tibialis anterior | Pax7 acetylation | SC pool | Down | Positive | Improve | [124] |
| Naito T, 2009 | Tibialis anterior | G-csf | SC number | Up | Positive | Improve | [125] |
| Ohno Y, 2016 | Left soleus | Mstn | SC number | Down | Positive | Improve | [31] |
| Price FD, 2014 | Tibialis anterior | Jak/stat | SC number | Down | Positive | Improve | [126] |
| Hillege MMG, 2022 | Tibialis anterior | TGF-β signaling | SC number | Down | Positive | Improve | [112] |
| Angione AR, 2011 | Tibialis anterior and gastrocnemius | Pparδ | SC number and proliferation | Down | Negative | Impair | [127] |
| Nishizawa S, 2013 | Left soleus | Hsfl | SC number and proinflammatory response | Down | Negative | Impair | [128] |
| Ahrens HE, 2018 | Right tibialis anterior | Klotho | SC number and function | Down | Negative | Impair | [129] |
| Sakamoto K, 2019 | Forearm muscle | R3hdml | SC number | Down | Negative | Impair | [130] |
| Bye-A-Jee H, 2018 | Tibialis anterior | ZFP36L1 and ZFP36L2 | SC number | Down | Negative | Impair | [131] |
| Tonami K, 2013 | Left tibialis anterior | Capn6 | Myoblast differentiation | Down | Positive | Improve | [132] |
| Accornero F, 2014 | Tibialis anterior | TGF-β | SC number and activity; decreased degeneration | Down | Positive; Positive | Improve | [133] |
| Van Ry PM, 2014 | Tibialis anterior | Laminin-111 | SC pool; fibrosis | Up | Positive; Negative | Improve | [134] |
| Hosoyama T, 2011 | Tibialis anterior | Rhl | SC pool; differentiation | Down | Positive; Negative | Improve | [135] |
| Rion N, 2019 | Unilaterally tibialis anterior | mTORC2 | SC pool replenishment | Down | Negative | Impair | [136] |
| Yoshida T, 2013 | Unilateral gastrocnemius | Angiotsenin II | SC pool and proliferation | Up | Negative | Impair | [137] |
| Armand AS, 2011 | Soleus or EDL | AIF | SC pool | Down | Negative | Impair | [138] |
| Milanesi A, 2017 | Right tibialis anterior or quadriceps femoris | Thyroid hormone receptor | SC pool | Down | Negative | Impair | [139] |
| Author, Year          | Injury Portions                                           | Target Molecule/Drug | Target Process                                                                 | Expression | Effects (Positive/Negative) | Regeneration (Impair/Improve) | Ref.  |
|----------------------|----------------------------------------------------------|----------------------|--------------------------------------------------------------------------------|------------|----------------------------|-------------------------------|------|
| Castets P, 2011      | Unilateral tibialis anterior and soleus muscles          | SelN                 | SC pool                                                                        | Down       | Negative                   | Impair                        | [140]|
| Fujimaki S, 2018     | Right tibialis anterior                                  | Notch1/Notch2        | SC pool and proliferation; myoblast differentiation; fibrosis                  | Down       | Negative; Positive; Positive | Impair                        | [141]|
| Johnston AP, 2011    | Tibialis anterior                                         | Ang II               | SC number; myoblast differentiation                                              | Down       | Positive; Negative          | Impair                        | [142]|
| Jaffar M N, 2016     | Right tibialis anterior                                  | Primary cilium        | SC self-renewal                                                                | —          | —                           | —                             | [143]|
| Leung C, 2020        | Tibialis anterior/Extensor digitorum longus              | Lgr5                 | SC replenish and myofiber formation                                             | Positive;  | Improve                    | Improve                       | [144]|
| Buono R, 2012        | Tibialis anterior and quadriceps                         | NO signaling         | SC self-renewal and proliferation                                              | Down       | Negative                   | Impair                        | [145]|
| Urciuolo A, 2014     | Tibialis anterior                                         | Collagen VI           | SC self-renewal                                                                | —          | —                           | —                             | [146]|
| Alexeev V, 2014      | Left gastrocnemius muscle                                | Adipose-derived stem cells | Migration of SCs                                                             | —          | —                           | —                             | [147]|
| Brien P, 2013        | Tibialis anterior/Extensor digitorum longus muscle group | P38α                 | Myoblast proliferation; differentiation                                         | Down       | Positive; Negative          | Impair                        | [148]|
| Hawke TJ, 2003       | Tibialis anterior                                         | p21                  | Myoblast proliferation; differentiation                                         | Down       | Positive; Negative          | Impair                        | [149]|
| Cortez-Toledo O, 2017| Tibialis anterior                                         | Nur77                | Myoblast proliferation                                                        | Down       | Negative                   | No effects                    | [150]|
| Alves, 2019          | Rectus femoral muscle                                     | Kinin-B2 receptor    | Myoblast proliferation and differentiation                                      | Up         | Positive; Negative          | Impair                        | [151]|
| Wu, 2014             | Right tibialis anterior                                  | Duxbl                | Myoblast proliferation and differentiation                                      | Up/Down    | Positive/Negative           | Improve/impair                | [152]|
| Chen Y, 2012         | Tibialis anterior                                         | miR-351              | Myoblast proliferation and differentiation                                      | Up/Down    | Positive/Negative           | Improve/impair                | [153]|
| Tseng C, 2019        | Gastrocnemius                                            | Sod1/Cat             | Myoblast proliferation and differentiation                                      | Up         | Positive                   | Improve                       | [154]|
| Jia Y, 2012          | Gastrocnemius                                            | EPO                  | Proliferation and survival of the SCs                                          | —          | Positive                   | Improve                       | [155]|
| Shibasaki H, 2019    | Tibialis anterior                                         | miR-188              | Myoblast fusion                                                                | Up/Down    | Positive/Negative           | Improve/impair                | [156]|
| Hawke TJ, 2007       | Tibialis anterior                                         | Xin                  | Myoblast proliferation and migration                                           | Down       | Positive                   | Improve                       | [157]|
| Meng, 2014           | Tibialis anterior                                         | RNF13                | Myoblast proliferation and differentiation                                      | Up         | Positive                   | Improve                       | [158]|
| Lee EJ, 2021         | Left gastrocnemius                                       | Glycyrrhiza uralensis-extracted compounds | Myoblast proliferation and differentiation                                      | —          | Positive                   | Improve                       | [159]|
| Galimov A, 2016      | Tibialis anterior                                         | FGF2                 | Myoblast proliferation                                                         | Up         | Positive                   | Improve                       | [160]|
| Armand, 2003         | Soleus                                                   | FGF6                 | Myoblast proliferation                                                         | Up/Down    | Negative/Positive           | Impair/improve                | [161]|
| Shi, 2010            | Tibialis anterior and gastrocnemius                      | Tceal7               | Myoblast proliferation; differentiation                                         | Up         | Negative; Positive          | —                             | [162]|
| Author, Year | Injury Portions | Target Molecule/Drug | Target Process | Expression | Effects (Positive/Negative) | Regeneration (Impair/Improve) | Ref. |
|--------------|-----------------|----------------------|---------------|------------|-----------------------------|-----------------------------|------|
| Pessemesse L, 2019 | Right tibialis anterior | p43 | Myoblast proliferation | Down/Up | Negative/Positive | Impair/improve | [158] |
| Ye, 2016 | Gastrocnemius | CaMKK2 | Myoblast proliferation and differentiation | Up/Down | Negative/Positive | Impair/Improve | [159] |
| Minetti GC, 2014 | Tibialis anterior | Gax2 | Myoblast proliferation, differentiation and fusion | Down | Negative | Impair | [160] |
| Zhang CC, 2021 | Tibialis anterior | Cyp4a14 | Myoblast proliferation and inflammatory response | Down | Negative | Impair | [161] |
| Ding, 2021 | Tibialis anterior | Tfr1 | Myoblast proliferation and differentiation | Down | Negative | Impair | [162] |
| Naito M, 2016 | Tibialis anterior | Dnmt3a | Myoblast proliferation | Down | Negative | Impair | [163] |
| Bae, 2020 | Tibialis anterior | Cdon | Myoblast proliferation and differentiation | Down | Negative | Impair | [164] |
| Rooney JE, 2009 | Left tibialis anterior | α7 integrin | Myoblast proliferation and differentiation | Down | Negative | Impair | [165] |
| Katsushi, 2020 | Tibialis anterior | Bach 1 | Myoblast proliferation and differentiation | Down | Negative | Impair | [166] |
| Yamashita, 2016 | Gastrocnemius | FOXO1 | Myoblast proliferation | Up | Negative | Impair | [167] |
| Al-Sajee D, 2015 | Plantaris/soleus, quadriceps muscles | Xin | Myoblast proliferation | Down | Negative | Impair | [110] |
| Girgenrath, 2006 | Tibialis anterior | Fn14 | Myoblast proliferation | Down | Negative | Impair | [168] |
| Martinet C, 2016 | Tibialis anterior | H19 | Myoblast proliferation | Down | Negative | Impair | [169] |
| Yahiaoui, 2008 | Tibialis anterior | MCP-1 | Myoblast proliferation | Up | Negative | Impair | [170] |
| Kursaka, 2017 | One leg of tibialis anterior | Egr3 | Myoblast proliferation | Down | Negative | Impair | [171] |
| Ochiai N, 2015 | Tibialis anterior | fad24 | Myoblast proliferation | Down | Negative | Impair | [172] |
| Zanou, 2012 | Tibialis anterior and extensor digitorium longus | Trpc1 | Myoblast migration and differentiation | Down | Negative | Impair | [173] |
| Yablonka-Reuveni Z, 2015 | Unilateral tibialis anterior | FGFR1 | Myoblast proliferation | Down | Negative | No effects | [174] |
| Ohtsubo, 2017 | Gastrocnemius | APOBEC2 | Myoblast differentiation and fusion | Down | Positive | Improve | [8] |
| He, 2019 | Extensor digitorum longus | Nicotine | Myoblast differentiation | —— | Positive | Improve | [175] |
| Wu, 2007 | Tibialis anterior | Sema4C | Myoblast differentiation | Up/Down | Positive/Negative | Improve/impair | [176] |
| Liu, 2012 | Tibialis anterior | miR-206 | Myoblast differentiation | Up | Positive | Improve | [177] |
| Song, 2018 | Tibialis anterior | Linc-smad7 | Myoblast differentiation | Up | Positive | Improve | [178] |
| Gatta L, 2017 | Right tibialis anterior | Trimeprazidine | Myoblast differentiation | —— | Positive | Improve | [180] |
| Gagan, 2011 | Tibialis anterior | miR-378 | Myoblast differentiation | Up | positive | Improve | [181] |
| Mikami T, 2012 | Tibialis anterior | Chondroitin sulfate | Myoblast differentiation | Down | Positive | Improve | [182] |
| Author, Year | Injury Portions | Target Molecule/Drug | Target Process | Expression | Effects (Positive/Negative) | Regeneration (Impair/Improve) | Ref. |
|--------------|-----------------|----------------------|----------------|------------|---------------------------|-----------------------------|-----|
| Lee KP, 2015 | Hindlimb muscle | miR-431              | Myoblast differentiation | Up         | positive                  | Improve                     | [27]|
| Storbeck CJ, 2013 | Tibialis anterior | SLK | Myoblast differentiation | Down       | Positive                  | Improve                     | [182]|
| Lei, 2013 | One leg of tibialis anterior | MMP-13 | Myoblast migration | Down/Up    | Negative/Positive         | Impair/improve               | [183]|
| Das, 2017 | Tibialis anterior | ACL | Myoblast differentiation | Down/Up    | Negative/Positive         | Impair/improve               | [184]|
| Yoshida T, 2014 | Gastrocnemius | AT2R | Myoblast differentiation | Down/Up    | Negative/Positive         | Impair/improve               | [185]|
| Huang Y, 2016 | Right tibialis anterior | Ccndbp1 | Myoblast differentiation | Down/Up    | Negative/Positive         | Impair/improve               | [186]|
| Chen SE, 2007 | Soleus | TNF-α | Myoblast differentiation and hypertrophy | Down/Up    | Negative/Positive         | Impair/improve               | [187]|
| He, 2021 | Tibialis anterior | IRE1α | Myoblast differentiation and hypertrophy | Down/Up    | Negative/Positive         | Impair/improve               | [188]|
| Luca E, 2020 | Tibialis anterior | miRNA network | Myoblast differentiation | Down       | Negative                  | Improve                     | [189]|
| Esteca MV, 2020 | Left tibialis anterior | Parkin | Myoblast differentiation | Down       | Negative                  | Impair                      | [190]|
| Ishii A, 2001 | Tibialis anterior | Tensin | Myoblast differentiation and fusion | Down       | Negative                  | Impair                      | [191]|
| Zhang M, 2020 | Tibialis anterior of one limb | Rbm24 | Myoblast differentiation | Down       | Negative                  | Impair                      | [190]|
| Lee, 2015 | Tibialis anterior | mir-431 | Myoblast differentiation | Down       | Negative                  | Impair                      | [192]|
| Fan, 2018 | Tibialis anterior | Hsp70 | Myoblast differentiation | Down       | Negative                  | Impair                      | [193]|
| Cerquone, 2018 | Tibialis anterior | PAK1 | Myoblast differentiation | Down       | Negative                  | Impair                      | [194]|
| Lee, 2020 | Tibialis anterior | PHF20 | Myoblast differentiation | Up         | Negative                  | Impair                      | [195]|
| Hayashi, 2016 | Tibialis anterior | AKAP6 | Myoblast differentiation | Down       | Negative                  | Impair                      | [196]|
| Li, 2020 | Tibialis anterior | LRTM1 | Myoblast differentiation | Down       | Negative                  | Impair                      | [197]|
| Lin, 2019 | Left gastrocnemius | MPM | Myoblast differentiation | Down       | Negative                  | Impair                      | [198]|
| Harada, 2018 | Tibialis anterior | H3mm7 | Myoblast differentiation | Down       | Negative                  | Impair                      | [199]|
| Tetsuaki, 2009 | Tibialis anterior | CT-1 | Myoblast differentiation | Up         | Negative                  | Impair                      | [200]|
| Paul, 2012 | Tibialis anterior | COPR5 | Myoblast differentiation | Down       | Negative                  | Impair                      | [201]|
| Faralli, 2011 | Tibialis anterior and gastrocnemius of one hind limb | Tshz3 | Myoblast differentiation | Up         | Negative                  | Impair                      | [202]|
| Liu N, 2014 | Tibialis anterior | MEF2A, C and D | Myoblast differentiation | Down       | Negative                  | Impair                      | [203]|
| Kielbasa OM, 2011 | Unilateral tibialis anterior | Myospryn | Myoblast differentiation | Up         | Negative                  | Impair                      | [204]|
| Verpoorten S, 2020 | Tibialis anterior | CD56 | Myoblast differentiation | Down       | Negative                  | Impair                      | [205]|
| André B, 2002 | Right gastrocnemius and soleus | Pop | Myoblast differentiation | Down       | Negative                  | Impair                      | [206]|
| Paolini A, 2018 | Tibialis anterior | Autophagy | Myoblast differentiation | Down       | Negative                  | Impair                      | [207]|
| Clow C, 2010 | Tibialis anterior | BDNF | Myoblast differentiation | Down       | Negative                  | Impair                      | [208]|
| Marshall JL, 2012 | Left quadriceps | SSPN | Myoblast differentiation | Down       | Negative                  | Impair                      | [209]|
| Chen SE, 2005 | Soleus | TNF-α | Myoblast differentiation | Down       | Negative                  | Impair                      | [210]|
| Ravel, 2014 | Tibialis anterior | Staufen1 | Myoblast differentiation | Up         | Negative                  | Impair                      | [211]|
| Langsdorf A, 2007 | Tibialis anterior | Sulfs | Myoblast differentiation | Down       | Negative                  | Impair                      | [212]|

Table 3. Cont.
| Author, Year | Injury Portions | Target Molecule/Drug | Target Process | Expression | Effects (Positive/Negative) | Regeneration (Impair/Improve) | Ref. |
|-------------|-----------------|----------------------|---------------|------------|----------------------------|-----------------------------|------|
| Liu H, 2011 | Tibialis anterior and soleus | β3-Integrin | Myoblast differentiation | Down | Negative | Impair | [212] |
| Watanabe S, 2007 | Right tibialis anterior | Lbx1 | Myoblast differentiation | Down | Negative | Impair | [213] |
| Fu D, 2015 | Tibialis anterior | Mdm2 | Myoblast differentiation | Down | Negative | Impair | [214] |
| Schroer, 2019 | Tibialis anterior | RGS12 | A switch from myoblast proliferation to differentiation | Down | Negative | Impair | [215] |
| Lim S, 2013 | Left tibialis anterior | CBR1 | Myoblast differentiation | Down | Negative | —— | [216] |
| Mammen AL, 2009 | Right tibialis anterior | Mi-2 | Myoblast differentiation | Up | Negative | —— | [217] |
| Wu Z, 2020 | Tibialis anterior | Andrographolide | Myoblast differentiation and fusion | —— | —— | Improve | [218] |
| Kurosaka, 2021 | Left tibialis anterior | STAT6 | Myoblast differentiation and fusion | Down | —— | Improve | [219] |
| Budai Z, 2021 | Tibialis anterior | TG2 | Myoblast fusion and conversion of macrophages from M1 to M2 | Down | Negative | Impair | [102] |
| Vijayakumar A, 2013 | Unilateral tibialis anterior | IGF-1R | Myoblast fusion | Down | Negative | Impair | [220] |
| Pryce BR, 2017 | Unilateral tibialis anterior | SLK | Myoblast fusion | Down | Negative | Impair | [221] |
| Redelsperger, 2016 | One tibialis anterior | Syncytin | Myoblast fusion | Down | Negative | Impair | [222] |
| Kaspar, 2013 | Tibialis anterior | 3′ untranslated region of c-Myb | Myoblast fusion | Down | Negative | Impair | [223] |
| Griffin, 2016 | Left tibialis anterior and gastrocnemius | ANO5 | Myoblast fusion | Down | Negative | Impair | [224] |
| Trapani L, 2012 | Right tibialis anterior | HMGR | Myoblast fusion | Down | Negative | Impair | [225] |
| Hamoud, 2018 | Tibialis anterior | BAB3 | Myoblast fusion | Down | Negative | Impair | [226] |
| Tamilarasan K P, 2012 | Gastrocnemius | Lipid accumulation | Myoblast fusion | Up | Negative | Impair | [227] |
| Yoshida N, 2019 | Tibialis anterior | (P)RR | Myoblast fusion | Up | Negative | Impair | [228] |
| Shibasaki H, 2019 | Tibialis anterior | mir-188 | Myoblast fusion | Up/Down | Positive/Negative | Improve/impair | [155] |
| Youm TH, 2019 | Tibialis anterior | Nox4/Ros | Myoblast fusion | —— | Positive | Improve | [229] |
| Teng, 2015 | One tibialis anterior | PLD1 | Myoblast fusion | Up | Positive | Improve | [230] |
| Krause MP, 2013 | Left tibialis anterior | Mustn1 | Myoblast fusion | Up | Positive | Improve | [231] |
| Kurosaka, 2016 | Tibialis anterior | TRPV1 | Myoblast fusion | Up | Positive | Improve | [232] |
| Singhal N, 2015 | Gastrocnemius, quadriceps, tibialis anterior | Galgt1 | Myoblast fusion; SC apoptosis | Down | Negative; Positive | Impair | [233] |
| Yalvac ME, 2017 | Left tibialis anterior and left gastrocnemius | Calpain-3 | Myoblast fusion; fibrosis | Down | Negative; Positive | Impair | [234] |
Table 3. Cont.

| Author, Year | Injury Portions | Target Molecule/Drug | Target Process | Expression | Effects (Positive/Negative) | Regeneration (Impair/Improve) | Ref. |
|--------------|-----------------|----------------------|----------------|------------|-----------------------------|-------------------------------|-----|
| Ogawa, 2015  | Tibialis anterior | Dcx                  | Myofiber maturation | Down       | Negative                     | Impair                        | [235]|
| Ohno Y, 2019 | Right tibialis anterior | Lactate             | Myotube formation | Up         | Positive                     | Improve                       | [236]|
| Hoshino S, 2013 | Right tibialis anterior | CHC22              | Myofiber maturation | Up         | Negative                     | Impair                        | [237]|
| Hu Z, 2010   | Unilateral tibialis anterior | PTEN                | Myofiber maturation; fibrosis | Down       | Positive                     | Improve                       | [25] |
| Agbulut O, 2001 | Gastrocnemius and soleus or tibialis anterior | Desmin             | Myofiber maturation; neuromuscular junctions | Down       | Negative                     | Impair                        | [238]|
| Cicchillitti, 2012 | Tibialis anterior | miR-210             | Myoblast differentiation | Down       | ——                           | No effects                    | [239]|
| Piccioni A, 2014 | Tibialis anterior | Shh                 | Activated SCs       | Up          | ——                           | Improve                       | [240]|
| Coco E, 2021 | Left tibialis anterior | Elevated CO₂ exposure | Myoblast differentiation and fusion | ——            | ——                           | Impair                        | [30] |
| Liu, 2017    | Tibialis anterior | Twist2              | Maintain SC state   | ——         | ——                           | ——                            | [241]|
4.2.2. Mechanisms of Self-Renewal of SC Pool in CTX-Induced Injury Models. (I) SC activation. In the damaged muscle, the quiescent SCs are activated to repair the skeletal muscle. Conversion of n-6 to n-3 polyunsaturated fatty acids (PUFAs), Salvador, testosterone, upregulation of Insl6, and so on, promote, while the lack of Nrf2, LCN2, and miRNA-501 inhibit the activation of SCs. (II) Myoblast proliferation. Activated SCs begin to proliferate and become myoblast. FGF2, RING finger protein 13 (RNF13) derived from macrophages, MKP-1 [63], and heat shock transcription factor 4 (Hsf4) [67], fibroblast growth factor 6 (FGF6) [157], p38 mitogen-activated protein kinase phosphatase 1 (MKP-1) [158], lack of Gαi2 and H19/Igf2, etc., inhibit myoblast proliferation. (III) Myoblast differentiation and fusion. The expended myoblasts experience differentiation and fuse with other muscle fibers to form multinuclear myotubes. Lack of SLK and APOBEC2, upregulation of miR-206, miR-378, MMP-13, and Cnddbp1 enhance; Parkin, tension, Rbm24, and Hsp70 deficiency inhibit the capacity of myoblast differentiation. Lack of ANO5, HMGCR, BAI3, and miR-188, lack of Gαi2, and so on, and the lack of Nox4/ROS, PLD1, Mustn1, and TRPV1 stimulate myoblast fusion. (IV) Maturation of myofibers. Lack of Dcx, PTEN, and desmin influence the myofiber maturation. The activated SCs proliferate to replenish the SC pool of the skeletal muscle. In this process, Angiotensin II, lack of mTORC2, AIF, SelN, and Notch1/Notch2 impair, while Lgr5, laminin-111, lack of PKCθ, Rb1, and Pax7 acetylation stimulate SC self-renewal or SC pool replenishment.

The capacity for myoblast proliferation is influenced by numerous cytokines. Pre-treatment with acetylated myostatin 1 (Ac-MIF1) and acetylated and amidated myostatin 2 (Ac-MIF2-NH2) stimulates muscle regeneration by increasing the capacity of myoblasts for proliferation and differentiation [242]. Chemokines including MCP-1, MIP-1α, or MIP-1β (CCL4) induce extracellular regulated protein kinase (ERK) 1/2 phosphorylation through a Gαi subunit-dependent manner, which promotes myoblast proliferation [170]. Ga2 also promotes myoblast differentiation through the protein kinase C (PKC)/glycogen synthase kinase 3β (GSK3β)/miR-1 pathway or the histone deacetylase (HDAC) inhibition [160]. Nitric oxide (NO) stimulates the proliferation of SCs via a cyclic guanosine 3′,5′-monophosphate (GMP)-dependent pathway [145]. Double homeobox gene (Duxbl1) [151] and factor for adipocyte differentiation 24 (fad24) [172] promote myoblast proliferation via increasing the cell cycle. The increased expression of anti-oxidant superoxide dismutase 1 (Sod1) and catalase (Cat) genes also facilitates the potential of proliferation and differentiation [153]. Additionally, the lack of H19 [169], hippo inhibition [117], and lack of heme oxygenase-1 (Hmox1) [67], fibroblast growth factor 6 (FGF6) [157], p38α, and p38y [148] have also been found to promote myoblast proliferation, although the mechanisms remain unknown. Tweak/Fn14 also contributes to myoblast proliferation but inhibits their differentiation and delays their regeneration [168]. In contrast, increased inflammation, cell cycle inhibition, the destruction of membrane integrity, and iron accumulation all lead to attenuated myoblast proliferation. The results show that the lack of mitogen-activated protein kinase phosphatase-1 (MKP-1) [63] and heat shock transcription factor 1 (HSF1) [128] increased the inflammation and secretion of proinflammatory cytokines, the lack of α7 integrin destroyed the sarcolemmal integrity [165], and impaired fibroblast...
growth factor (FGF) responsiveness induced by deficiency of Cdon or fibroblast growth factor receptor 1 (FGFR1) led to the impairment of myoblast proliferation [164,174]. Lack of early growth response3 (Egr3) and the overexpression of calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2) might induce cell cycle arrest by the inactivation of nuclear factor kappa-B (NF-κB) and the activation of AMPK/p-cdc2-Tyr15 signaling, respectively [159,171]. Peroxisome proliferator-activated receptor δ (PPARδ) deficiency reduced forkhead box protein O1 (FOXO1) expression, which then impaired proliferation; FOXO1 overexpression also induced the expression of cell cycle inhibitors p57 and Gadd45α, which decreased the capacity for myoblast proliferation [127,167]. Iron accumulation and ROS production induced by transferrin receptor 1 (Tfr1) deletion also led to defective myoblast proliferation via the Tfr1–Slc39a14–iron axis [162]. Additionally, the deletion of Notch1 and/or Notch2 [141] and lack of nuclear T3 receptor TRα1 (p43) [158] also inhibited myoblast proliferation. However, the lack of Nur77 did not impair muscle regeneration even though it inhibited myoblast proliferation [150].

MicroRNAs are important regulators in SC activation and myoblast proliferation. The overexpression of miR-378 attenuates the activation and differentiation of SCs in an insulin-like growth factor 1 receptor (IGF1R)-dependent manner, which then delays the regeneration [118]. The expression of miR-29a, induced by fibroblast growth factor 2 (FGF2), reduces the expression of basement membrane members, which results in dismantling of the basement membrane, further providing a suitable environment for myoblast proliferation [107].

Epigenetic regulation is also involved in muscle regeneration. DNA methyltransferases 3a (Dnmt3a) ablation in SCs leads to hypomethylation of p57Kip2, which further induces a higher expression of p57Kip2, and then impairs the SC proliferation and attenuates the regeneration of damaged skeletal muscle [163]. Mixed lineage leukemia protein-1 (MLL1) facilitates the proliferation of myoblasts and Pax7+ SCs by epigenetically increasing the expression of Myf5 by mediating the trimethylation of lysine 4 on the histone H3 protein subunit (H3K4me3) enriched on the Myf5 promoter [123].

4.2.2. Mechanisms of Self-Renewal of SC Pool in CTX-Induced Injury Models

During regeneration, the self-renewal of SCs is also essential for the repair of damaged muscle (Figure 2). The activated SCs downregulate MyoD expression, and then replenish the SC pool through both symmetric cell division and asymmetric cell division [104,143]. In this process, primary cilia, harbored on the surface of quiescent SCs, has been shown to be an intrinsic factor controlling the self-renewal of SCs. Upon SC activation, primary cilia disassemble, and SCs enter the cell cycle. Upon exit from the cell cycle, the primary cilia reassemble again at the surface of a minority of SCs that are committed to self-renewal [143]. Disruption of the cilia reassembly impairs the self-renewal of SCs [143]. Additionally, the lack of selenoprotein N (SelN) [140], angiotensin II/Ang II AT1 receptor (AT1R) [137], and thyroid hormone receptor alpha (TRα) deficiency [139] resulted in a reduced SC pool and impaired regeneration of damaged muscle. Mammalian target of rapamycin complex 2 (mTORC2) depletion does not affect the myogenic function of SCs but impairs the replenishment of the SC pool upon repeated CTX injury [136]. Lack of collagen VI reduces the self-renewal capacity of SCs and impairs muscle regeneration [146].

In contrast, using the CRISPR/Cas9 mutagenesis technique, Sincennes et al. abolished Pax7 acetylation in mice and demonstrated that the lack of Pax7 acetylation led to reduced numbers of asymmetric stem cell divisions, expansion of the SC pool, and increased numbers of oxidative II A myofibers [124]. PKCθ deficiency upregulates Pax7 expression and activates Notch signaling for the maintenance of the self-renewal capacity of SCs in CTX-injured mdx mice [121]. Retinoblastoma (Rb) ablation in SCs increases the cell cycle re-entry of quiescent SCs and promotes the expansion of SCs. However, sustained retinoblastoma 1 (Rb1) loss impairs muscle fiber formation [135]. In addition, Klotho rejuvenates aged SCs and maintains the function of SCs by inhibiting the Wnt signaling pathway [129].
4.2.3. Mechanisms of Myoblast Differentiation in CTX-Induced Injury Models

The mechanisms of myoblast differentiation in Figure 2 and Table 3 show that the upregulation of myogenic regulatory factors (MRFs) such as MyoD and myogenin is associated with the increased capacity of myoblast differentiation, which further contributes to skeletal muscle regeneration in CTX-induced injury models. Research suggests that A-kinase anchoring protein 6 (AKAP6) [195], andrographolide [218], mouse double minute 2 homolog (Mdm2)/CCAAT/enhancer-binding protein β (C/EBPβ) [214], apolipoprotein B mRNA editing enzyme catalytic polypeptide 2 (APOBEC2) knockout [8] induces the expression of MyoD, myogenin, MyoG, and desmin. Leucine-rich repeats and transmembrane domains 1 (LRTM1) inhibit the recruitment of p52Shc to FGFR1 and inhibit the activation of ERK, further reducing the inhibition of cyclin dependent kinase 4 (CDK4) on the transcriptional activity of MyoD [196]. The increased MyoD interacts with its targets transcription elongation factor A-like 7 (Tceal7) and R3h domain containing-like (R3hdm1) and promotes myoblast differentiation [1]. Additionally, cyclin D-type binding-protein 1 (Ccndbp1) can bind to MyoD and regulate muscle differentiation [3,186]. The energy metabolism in cells also influences myoblast differentiation. Micropeptide in mitochondria (MPM) increases oxygen consumption and adenosine triphosphate (ATP) synthesis and promotes myoblast differentiation [197]. The expression of the type 1 canonical subfamily of transient receptor potential channels (Trpc1) promotes the influx of calcium in myoblasts during differentiation and activates the phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR/p70S6K pathway [173]. The decrease in chondroitin sulfate (CS) also stimulates the activation of PI3K/Akt signaling [181], which leads to faster regeneration [243]. Additionally, trimetazidine modulates the metabolic shift from free fatty acid β-oxidation to glucose oxidation by stimulating AMPK/PGC1α, and inducing autophagy, both of which contribute to myoblast differentiation [179]. Furthermore, the lack of signal transducer and activator of transcription 6 (STAT6) increases myoblast differentiation in an IL-4-independent way [219]. Angiotensin type 2 receptor (AT2R) inhibits the activation of ERK1/2 signaling to promote myoblast differentiation and fusion [185]. Inositol requiring enzyme 1 (IRE1) suppresses the expression of myostatin through its RNase-dependent RIDD activity, which then promotes the differentiation of myoblasts [188].

In contrast, the increased oxidation state impairs myoblast differentiation. Nonalcoholic fatty liver disease (NAFLD) reduces the SC pool and impairs SC differentiation, leading to attenuated skeletal muscle regeneration. This may be associated with TNF-α upregulation and increased levels of oxidative stress marker nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-2 (NOX 2) [47]. The inhibition of carbonyl reductase1 (CBR1) leads to increased ROS levels and diminishes myoblast differentiation [216]. Iron overload impairs myoblast differentiation through oxidative stress-induced inactivation of the mitogen-activated protein kinase (MAPK) signaling pathway [45]. Lack of Hsp70 [16] and TNF-α receptors p55 and p75 [187,209] also downregulate p38MAPK activation, which further impairs myoblast differentiation. Moreover, decreased expression of MRFs such as MyoD and myogenin also impairs differentiation. Overexpression of ladybird homeobox 1 (Lbx1) [213] and the tripartite motif domain of myospryn [203] inhibit the expression of MyoD and myogenin. High levels of cardioptrophin-1 (CT-1) repress the expression of the MRFs such as MyoD through the activation of mitogen-activated protein kinase kinase (MEK)-MAPK signaling [199]. Protein-activated kinase 1 (PAK1) inhibitor IPA-3 decreases the expression of myogenin and reduces p38 phosphorylation [193]. Teashirt-3 (Tshz3) cooperates with BRG1-associated factor 57 (BAF57) and inhibits the MYOD-dependent activation of Myog [201]. Additionally, HS 6-O-endosulfatases (Sulfs) mutation and lack of tensin lead to reduced withdrawal from the cell cycle and delayed myoblast differentiation [191,211]. The deletion of RNA binding motif protein 24 (Rbm24) also regulates the alternative splicing of myogenic associated genes such as myocyte enhancer factor 2d (Mef2d), Rho-associated protein kinase 2 (Rock2), further inhibiting myoblast differentiation [106].
MicroRNAs are involved in the regulation of myoblast differentiation. The overexpression of miR-351 protects differentiating myoblasts from apoptosis by regulating the target gene E2f3 and contributes to myoblast differentiation [152]. In a normoxic state, miR-210 induces myoblast differentiation in a hypoxia-inducible factor 1-α (Hif1a)-dependent manner [239]. Overexpression of Linc-smad7 increases the expression of smad7 and insulin-like growth factor 2 (IGF2), which then induces myoblast differentiation [178]. In addition, miR-431 directly interacts with the 3′ untranslated region of Smad4. Ectopic miR-431 injection greatly reduces Smad4 levels and improves muscle regeneration in CTX-induced skeletal muscle injury models, whereas the inhibition of miR-431 significantly represses myoblast differentiation [192]. The inhibition of miR-188 reduces the expression of myogenic regulator factor 4 (MRF4) and Mef2c and impairs myoblast differentiation, whereas the overexpression of miR-188 has the opposite effect [155]. Knockdown of transactivating response RNA-binding protein (Trbp) downregulates the expression of miR-1a and miR-133a and reduces myotube formation [244]. Intriguingly, MyoR, a muscle-restricted basic helix–loop–helix transcription factor that antagonizes the actions of MyoD, is found to be anticorrelated with miR-378 during CTX-induced muscle regeneration. MyoD binds to the miR-378 gene and causes both transactivation and chromatin remodeling, thus upregulating miR-378 during myogenic differentiation. The 3′ untranslated region of MyoR contains a direct binding site for miR-378. The presence of this binding site significantly reduces the ability of MyoR and prevents the MyoD-driven transdifferentiation of fibroblasts [180].

Epigenetic regulation is also involved in myoblast differentiation. Histone- and protein arginine methyl transferases 5 (PRMT5)-associated protein COPR5 is required for cell cycle exit and myoblast differentiation. The silencing of COPR5 reduces PRMT5 recruitment to the promoters of p21 and MYOG by hindering interaction with the Runx-related transcription factor 1 (RUNX1)-core binding factor-β (CBFβ), which then inhibits the expression of p21 and MYOG and further impairs myoblast differentiation [200]. IGF-1 induces the phosphorylation and activation of ATP citrate lyase (ACL) through the PI3K/AKT pathway. The activated ACL catalyzes the conversion of citrate into oxaloacetate and acetyl-CoA, and acetyl-CoA can be further utilized by histone acetylases to acetylate H3 (K9/14) and H3 (K27) at the MyoD locus to increase MyoD expression, thereby promoting myoblast differentiation [184].

4.2.4. Mechanisms of Myoblast Fusion in CTX-Induced Injury Models

Differentiated myoblasts fuse with damaged fibers or new myotubes by cell–cell recognition, adhesion, migration, and membrane fusion, subsequently forming multinucleated myotubes [106,230]. This is a dynamic and coordinated process involving many proteins (Figure 2, Table 3).

In terms of stimulating fusion, anoctamin 5 (ANO5) stimulates the repair of the sarcolemmal membrane and facilitates myoblast fusion [224]. Stabilin-2 activates the G-protein coupled receptor (GPCR) activity of BAI3 and then recruits Elmo to the membrane to stimulate myoblast fusion [226]. NADPH oxidase 4 (Nox4) induces the expression of myomarker fusion protein (Tmeme8c) via Nox4-mediated ROS production and then contributes to myoblast fusion [229]. The activation of phospholipase D1 (PLD1) on the plasma membrane facilitates mononucleated myoblast fusion with nascent myotubes [230]. Inhibition of the hierarchical non-clustered miRNA network including highly active (miR-29a), moderately active (let-7), and mildly active (miR-125b, miR-199a, miR-221) networks, stimulates the activation of focal adhesion kinase and AKT and MAPK signaling, and leads to the formation of myotubes [189]. Transient receptor potential cation channel vanilloid I (TRPV I) can be activated by IL-4 and calcium signaling, which then facilitates myoblast fusion instead of proliferation [232]. Syncytin contributes to myoblast fusion, and this effect is male-specific [222].

The mechanism of inhibition of myoblast fusion involves the upregulation of TGF-β via calpain-3 (CAPN3) deficiency, thus leading to defective myoblast fusion [234]. C1q-like 1-4 interacts with BAI3 to repress myoblast fusion [226]. Lack of IGF-1 receptor (IGF-1R)
signaling leads to reduced fiber fusion via growth hormone receptor-independent signaling [229]. The expression of (Pro)renin receptor ((P)RR) activates the Wnt/β-catenin and Yes-associated protein (YAP) signaling pathways, and decreases myoblast fusion [228]. In addition, transglutaminase 2 (TG2) [102], constitutive expression of c-Myb lacking its 3′ untranslated region (3′ UTR) [223], inhibition of 3-hydroxy 3-methylglutaryl coenzyme A reductase (HMGR) [225], myasthenia gravis [46], and the lack of ste20-like kinase (SLK) [221] also impair the capacity of myoblast fusion and decrease the fusion index.

4.2.5. Mechanisms of Myotube Maturation in CTX-Induced Injury Models

Fused multinucleated myotubes undergo terminal differentiation and eventually become mature myofibers. Kruppel-like factor (Klf5) (Table 3) is shown to interact with MyoD and Mef2 to regulate terminal differentiation [3]. Doublecortin (Dcx) facilitates myofiber maturation [235]. Sema4C stimulates the phosphorylation of p38 and activates the p38/MAPK signaling pathway to promote terminal differentiation [176]. The expression of clathrin heavy chain like 1 (CHC22) in CTX-induced injury muscle, however, diminishes glucose transporter 4 (Glut4) response and further impairs fiber maturation [237].

4.3. Fibrosis in CTX-Induced Injury Models

Fibrosis is an important stage for regeneration (Figure 3). In this process, the temporary extracellular matrix (ECM) components serve as a scaffold for new fibers and stabilize muscle tissue [89]. In damaged skeletal muscle, fibro/adipogenic progenitors (FAPs) are considered as the main source of fibroblasts [245]. After injury, FAPs are activated and begin to proliferate. This increases FAPs in the necrotic area, which need to be removed in time. Failure to clear FAPs will result in their differentiation into fibroblasts and adipocytes [246]. Fibroblasts secrete extracellular matrix proteins and growth factors and then differentiate into myofibroblasts to increase α-smooth muscle actin (α-SMA) expression and ECM synthesis, finally resulting in fibrosis [247]. Studies on the regulation of FAPs show that (Table 4) IL-4 secreted by infiltrated eosinophils stimulates the activation of FAPs in an IL-4-dependent way. IL-4/IL-13 signaling in FAPs contributes to proliferation and adipogenic differentiation of FAPs is inhibited to facilitate regeneration [55]. IL-1α and IL-1β inhibit the adipogenic differentiation of FAPs, and epidermal growth factor (EGF) and betacellulin (BTC) stimulate the proliferation of FAPs [248]. Lack of TGF-β1 in macrophages inhibits FAP proliferation and reduces fibrosis [249]. Inactivation of retinoic acid (RA) signaling in FAPs leads to adipogenic differentiation, which then impairs regeneration [246].

![Figure 3. Fibrosis in CTX-induced injury models](image-url)

After injury, FAPs are activated and begin to proliferate and then differentiate into fibroblasts and adipocytes. Fibroblasts secrete extracellular matrix proteins and growth factors, and differentiate into myofibroblasts to increase α-SMA expression and ECM synthesis, which may provide scaffolds for the skeletal muscle regeneration while abnormal deposition of ECM finally results in fibrosis. In CTX-induced injury muscle, increases in miR-199a-5p, growth differentiation factor 11 (GDF11), platelet-derived growth factor receptor beta (PDGFRβ), lack of GDF-associated serum protein-1 (Gasp1) and/or Gasp2, and a prior burst of double homeobox 4 (DUX40) induce the deposition of collagen and contribute to fibrosis. In contrast, laminin-111 and Losartam therapy reduce fibrosis. Additionally, IL-4/IL-13 signaling, EGF and BTC, and the RA signaling pathway also regulate the fate of FAPs in skeletal muscle regeneration.
| Author, Year       | Injury Portions                                      | Target Molecule/Drug | Target Process                      | Expression | Effects (Positive/Negative) | Regeneration (Impair/Improve) | Ref.   |
|-------------------|-----------------------------------------------------|----------------------|-------------------------------------|------------|-----------------------------|-----------------------------|-------|
| Heredia JE, 2013  | Unilateral tibialis anterior                        | IL-4                 | FAP proliferation                    | Down       | Negative                     | Impair                       | [55]  |
| Vumbaca S, 2021   | Tibialis anterior, quadriceps, and gastrocnemius    | IL1α/IL1β and extracellular vesicles | FAP proliferation and differentiation | Up         | Positive                     | ——                          | [248] |
| Zhao L, 2020      | Tibialis anterior                                    | RA signaling         | FAP proliferation                    | Up         | positive                     | Improve                      | [246] |
| Zanotti S, 2018   | Tibialis anterior                                    | Exosome              | Fibrosis                            | Up         | Positive                     | Impair                       | [247] |
| Horii N, 2018     | Tibialis anterior                                    | C1q/Wnt and resistance training | Fibrosis                           | Up         | positive                     | Impair                       | [34]  |
| Murray, 2017      | Tibialis anterior                                    | αV intergin          | Fibrosis                            | Down       | Negative                     | Improve                      | [245] |
| Burks, 2011       | Tibialis anterior                                    | Losartam             | Fibrosis                            | ——         | Negative                     | Improve                      | [250] |
| Zanotti S, 2018   | Tibialis anterior                                    | Exosome miR-199a-5p/CAV1 | Fibrosis                           | Up         | positive                     | Impair                       | [247] |
| Murray, 2017      | Tibialis anterior                                    | αV intergin          | Fibrosis                            | Down       | Negative                     | Improve                      | [245] |
| Zhao L, 2020      | Tibialis anterior                                    | Losartam             | Fibrosis                            | ——         | Negative                     | Improve                      | [250] |
| Zanotti S, 2018   | Tibialis anterior                                    | Exosome miR-199a-5p/CAV1 | Fibrosis                           | Up         | positive                     | Impair                       | [247] |
| Murray, 2017      | Tibialis anterior                                    | αV intergin          | Fibrosis                            | Down       | Negative                     | Improve                      | [245] |
| Burks, 2011       | Tibialis anterior                                    | Losartam             | Fibrosis                            | ——         | Negative                     | Improve                      | [250] |
| Ding, 2016        | Tibialis anterior                                    | TAR RNA-binding protein (Trbp) | Fibrosis; myofiber formation       | Down       | Positive; Negative          | Impair                       | [244] |
| Ogasawara S, 2018 | Left gastrocnemius                                  | CatK                 | Fibrosis; inflammation and cell apoptosis | Down       | Negative                     | Improve                      | [252] |
| Lee SJ, 2010      | Tibialis anterior                                    | Follistatin           | Fibrosis; myofiber maturation       | Down       | Negative                     | Improve                      | [253] |
| Rinaldi F, 2016   | Posterior compartments of the lower extremities     | GDF11                | Collagen deposition                 | Up         | Positive                     | No effects                   | [254] |
| Mignemi NA, 2017  | Gastrocnemius                                        | Plasmin              | Calcification                       | Down       | Negative                     | Impair                       | [255] |
| Lee YS, 2013      | Right gastrocnemius                                  | Gasp1 and/or Gasp2   | Calcified fibers and fibrosis       | Down       | Positive                     | Impair                       | [256] |
| Zhao Y, 2009      | Tibialis anterior                                    | Tie2-expressing      | Heterotopic ossification            | ——         | ——                          | ——                          | [257] |
| Lounen V, 2009    | Quadriceps                                          | Tie2-expressing      | Heterotopic ossification            | ——         | ——                          | ——                          | [258] |
| Drouin G, 2019    | Tibialis anterior                                    | VEGF                 | Apoptosis                           | Up         | Negative                     | Improve                      | [259] |
| Arsic N, 2004     | Tibialis anterior                                    | JNK and iNOS signaling | Cell apoptosis                      | Down       | Negative                     | Improve                      | [260] |
| Sinha-Hikim I, 2007| Gastrocnemius                                       | MKP-5                | myofiber apoptosis                  | Down       | Negative                     | Improve                      | [261] |
| Min K, 2017       | Gastrocnemius/Soleus                                 | serpina3n            | Stabilization of myofiber plasm membrane | Up         | Positive                     | Improve                      | [262] |
| Tjondrokoesoemo A, 2016 | Tibialis anterior                                 | serpina3n            | Stabilization of myofiber plasm membrane | Up         | Positive                     | Improve                      | [263] |
Additionally, studies have also shown that increases in miR-199a-5p [247], growth differentiation factor 11 (GDF11) [254], and platelet-derived growth factor receptor beta (PDGFRβ) [245], together with the lack of GDF-associated serum protein-1 (Gasp1) and/or Gasp2 [256] and a prior burst of double homeobox 4 (DUX4) [251], induced the deposition of collagen and contributed to fibrosis. In contrast, laminin-111 reduced fibrosis and facilitated skeletal muscle regeneration [165]. Losartam therapy also reduced fibrosis by inhibiting the TGF-β signaling pathway [250].

4.4. Calcification in CTX-Induced Injury Models

Calcification occurs after muscle injury. Under normal conditions, calcification can be resorbed. While in a pathological state, continuous calcification can induce chronic inflammation and/or loss of muscle function [264]. Studies have revealed that (Table 4) after CTX injection, Tie2-expressing endothelial precursors are the main contributor to calcification in a mouse model of dysregulated bone morphogenetic protein (BMP) signaling [258]. Moreover, the inflammatory microenvironment induced by CTX injection is also necessary for calcification in injured muscle [258]. At the early stage after injury, calcific nodules are present in mitochondria, which are mediated by cell death and can be cleared by infiltrated macrophages [257]. Additionally, calcification in damaged muscle may also occur in connection with reduced plasmin, and this is independent of its canonical fibrinolytic function [255]. The hypoxia state induced by CTX injury can induce osteogenic differentiation and mineralization of muscle resident stromal cells and further stimulate the formation of myofiber calcification [259].

4.5. Angiopoiesis and Neurogenesis in CTX-Induced Injury Models

In CTX-induced injury models, the capillaries are destroyed, and endothelial cells are activated to repair the skeletal muscle endothelium. It is reported that (Table 5) macrophage cells derived from bone marrow can express endothelium-related markers such as Tie2 and CD31 to promote angiogenesis [265]. Angiotensin II derived from differentiated muscle myoblasts stimulates the migration of endothelial cells, which also further facilitates angiopoiesis [266]. In contrast, CCR2 deficiency leads to decreased vascular endothelial growth factor (VEGF) production and delayed angiogenesis in injured muscle, which then impairs regeneration [81].
Table 5. Angiogenesis and neurogenesis in CTX-induced injury models.

| Author, Year | Injury Portions | Target Molecule/Drug | Target Process | Expression | Effects (Positive/Negative) | Regeneration (Impair/Improve) | Ref. |
|--------------|-----------------|----------------------|----------------|------------|----------------------------|-------------------------------|------|
| Bellamy LM, 2010 | Unilateral tibialis anterior | Angiotensin II | Angiogenesis | Down | Negative | Impair | [266] |
| Ieronimakis N, 2012 | Tibialis anterior, quadriceps, gastrocnemius | Bone marrow-derived cells | Angiogenesis | —— | Positive | Improve | [265] |
| Mellows B, 2017 | Tibialis anterior | Extracellular vesicles-derived from amniotic fluid stem cell | Angiogenesis | —— | Positive | Improve | [267] |
| Hosaka Y, 2002 | Right tibialis anterior | α1-Syntrophin | Hypertrophy and neuromuscular junctions | Down | Positive; Negative | Improve | [268] |
| Daneshvar N, 2020 | Left tibialis anterior | Premature satellite cell activation | Maturation of neuromuscular junctions | Up | Negative | Improve | [269] |
| Kurosaka M, 2021 | Tibialis anterior | M2 macrophage | Motor innervation regeneration | —— | —— | Improve | [219] |
| Sawano S, 2014 | Tibialis anterior | M2 macrophage | Motor innervation regeneration | —— | —— | Improve | [270] |
| Randazzo D, 2019 | Unilaterally tibialis anterior | Tubb6 | Microtubule organization | Up | Negative | —— | [15] |
In terms of neurogenesis, M2 macrophages infiltrate damaged muscle, produce hepatocyte growth factor (HGF), and then stimulate the expression of semaphorin 3A (Sema 3A) in myoblasts to regulate the regeneration of motor innervation in injured muscle [270,271]. Pre-activation of satellite cells delays the maturation of the neuromuscular junction by reducing the expression of semaphoring (Sema) 3A and S100B [269]. Lack of desmin leads to disrupted neuromuscular connections [238].

4.6. Other Regeneration-Related Genes in CTX-Induced Injury Models

In addition to the mechanism described above, there are a large number of genes involved in skeletal muscle regeneration in CTX-induced injury models such as Tsukushi, Dicer, mesoderm specific transcript (Mest), filamin C, LYVE-1, and so on (Table 6). However, in these studies, the special role of these genes has not been explored. Further experiments are needed to elucidate their function.

Table 6. Single gene in the CTX-induced skeletal muscle injury model.

| Author, Year | Injury Portions | Target Molecule | Expression | Regeneration (Impair/Improve) | Ref. |
|--------------|-----------------|-----------------|------------|-----------------------------|-----|
| Kim DS, 2015 | Left tibialis anterior | TLR2 | Down | Improve | [272] |
| Oikawa S, 2019 | Tibialis anterior | Dicer | Down | Impair | [273] |
| Hiramaki Y, 2015 | Tibialis anterior | Mest | Down | Impair | [274] |
| Norton CR, 2013 | Left tibialis anterior | Snail /Sna13 | Down | No effects | [275] |
| Call JA, 2017 | Left tibialis anterior and left flexor digitorum longus | Ulk1 | Down | —— | [276] |
| Chaturvedi N, 2020 | Left gastrocnemius | S100A1 | Down | —— | [277] |
| Parks CA, 2019 | Left tibialis anterior | Trim33 | Down | No effects | [278] |
| Goetsch SC, 2005 | Gastrocnemius | Filamin C | Up | —— | [279] |
| Wardrop KE, 2011 | Left tibialis anterior | LYVE-1 | Down | —— | [280] |
| Merkulova T, 2000 | Extensor digitorum longus and tibialis anterior | β enolase | Up | —— | [281] |
| Yuasa K, 2008 | Tibialis anterior | mir-206 | Up | —— | [282] |
| Casciola-Rosen L, 2012 | Right anterior tibias | Aldolase A | Up | —— | [283] |
| Mammen AL, 2011 | Right tibialis anterior | UFD2a | Up | —— | [284] |
| Nakamura K, 2010 | Right gastrocnemius | GNE | Up | —— | [285] |
| Sato Y, 2013 | Left gastrocnemius | Sema3A | Up | —— | [286] |
| Garry, 2000 | Hind limbs | MNF | Down | Impair | [287] |
| Kemp MW, 2009 | Tibialis anterior | Syncoilin | Up | —— | [288] |
| Miura P, 2005 | Right tibialis anterior | Urophin A | Up | —— | [289] |
| Wang Q, 2022 | Tibialis anterior | Tsukushi | Down | Impair | [290] |
| McCullagh KJ, 2008 | Unilateral tibialis anterior | Syncoilin | Down | No effects | [291] |
| Demonbreun AR, 2010 | Quadriiceps or gastrocnemius/soleus | Ferlin | Up | —— | [292] |
| Maeda Y, 2017 | Right tibialis anterior | CXCL12 | Up | Improve | [293] |
| Darabi K, 2008 | Tibialis anterior | Pax3 | Up | Improve | [294] |
| Di Rocco A, 2015 | Tibialis anterior | RARγ | Down | Impair | [295] |
| Bryer SC, 2007 | Extensor digitorum longus and tibialis anterior | uPAR | —— | No effects | [296] |
| Bryan BA, 2005 | Tibialis anterior | GEFT | Up | Improve | [297] |
| Mathes AL, 2011 | Tibialis anterior | TLR-3 | Down | Impair | [298] |
| Wu G, 2010 | Forelimb leg muscle | Chkb | Down | No effects | [299] |
| Yan Z, 2003 | Tibialis anterior | E2H | Down | Impair | [299] |
| Fujita R, 2014 | Left tibialis anterior | IL-6R | Down | Improve | [300] |
| Wu G, 2009 | Gastrocnemius | Chkb | Down | Impair | [301] |
| Wada E, 2019 | Tibialis anterior | Emerin and lamin A/C | Down | Impair | [302] |
| Mofarrah M, 2015 | Unilateral tibialis anterior | Ang-1 | Up | Improve | [303] |
| Gattazzo F, 2014 | Tibialis anterior | Cyclosporin A | Up | Improve | [304] |
| Kim MH, 2011 | Unilaterally tibialis anterior | Akt | Up | Improve | [243] |
| Lazzar I, 2007 | Soleus | Spry | Down | —— | [305] |
| Armand AS, 2003 | Unilateral soleus | Follistatin and myostatin | Up/Down | Improve | [306] |
| Li C, 2013 | Right gastrocnemius | Prosaposin | Up | —— | [307] |
4.7. Non-SC Stem Cells Regulate Regeneration in CTX-Induced Injury Muscle

Non-SC stem cells are also involved in the regulation of regeneration (Figure 4). The results (Table 7) show that bone marrow-derived cells [308,309], pulp cells [310], bone marrow-derived human MSCs [311], hematopoietic stem cells [312], muscle precursor cells [313,314], capillary stem cells [315], adipose-derived mesenchymal stem cells [316], and human amniotic fluid stem cells [317,318] settle in the injured sites and differentiate into myogenic cells to stimulate the skeletal muscle regeneration in CTX-induced injury models. Additionally, mobilization of bone marrow stem cells also accelerates the muscle regeneration [319].

![Figure 4](image-url)

**Figure 4.** Non-SC stem cells regulate regeneration in CTX-induced injury muscle. Transplantation of hematopoietic stem cells, adipose-derived mesenchymal stem cells, bone marrow-derived mesenchymal stem cells, and amniotic fluid stem cells stimulate regeneration in the damaged skeletal muscle.

**Table 7.** Non-SCs in the CTX-induced skeletal muscle injury models.

| Author, Year | Injury Portions | Target Molecule/Drug | Regeneration | Ref |
|--------------|-----------------|----------------------|--------------|-----|
| Kano K, 2020 | Gastrocnemius   | Capillary stem cells | Improve      |     |
| Liu Y, 2007  | Unilateral tibialis anterior | FLk-1+ AD-MSCs | Improve      |     |
| Kim JA, 2013 | Left tibialis anterior | hAFC cells transfected with MyoD | Improve |     |
| Xuan W, 2021 | Tibialis anterior | Pluripotent stem cells-derived skeletal muscle | Improve |     |
| Naldaiz-Gastesi N, 2019 | Tibialis anterior | Human cremaster muscle-derived precursor cells | Improve |     |
| Mori J, 2008 | Tibialis anterior | CD45+; Sca-1+ hematopoietic stem cells | Improve |     |
| Abedi M, 2014 | Tibialis anterior | Hematopoietic stem cells | Improve |     |
| Hwang Y, 2014 | Tibialis anterior | Human embryonic stem cells | Improve |     |
| Piccoli M, 2012 | Tibialis anterior | Human embryonic stem cells | Improve |     |
| Yang R, 2010 | Right tibialis anterior | Clones of ectopic stem cells | Improve |     |
| Rousseau J, 2010 | Tibialis anterior | Muscle precursor cells | Improve |     |
| Gang EJ, 2009 | Tibialis anterior | Mesenchymal stem cells | Improve |     |
| Jung JE, 2017 | Gastrocnemius and masseter | Pulp-derived cell | Improve |     |
| de la Garza-Rodea AS, 2011 | Tibialis anterior | BM-hMSCs | Improve |     |
| Bosso, 2004 | Tibialis anterior | Human adult BM | Improve |     |
| Ma, 2012 | Tibialis anterior | Human AF-amniotic fluid stem cells | Improve |     |
| Fukuda S, 2002 | Tibialis anterior | Bone marrow and fetal liver cells | Improve |     |
| Luth ES, 2008 | Tibialis anterior, quadriceps, and gastrocnemius | Bone marrow side population cells | Improve |     |
| Zheng JK, 2006 | Tibialis anterior | Human embryonic stem cells | Improve |     |
| Căzăk D, 2011 | Right tibialis anterior | Skeletal muscle side population | Improve |     |
| Meeson AP, 2004 | Tibialis anterior | Skeletal muscle side population | Improve |     |
| Drapeau C, 2010 | Right tibialis anterior | Mobilization of bone marrow stem cells | Improve |     |
| Kowalski K, 2016 | Gastrocnemius | Sdf-1 and granulocyte-colony stimulating factor | Improve |     |
| Mitchell R, 2019 | Tibialis anterior | ADSC secretome | Improve |     |
| Tobin S, 2021 | Tibialis anterior; quadriceps; gastrocnemius | Young/aging macrophages | Improve/improve |     |
5. Conclusions

Skeletal muscle has a tremendous capacity for regeneration after injury. This is largely due to muscle SCs. In order to learn about the mechanisms of regeneration, skeletal muscle regeneration has been studied for decades in numerous injury models. However, differences in injury exist among the different models, which makes their comparison difficult. In the CTX-induced injury model, a transient and reproducible acute injury is induced without affecting the vasculature or nerves, and this allows for the possibility of performing molecular and biochemical analyses of the whole muscle. Additionally, CTX injury models have a relatively low level of harm for animals in contrast to crushing models, which are invasive and associated with the risk of infection. This explains why CTX-induced injury models have been widely used in exploring the mechanisms of muscle regeneration. To understand the regeneration mechanisms in CTX-induced injury models, we explored all the studies and summarized the characteristics and injury positions, different models of CTX injury, and functional factors involved in the process of regeneration. The results show that the process of regeneration is similar in different mouse strains but that differences exist between gender. Regeneration is impaired in obese, diabetic, and aging mice, whereas exercise, electrical stimulation, and overloading facilitate the regeneration of damaged muscle. Non-SCs transplanted in damaged muscle following CTX injury can also differentiate into myogenic cells and facilitate myogenesis. The emphasis throughout was on the process of regeneration, the changes in the functional proteins involved in the processes of clearance of necrotic fiber debris, M1 to M2 macrophage conversion, SC activation, myoblast proliferation, differentiation and fusion, and fibrosis and calcification, which influence the final outcome of the regenerative activity. However, the inflammatory process in muscle injury and repair is complex, with different effects on muscle regeneration observed in various studies. Additionally, angiopoiesis and neurogenesis also influence the outcome of regeneration, which are easily ignored. Thus, further experiments are needed to explore the mechanisms of inflammatory response during muscle regeneration.

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