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Review

Impaired skeletal muscle regeneration in diabetes: From cellular and molecular mechanisms to novel treatments

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SUMMARY

Diabetes represents a major public health concern with a considerable impact on human life and healthcare expenditures. It is now well established that diabetes is characterized by a severe skeletal muscle pathology that limits functional capacity and quality of life. Increasing evidence indicates that diabetes is also one of the most prevalent disorders characterized by impaired skeletal muscle regeneration, yet underlying mechanisms and therapeutic treatments remain poorly established. In this review, we describe the cellular and molecular alterations currently known to occur during skeletal muscle regeneration in people with diabetes and animal models of diabetes, including its associated comorbidities, e.g., obesity, hyperinsulinemia, and insulin resistance. We describe the role of myogenic and non-myogenic cell types on muscle regeneration in conditions with or without diabetes. Therapies for skeletal muscle regeneration and gaps in our knowledge are also discussed, while proposing future directions for the field.

INTRODUCTION

Diabetes represents a major public health challenge, significantly affecting both human well-being and healthcare costs. Despite significant investments in research and healthcare, the prevalence and incidence of diabetes continue to increase.[1,2] Diabetes can be mainly divided into two types caused by insulin deficiency (type 1) or insulin resistance (type 2). However, regardless the form of diabetes, resultant comorbidities often overlap.[3,4] For instance, both type 1 and type 2 diabetes are characterized by a progressive decline in skeletal muscle mass and function, known as diabetic myopathy.[5–9] This complication directly contributes to the progression of other comorbidities, such as obesity and hyperglycemia, due to the essential role of skeletal muscle for locomotion, energy metabolism, and whole-body glucose homeostasis.[10–12] Under conditions with obesity and diabetes, skeletal muscle undergoes further structural, functional, and metabolic alterations, including muscle fiber atrophy,[13] altered myokine secretion,[14] impaired mitochondrial structure and bioenergetics,[15] fiber-type shifting and reduced oxidative enzyme activity,[16] which lead to decreased muscle strength,[8] impaired functional capacity, and ultimately increased mortality.[9,17–19]

Diabetes also impacts the ability of skeletal muscle to regenerate when injured,[20,21] which may contribute to the manifestation of complications such as chronic limb-threatening ischemia and foot ulcers. Diabetes creates an unfavorable environment for muscle repair, with excessive fibrosis and delayed myofiber maturation.[22] Muscle regeneration is a complex process orchestrated by multiple myogenic and non-myogenic cell types. Although muscle stem cells (MuSCs), also called satellite cells (SCs), have traditionally been implicated as the primary cell population to be responsible for normal muscle regeneration,[23] non-MuSCs, such as fibro-adipogenic progenitors (FAPs), vascular endothelial cells, and immune cells, have gained attention for their role in muscle regeneration and health.[24–28] Recent advances in RNA sequencing (RNA-seq) technologies, such as single-cell RNA-seq (scRNA-seq) and single-nucleus RNA-seq (snRNA-seq), have enabled the identification of novel cell subpopulations associated with muscle regeneration including their regulatory mechanisms.[29–35] In this review, we aim to describe how diabetes and its associated comorbidities (e.g., obesity and dyslipidemia) impact skeletal muscle regeneration. First, we summarize muscle abnormalities that have been observed in patients with diabetes and may play an important role in muscle regeneration. Then, we describe the role of myogenic and non-myogenic cell types in muscle regeneration in conditions without and with diabetes. Next, we discuss the molecular mechanisms underlying diabetes-associated impairments in muscle regeneration. Lastly, we discuss therapies for skeletal muscle repair and associated knowledge gaps, while proposing future directions for the field.

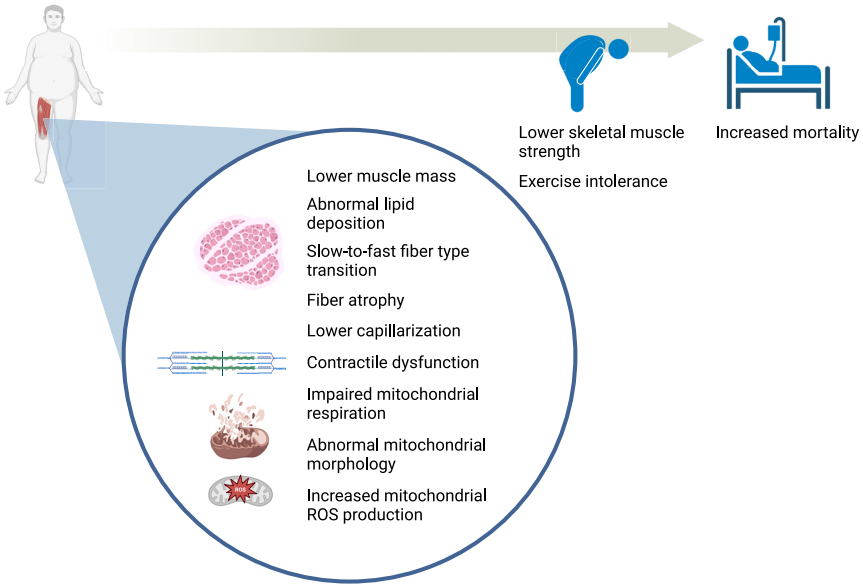

Figure 1. Skeletal muscle alterations in diabetes

Patients with diabetes develop several morphological, functional, and metabolic skeletal muscle alterations that lead to exercise intolerance and increased mortality.

SKELETAL MUSCLE ABNORMALITIES IN DIABETES

Several skeletal muscle alterations have been observed in people with diabetes and animal models of diabetes. However, it is important to note that this disease is accompanied by multiple comorbidities, such as obesity, hypertension, and dyslipidemia, which have independent and synergistic impacts on skeletal muscle structure, function, and metabolism.[21,36–40] The multifactorial etiology of diabetes[41] has complicated the identification of relevant therapeutic targets. Furthermore, other factors, including aging, lack of physical activity, and malnutrition, also play an important role in diabetes-associated skeletal muscle deficits. While an in-depth examination of the skeletal muscle pathology of diabetes is beyond the breadth of this review, we summarize some muscle abnormalities that have been observed in people with diabetes and may play an important role in muscle regeneration.

Skeletal muscle mass is negatively associated with diabetes incidence, insulin resistance, and glycated hemoglobin levels.[42] Compared with normoglycemic controls, patients with type 2 diabetes show a decline in lean mass,[43] muscle mass,[43–45] muscle strength,[8] and exercise capacity.[9] Of note, patients with diabetes and lower muscle mass have higher mortality than patients with preserved muscle mass.[46] Abnormal lipid deposition,[47–51] fiber atrophy,[52] a slow-to-fast fiber-type shift,[16,53,54] and excessive activity of growth promoting pathways (i.e., elevated gene expression of embryonal and perinatal myosin heavy chains [*MYH3* and *MYH8*])[55] have also been observed in people with diabetes. Moreover, both type I and type II muscle fibers (see Box 2 for a description of skeletal muscle fiber types) of individuals with diabetes have lower myosin ATPase activity (a marker of impaired contractility), which significantly correlates with the degree of insulin sensitivity and exercise capacity.[16] This was observed in patients with obesity and diabetes vs. body mass index (BMI)-matched controls, and muscle alterations can therefore not be explained by increased body weight.[16] Furthermore, skeletal muscle cells cultured from people with or without diabetes demonstrate that altered secretion of myokines[14] and lipid accumulation[56,57] are intrinsic features of skeletal muscle in diabetes. Oxygen transport and utilization are also severely affected by diabetes. People with diabetes have reduced capillarization, which closely correlates with plasma insulin concentrations.[54] They also show abnormal mitochondrial ultrastructure,[58] impaired mitochondrial respiration,[53] and dysregulated mitochondrial enzyme activities,[58,59] which subsequently increase the production of reactive oxygen species (ROS).[60] Overall, diabetes is characterized by a severe muscle pathology that limits functional capacity and quality of life (Figure 1).

SKELETAL MUSCLE REGENERATION IN DIABETES

Skeletal muscle regeneration is the process by which muscle tissue repairs itself *ad integrum* following injury or damage. This process involves the coordination of multiple cell types and biological processes and can be divided into several phases, including degeneration (necrosis), inflammation, regeneration, maturation remodeling, and functional recovery[61] (Figure 2). Although the duration of each phase can vary depending on the severity and location of the injury and the age and health of the organism, the overall dynamic of muscle regeneration is comparable between mammals (e.g., mouse, rat, and human) and can be characterized at molecular, morphologic, and functional levels. This review categorizes the process of muscle regeneration into three phases and describes the events that occur in each stage in conditions without and with diabetes. However, it is important to note that while certain cells or molecules have a crucial role in a specific phase, they may also contribute to the entire process of muscle regeneration.

Degeneration and inflammation

Injury to skeletal muscle can occur as a result of disease (e.g., muscle dystrophy), trauma, exposure to myotoxic agents, ischemia, exposure to extreme temperatures, and the muscle's own contraction. To better understand and treat these injuries, scientists have developed several injury models (Box 1). From a clinical perspective, muscle injuries can be classified as mild, moderate, or severe according to the functional disability they produce. Muscle regeneration typically begins with muscle necrosis/degeneration, which can last for hours to a few days. This phase is characterized by the breakdown and disintegration of damaged muscle fibers and loss of contractile proteins, which

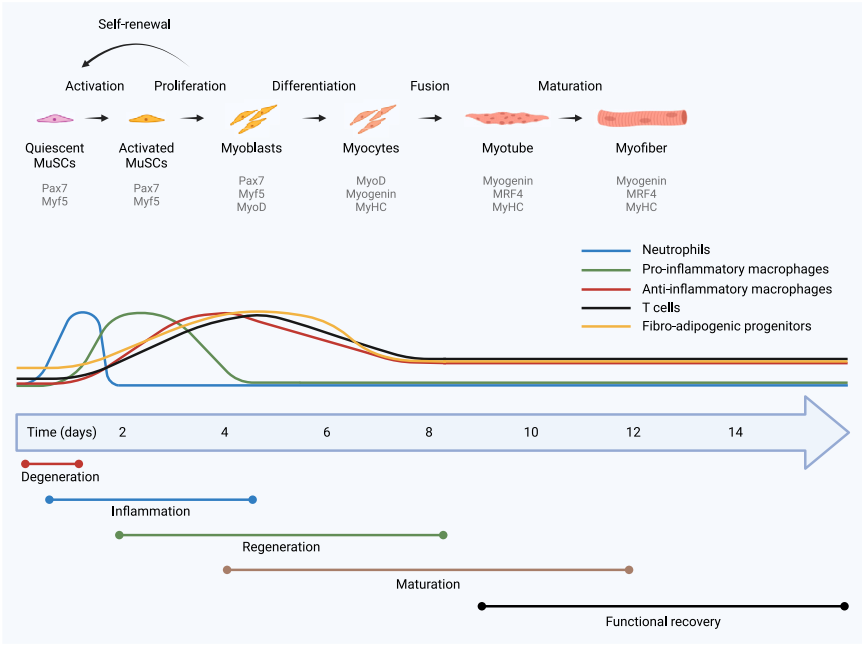

Figure 2. Skeletal muscle regeneration

The regenerative program activated by skeletal muscle tissue in response to injury involves the coordination of multiple cell types and biological processes that can be divided into several interrelated and time-dependent phases, namely degeneration, inflammation, regeneration, maturation, and functional recovery. From a myogenic-centric point of view, during muscle injury, muscle stem cells (MuSCs) (marked by Pax7 and Myf5) are activated ($Pax7^+$ and $Myf5^+$) and undergo rapid proliferation to form a population of myoblasts ($Pax7^+$, $Myf5^+$, and $MyoD^+$), which then differentiate into myocytes ($MyoD^+$, $Myogenin^+$, and $MyHC^+$) that fuse to form new muscle fibers ($Myogenin^+$, $MRF4^+$, and $MyHC^+$). This process is essential for restoring muscle function.

result in a severe decline in force production[62,63] and increased serum levels of muscle proteins, such as creatine kinase,[64] lactate dehydrogenase,[65] alpha-actin,[66,67] and troponin I,[68] which are usually restricted to the myofiber cytosol.[61,69] Indeed, increased serum creatine kinase can be observed after vigorous intensity exercise[64,65] and in the course of degenerative disorders including muscular dystrophies.[70,71] Circulating muscle-specific micro RNAs (miRNAs), such as miR-378a-3p and miR-434-3p, are also potential biomarkers of muscle damage.[72] At a histological level, muscle degeneration is characterized by loss of dystrophin,[73] swollen and deeply eosinophilic myofibers with intense nuclear condensation (pyknosis), broken capillaries, and lack of cross striations.[74] Muscle degeneration immediately triggers inflammatory reactions that are essential for successful tissue remodeling. The complement system—a collection of nine major complement proteins found in the bloodstream[75]—serves as the first sensor of the muscle injury,[76] promoting infiltration of neutrophils, macrophages, and mast cells to the lesion site.[77,78] Indeed, mice with genetic ablation or inactivation of complement C3 show reduced neutrophil/macrophage infiltration and impaired muscle regeneration following cardiotoxin-induced injury.[79] Neutrophils infiltrate damaged muscle within a few hours and attain their highest concentration about 12–24 h post-injury, after which they rapidly return to their usual levels.[80,81] Neutrophils create an inflammatory environment by releasing pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interferon-γ (IFN-γ), and interleukin-1β (IL-1β), which further promote the recruitment of peripheral neutrophils[80,82] and other immune cell populations.[83] This is closely linked, both in time and location, to the initial stages of myogenesis, when MuSCs are activated and commence to proliferate and differentiate. TNF-α and IFN-γ also stimulate macrophages into a pro-inflammatory state. In culture conditions, these macrophages are referred to as M1 macrophages as they are activated by pro-inflammatory T helper 1 (T_H1)-type cytokines.[84–86] This distinguishes them from M2 macrophages, which are triggered by T_H2-type cytokines and are associated with responses to anti-inflammatory reactions and tissue remodeling (as discussed later). However, the distinction between M1 and M2 macrophage phenotypes, although useful, only represents two opposite ends of a wide range of phenotypes and does not portray the full diversity present within macrophage populations.[87] A different signature of macrophages is observed during *in vivo* regeneration, where $Ly6C^+$ macrophages trigger an inflammatory response whereas $Ly6C^-$ macrophages dampen the inflammation and promote tissue regeneration.[88–92] These observations highlight the highly dynamic and divergent nature of the macrophage response *in vitro* vs. *in vivo* conditions. Diversity of macrophages is also affected by aging, leading to unique macrophage subpopulations[93] and altered macrophage response during muscle regeneration following exercise.[94,95] Lineage tracing, bone marrow transplant experiments, and scRNA-seq analysis have revealed that skeletal muscle-resident macrophages differ from resident macrophages in other tissues and consist of functionally diverse subsets that appear to facilitate muscle regeneration.[96] In-depth analyses of the diversity, origins, and functions of skeletal muscle-resident macrophages, including their interactions with infiltrating monocyte-derived macrophages, would therefore help develop macrophage-targeted therapies. Mast cells also play an important role in the early stage of muscle regeneration; they degranulate and release inflammatory mediators including TNF-α, IL-1, and histamine to recruit more mast cells, neutrophils, and other immune cells to the injury site.[97,98]

In diabetes, the chronically altered inflammatory state of the disease may worsen injury-related muscle degeneration and inflammation.[115] For instance, after damaging resistance exercise, patients with type I diabetes had a higher incidence of myofibers showing some degree of ultrastructural damage as compared with control subjects—18 times more vs. 9 times more, respectively.[116] Another study conducted in individuals undergoing below-knee amputation surgery, with and without diabetes, revealed that those with diabetes showed signs of muscle degeneration such as myofiber necrosis, myofiber splitting, and hypercontracted myofibers.[117] These observations

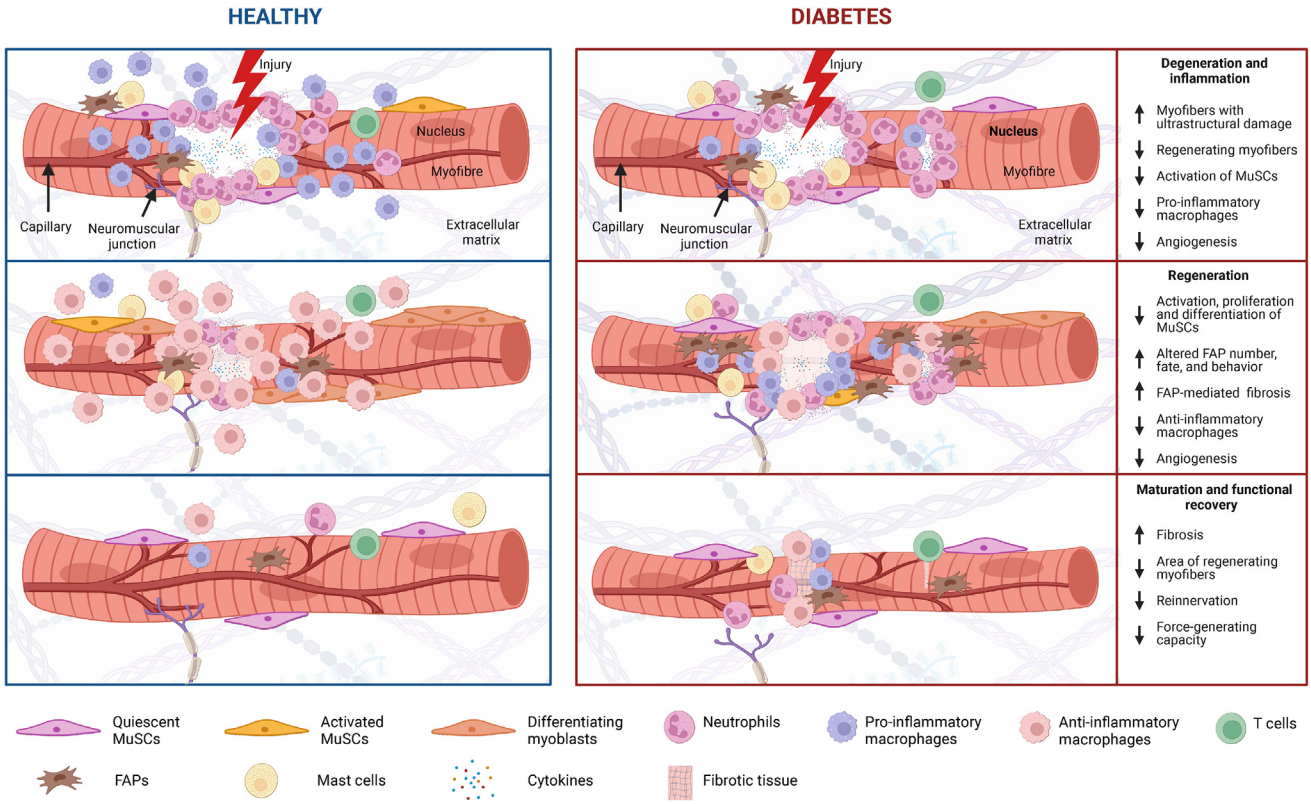

Figure 3. Skeletal muscle regeneration in diabetes

Diabetes and its associated complications, including obesity and hyperglycemia, impact multiple cell populations (MuSCs, neutrophils, macrophages, T cells, FAPs, and mast cells) that play a vital role in the process of muscle regeneration (i.e., degeneration and inflammation, regeneration, and maturation and functional recovery).

suggest that diabetes does not only affect muscle regeneration when injured but is also characterized by chronic muscle degeneration induced by intrinsic metabolic perturbations (e.g., insulin signaling defects, lipotoxicity, and increased inflammation). Indeed, diabetes has previously been described as a degenerative disease targeting multiple organs and tissues including the kidney, liver, nerves, blood vessels, and musculoskeletal tissues.[118–121] Changes in the initial stages of muscle regeneration have also been noticed in mice with diabetes subjected to myotoxin-induced injury.[22,122–124] Akita mice, a genetic type 1 diabetes model, display a reduced ability for macrophage infiltration within the first few days (5 days) after injury.[22] These mice have a mutation in one allele of the insulin-2 (*Ins2*) gene, which leads to pancreatic beta cell dysfunction and hyperglycemia without obesity.[125,126] Similarly, compared with wild-type (WT) mice (controls), *ob*/*ob* and *db*/*db* mice—two well-characterized models of obesity and insulin resistance (induced by mutations in the genes encoding leptin) and obesity and diabetes (induced by mutations in the genes encoding leptin receptor), respectively—show impaired infiltration of macrophages to the lesion site at day 3 post-injury, while neutrophil accumulation remains unchanged.[123] Angiogenesis (as demonstrated by $CD31^+$ cell accumulation) following muscle injury is also impaired in both *ob*/*ob* and *db*/*db* mice.[123] Taken together, evidence suggests that both type 1 and type 2 diabetes hinder the early stages of muscle regeneration following injury. However, there is still a need to investigate the impact of diabetes on other crucial factors that control injury-induced degeneration and inflammation, such as the complement system and mast cells. Additionally, studies have not included assessments of skeletal muscle function that could offer important insights into how diabetes affects the initial phases of muscle regeneration.

Regeneration

Following the first wave of immune cells (i.e., neutrophils, pro-inflammatory macrophages, and mast cells), skeletal muscle regeneration is marked by MuSC activation and expansion, which is accompanied by the infiltration of T cells and eosinophils,[61,127] and a macrophage shift toward an anti-inflammatory phenotype.[25,91,128] MuSCs reside between the basal lamina and sarcolemma of myofibers. They are mitotically quiescent until required for muscle growth or regeneration. Upon muscle injury, MuSCs become activated and enter a state of proliferation, which has a dual role: the generation of committed cells that differentiate into myoblasts and contribute to the repair of damaged muscle tissue and the replenishment of the stem cell pool after exploitation. During this time, T cells[129] and eosinophils[130] also infiltrate the injury site. T cells appear at the injury site about 3 days post-injury and remain to be detected until 10 days post-injury (cardiotoxin injury).[131] T cells release several cytokines including TNF-α, IFN-γ, IL-1β, and IL-13 to modulate the microenvironment of the lesion site.[132] Mice lacking T cells

Box 1. Skeletal muscle injury models

ECCENTRIC CONTRACTION-INDUCED MUSCLE INJURY

Eccentric muscle contractions occur when a muscle lengthens while generating force. This normally happens when the resistance or load on the muscle is greater than the force generated by the muscle.[99–101] Of note, not all eccentric contractions induce injury.[102] The extent of muscle damage varies between voluntary (e.g., downhill treadmill running) and electrically evoked lengthening contractions.[103,102,104] The severity of muscle injury induced by electrically evoked lengthening contractions can be controlled precisely by altering the number of contractions and the stretching intensity.[103,105] Compared with other injury models (e.g., myotoxin or chemical injury), eccentric-contraction-induced muscle injury is a more physiologically relevant injury model in relation to daily activities.[103,105]

VOLUMETRIC MUSCLE LOSS

Volumetric muscle loss injuries are the result of traumatic or surgical loss of skeletal muscle tissue with resultant functional impairment. These represent a challenging clinical issue for both military and civilian medicine. Numerous research initiatives related to volumetric muscle loss injuries aim to regenerate the lost muscle tissue and thereby enhance muscle strength.[106,107] Volumetric muscle loss is induced by the removal of muscle tissue, which can be achieved by different tools and procedures. While small variations in tissue removal can influence functional outcomes, the connection between these variables is not strictly linear. Instead, these parameters are influenced by multiple factors, including the shape of the injury and the muscle anatomy.[108]

FREEZE INJURY

Freeze injury is physically induced by exposing skeletal muscle to an extremely cold probe, leading to a strong degenerative and inflammatory reaction. This type of injury destroys not only muscle fiber cells but also mononuclear cells. Muscle regeneration is therefore accomplished by MuSCs from regions outside the injury zone, which need to migrate into the injured area and interact with inflammatory cells. Consequently, the duration required for observable histological recovery of the affected area is generally longer compared with other forms of physical or chemical injury.[109]

MYOTOXIN INJURY

Myotoxins (e.g., cardiotoxin and notexin) are a family of proteins commonly found in snake venoms that can cause severe muscle damage/necrosis and significantly impair muscle function. Researchers typically inject myotoxins directly into the muscles of interest, which destroys the muscle fibers but leaves the ECM intact and does not explicitly target MuSCs, allowing them to regenerate the tissue. Intramuscular injections are relatively simple and allow the muscle to fully recover its contractile features. This is a reproducible and consistent injury model that is ideal for addressing detailed molecular inquiries about skeletal muscle regeneration.[108,110,111]

CHEMICAL INJURY

Chemical agents, such as barium chloride, have been used to induce muscle injury and study muscle regeneration. Similar to myotoxins, chemical agents can be injected directly into the muscles, which damage myofibers while preserving their associated MuSCs. Motor innervation and capillarity also appear disrupted, further compromising muscle integrity. The advantages of chemical injury lie in its simplicity of application and its ability to consistently produce similar results.[112,113]

ISCHEMIA

Ischemia occurs when there is a lack of blood flow and oxygen in the body. Ischemia models, particularly those involving permanent ligation of vessels leading to muscles, lead to muscle loss and relatively limited functional recovery compared with other injury models. Ischemia/reperfusion (I/R) injury models differ from permanent ligation as they involve the reestablishment of blood flow after a few hours of acute ischemia, which can result in swelling, destruction of capillaries, and potentially organ failure.[108] Compared with injections of myotoxins, I/R models are less effective in promoting muscle recovery.[114]

RE-INJURY

This model involves inducing two consecutive muscle injuries (e.g., two lesions performed with a 1-month interval) to investigate MuSC pool maintenance or depletion after more than one round of regeneration.[74]

Box 2. Skeletal muscle fiber types

Muscle fibers have been categorized based on various criteria, including their color (red vs. white), shortening velocity (fast vs. slow), fatigability (fatigable vs. fatigue resistant), metabolic pathways (oxidative vs. glycolytic), and protein isoform expression. Notably, fatigue resistance and oxidative capacity often correlate with mitochondrial content. The traditional view of skeletal muscle fiber diversity suggests that the variety of patterns of activity imposed by motor neurons dictates the typology of the fibers they innervate, wherein fiber type is determined by MyHC isoform features. This classification first relied on ATPase pH lability and later on MyHC expression. The predominant classification for adult human limb muscles comprises three fiber types: type I (slow, oxidative, and resistant to fatigue), IIa (fast, oxidative, and intermediate metabolic properties), and IIx (fastest, glycolytic, and prone to fatigue). Humans may also express other types of myosin, such as embryonic, neonatal, and extraocular, depending on specific conditions and muscle types.[231,232] Interestingly, however, novel transcriptomic and proteomic analyses applied to single muscle fibers from human vastus lateralis muscle have recently questioned the MyHC-based classification, identifying ribosomal specialization as a major driver of skeletal muscle heterogeneity.[233]

Of note, a single muscle fiber can simultaneously express multiple types of MyHC. These "hybrid" fibers have been observed to increase with exercise, aging, and certain pathologies. Thus, there is ongoing discussion regarding whether distinct fiber types (type I, type IIa, and type IIx in humans) exist, or if fiber diversity is more accurately represented as a continuum.[232]

Muscle fiber types can transform in response to mechanical stimuli (e.g., exercise) and metabolic perturbations. For example, high physical activity promotes fast-to-slow twitch transformation, whereas cardiometabolic disorders, including heart failure,[234–236] obesity,[237] and diabetes[17,51,202,203] are associated with a shift toward fast-twitch phenotype. It is worth noting that fiber types may not share similar properties across different species. For example, unlike IIx fibers in rats and mice, human IIx fibers exhibit the lowest level of succinate dehydrogenase activity among all other fiber types.[231] Interpreting research findings from animal studies therefore requires careful consideration.

show impaired muscle regeneration, while transplantation of T cells ($CD3^+$ cells) or injection of the combination of IL-1α, IL-13, TNF-α, and IFN-γ rescue muscle regeneration deficits.[133] Eosinophils, on the other hand, stimulate expansion of FAPs by creating a transitional niche favorable to remove the muscle debris generated by the injury and prevent FAPs differentiation into adipocytes.[130] Simultaneously, pro-inflammatory macrophages help remove necrotic debris[128] by secreting TNF-α, IL-6, and IL-1β, which also stimulate migration, proliferation, and differentiation of MuSCs[134,135] and prevent excessive FAP expansion.[136] Other macrophage-derived factors/molecules, including insulin-like growth factor 1 (IGF-1), glutamine, nicotinamide phosphoribosyltransferase (NAMPT, which is also known as visfatin or pre-B-cell colony-enhancing factor (PBEF) in humans), and meteorin-like (METRNL) have also shown to improve muscle regeneration by regulating inflammation[92] and MuSC proliferation[137–139] and differentiation.[139] As the tissue begins to repair, there is a shift in the macrophage population from a pro-inflammatory to an anti-inflammatory phenotype.[25,29,127,140,141] This was recently confirmed by scRNA-seq experiments.[29] Anti-inflammatory macrophages stimulate MuSCs,[25,141,142] endothelial cells,[26,143–146] and fibroblastic cells[147] to promote myogenesis, angiogenesis, and matrix remodeling, respectively.[83] As such, depletion of macrophages impairs muscle regeneration and MuSC differentiation and prevents muscle growth.[25,148]

Activation, proliferation, and differentiation of MuSCs are attenuated in both type 1[116,149,150] and type 2[123,151] diabetes (Figure 3). Histological analyses show that compared with healthy individuals, people with diabetes display fewer MuSC and a slower initiation of MuSC proliferation following damaging exercise.[116] Alterations in MuSCs have also been noted in animal models of diabetes and diet-induced obesity and insulin resistance. For instance, mice fed with a high-fat diet (HFD) for 3 months exhibited lower expression of genes important for myogenesis (*Pax7*, *Myf5*, *Myod*, and *myogenin*) after cardiotoxin injury.[124] HFD mice have also shown a reduction in the number (as demonstrated by immunohistochemistry staining against embryonic myosin heavy chain [eMHC])[124] and size (as indicated by a reduction in myofibers with central nuclei)[122] of regenerating myofibers, coupled with lower activity of AMP-activated protein kinase (AMPK),[124] an important regulator of MuSC homeostasis (as described later). In another study, mice fed with a HFD for 6 weeks led to transient impaired myofiber regeneration with reduced MuSC activation but without changes in MuSC content.[152] Akita mice also exhibited decreased MuSC activation within the first 5 days after injury.[22] Similarly, after cardiotoxin injury, both *ob/ob* and *db/db* mice showed impaired MuSC proliferation and reduced accumulation of myoblasts, which delayed muscle regeneration.[123] However, this study measured cell proliferation viathymidine analog 5-bromo-2′-deoxyuridine (BRDU) incorporation but without staining for PAX7 or myogenic differentiation factor (MYOD), which may limit the conclusions.[123] HFD in rodents leads to obesity, hyperinsulinemia, and altered glucose homeostasis.[126] While HFD animal models may reflect the human situation more accurately than genetic models, the evidence generally suggests that conditions with obesity and diabetes hinder the early stages of muscle regeneration following injury.[21]

Non-MuSC populations, such as FAPs, are also required to regulate muscle regeneration. FAPs are muscle-resident mesenchymal stem cells (MSCs) that express high levels of platelet-derived growth factor receptor α (PDGFRα) and have the potential to produce adipocytes, fibroblasts, and osteocytes (under specific conditions) but generally fail to differentiate into myogenic cells.[153–156] In homeostatic muscle, FAPs are in a quiescent state.[24,27,28] In contrast to MuSCs, whose resting state is marked by *Pax7* expression, markers of FAP quiescence are less characterized. Upon muscle damage, the local increase of cytokines (IL-4 and IL-13), released by immune cells, stimulates FAPs ($OSR1^+$) to proliferate and phagocytize necrotic debris, while producing new matrix components that serve as a scaffold

for guiding the formation of new fibers.[130,157,158] This is orchestrated by several molecular players, including follistatin (FST), IGF-1, IL-6, CCN family member 4/WNT1-inducible-signaling pathway protein 1 (CCN4/WISP-1), and bone morphogenetic protein 3B (BMP-3B) that stimulate MuSC proliferation and differentiation.[24,159–161] FAP cilia may also influence myogenesis by suppressing adipogenesis.[162] Technologies such as scRNA-seq and snRNA-seq have revealed the cellular heterogeneity of FAPs and their intricate regulatory network during muscle regeneration.[29,163,164]

In the context of diabetes, however, the role of FAPs in skeletal muscle homeostasis remains poorly explored, although recent experiments suggest that impairments are likely to occur.[165] Human skeletal muscle was found to contain a subpopulation of FAPs—marked by expression of CD90—that display greater cell division, collagen production, and glycolysis. This population was increased in the muscle of people with diabetes. Moreover, 3 months of metformin treatment reduced FAP content in patients, and $CD90^+$ FAPs treated with metformin showed a decrease in oxygen consumption, proliferation, and adipogenesis, while increasing glycolysis and collagen I expression. Together, this suggests that metformin may alter the activity of $CD90^+$ FAPs in people with diabetes to ultimately reduce tissue fibrosis.[165] Preclinical experiments have also provided important insights into this. KKAy, *db*/*db*, and diet-induced obese mice show impaired muscle regeneration and increased fat deposition after cardiotoxin-induced muscle injury. Importantly, deposited fat is PDGFRα positive, indicating it to be of FAP cell origin.[166] Overall, evidence suggests that diabetic conditions may impact the role of FAPs in maintaining muscle homeostasis and supporting muscle regeneration, although more research is clearly needed.

Maturation and functional recovery

Efficient muscle regeneration requires the formation and maturation of new myofibers, which can be identified by the peripheralization of nuclei in mature myofibers.[61] To that end, MuSCs and differentiating myoblasts need the structural and functional assistance of other cells and molecular regulators. Myofiber branching or splitting can be observed during the late stage of muscle regeneration although new evidence suggests that this is more likely to be fusion of myotubes showing incomplete regeneration, at least after a necrosis-inducing event.[167] The full recovery of a muscle after injury also involves the proper reconstitution of extracellular matrix (ECM), vascular network, and innervation since these undergo extensive degradation. Within a week after injury, there is an increase in the deposition of matrix, which is mainly caused by the activity of fibroblasts in response to locally produced mediators such as transforming growth factor (TGF)-β1.[168] The ECM is composed of multiple proteins, proteoglycans, and glycoproteins that are crucial for providing structural support, transmitting forces, and regulating the stem cell niche.[169] Different collagen types can be labeled to assess the composition of the matrix and deposition of connective tissue. Yet, although specific markers can provide valuable and precise outcomes, standard histological techniques, such as Masson's Trichrome staining and Picrosirius red staining, can also uncover the regeneration of the matrix or the excessive accumulation of connective tissue.[61,170,171] Muscle regeneration is complete once regenerated myofibers recover their contractile properties and functional performance, which requires reinnervation of neuromuscular junctions.[61] However, full neuromuscular recovery may never be attained in some cases, such as venom-induced muscle injury.[172] Notably, it has been shown that MuSCs, besides their primary role in forming or repairing injured myofibers, also play a crucial role in controlling myofiber innervation,[173–176] in part by increasing the expression of the chemorepulsive semaphorin 3A.[174] The most reliable indicator of successful muscle recovery after injury is the restoration of the physiological capacity for generating force, which can be evaluated through *in vivo*, *in situ*, and *in vitro* measurements.[63,177]

Preclinical experiments suggest that the formation of new fully functional myofibers after injury is impaired and/or delayed by conditions with diabetes, although results are still inconsistent. For example, compared with WT mice, Akita mice, which spontaneously develop a non-obese diabetic phenotype, including insulin deficiency, hyperglycemia, and hyperlipidemia, showed a significant loss of myofiber area in regenerating muscle at 10 and 35 days post-injury. In addition, necrosis was still present in the muscles of Akita mice but not in those of WT mice.[22] Notably, impairments in muscle weight and force can persist 56 days post-injury (myotoxic injury) in Akita mice.[178] Similarly, HFD mice have shown smaller regenerating myofibers, marked by centralized nuclei[122] or eMHC expression,[152] as well as prolonged necrosis at 10,[152] 12, and 21[122] days post-injury (cardiotoxin injury). In contrast, another study found that at 10 days post-injury, the total regenerated muscle area was similar between WT and HFD mice, whereas this was reduced in *db*/*db* mice.[123] Consistently, a recent study noted that muscle sections from *db*/*db* mice at ~5 days post-injury had smaller myofibers expressing eMHC,[179] a protein that is expressed in early-regenerating myofibers.[180] However, at 14 or 30 days post-injury, the injured muscles in *db*/*db* mice were fully repaired, suggesting a partial functionality of MuSCs in *db*/*db* mice.[179] Discrepancies between studies may be explained by differences in animal models (including the presence or absence of comorbidities, e.g., obesity, hypertension, and hyperlipidemia), type and severity of injury and time points of tissue harvesting. Importantly, most preclinical studies have not implemented assessments of skeletal muscle contractile properties after injury, which would provide important insights into the restoration of force-generating capacity. In this context, people with type 1 diabetes have shown lower strength recovery at 48 and 96 h after exercise.[116] Of note, patients were physically active young adults, which rule out the effects of physical activity and age on the recorded outcomes. This has important implications, as patients with this disease may require longer recovery times following exercise/injury.[116] Poor recovery practices may increase the risk of frailty and sarcopenia (age-related loss of muscle strength and mass[181]). Indeed, the incidence of frailty is higher in people with diabetes[182] and is recognized in clinical guidelines for diabetes management.[183] Of note, adjustment for several risk factors for disability (e.g., age, race, BMI, and chronic impairments including knee osteoarthritis, hypertension, stroke, coronary heart disease, heart failure, and peripheral nerve dysfunction) does not significantly attenuate the risk for functional limitations and disability associated with diabetes.[184]

The initial indication of a functional recovery is marked by the emergence of newly formed neuromuscular junctions connecting the surviving axons with the regenerated muscle fibers. To date, no studies have investigated the impact of diabetes on neuromuscular junction adaptations after injury. However, impairments are likely to occur, as peripheral nerve dysfunction is a common complication of diabetes.[185–188] This complication further exacerbates muscle atrophy and weakness, leading to decreased functional capacity and increased fall risk. Moreover, alterations in FAPs, as may occur in diabetes (as previously discussed), can induce denervation at neuromuscular junctions leading to fiber atrophy and muscle weakness.[159] Further, we recently found that muscles from rats with obesity and diabetes exhibit transcriptional changes related to impaired axon guidance after synergist ablation surgery,[189] a model induced by surgical removal of all or part of synergistic muscles to generate chronic functional overload that causes hypertrophy via upregulation of the serine/threonine-specific protein kinase (AKT)-mTOR pathway[190] and activation, proliferation, and fusion of MuSCs into myofibers.[191–193] Other studies have confirmed that overload-induced muscle hypertrophy is impaired in animals with obesity and diabetes.[194,195] However, it is important to note that this model differs from injury models induced by injection of myotoxin, crush, or freeze, all of which cause more severe damage in many cellular structures in addition to myofibers. Thus, the relevance to human muscle adaptation, for example, in response to exercise training, must be interpreted with caution.

Increased production of ECM components in skeletal muscle is a common feature of overweight individuals with diabetes. In both human and rodent models, the presence of insulin resistance in skeletal muscle is associated with increased collagen accumulation.[196] The progression of insulin resistance, particularly in conditions of overfeeding, involves the participation of intramuscular connective tissue, integrins (cell surface receptors), and matrix metalloproteinases (MMPs).[197,198] Notably, MMP-2 and MMP-9 play key roles in the regenerative process by being highly expressed after muscle damage, facilitating repair and remodeling.[199] These enzymes are responsible for breaking down all ECM components. In HFD mice, reduced MMP-9 activity in skeletal muscle is associated with increased muscle collagen deposition and insulin resistance.[200] Another group of proteins known as tissue inhibitors of metalloproteinases (TIMPs), including TIMP-1, -2, and -4, act as inhibitors of various MMPs.[201] People with metabolic disorders and/or type 2 diabetes typically have higher levels of TIMP-1 and -2.[202] Taken together, accumulating evidence indicates that diabetic and obese conditions limit the maturation of new myofibers after injury, which subsequently delay functional recovery (Figure 3). However, in-depth muscle functional assessments, in combination with molecular analyses, are still needed before drawing definitive conclusions.

MECHANISMS UNDERLYING IMPAIRED SKELETAL MUSCLE REGENERATION IN DIABETES

Abnormal muscle fiber-type distribution

Skeletal muscle fibers are classified depending on their morphological, metabolic, and contractile features (see Box 2). Several[16,54,203,204] but not all[205,206] human studies have reported that type 2 diabetes is characterized by a lower percentage of type I skeletal muscle fibers, whereas the type II fiber fraction is increased. This has also been noted in people with type 1 diabetes[207] and animal models of diabetes.[208,209] An increased proportion of type II fibers may disrupt effective skeletal muscle remodeling. Human studies show that type II fibers are more susceptible to damage after eccentric muscle contractions, such as eccentric bicycle exercise,[210] walking backward downhill on an inclined treadmill,[211] and electrically stimulated eccentric contractions of the vastus lateralis muscle.[167] It has also been observed that the interface region between muscle and tendon is greater in type I fibers compared with type II, indicating that type II fibers are less resilient to strain and, consequently, more prone to injury.[212] Moreover, age-related muscle atrophy affects mainly type II muscle fibers[213,214] and is accompanied by a type-II-fiber-type-specific decline in MuSC number and function.[215–218] Indeed, type II fibers have less regenerative capacity than type I fibers due to smaller number of nuclei and MuSCs[219]; this is evident when comparing slow-twitch muscles vs. fast-twitch muscles[220,221] but also in single muscle fibers.[222] Importantly, the phenotype of MuSCs from adult muscle fibers closely resembles both their fiber of origin and the fiber they tend to form.[223,224] These observations—the increased percentage of type II muscle fibers in people with diabetes, and the preferential damage and poor regenerative capacity of type II fibers observed in non-diabetic cohorts—suggest that abnormal fiber-type distribution may be one of the mechanisms underlying impaired muscle regeneration in diabetes. However, this remains to be directly confirmed in individuals with diabetes subjected to muscle injury (e.g., eccentric-induced muscle injury), while implementing in-depth fiber-type-specific analyses. It is important to take into account that skeletal muscle fiber-type specification is changeable during muscle regeneration.[225] A fast-to-slow fiber-type transition has been observed after cardiotoxin injury[225,226] and is thought to be mediated by injury-induced transient ischemia[226] and increased expression of peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α),[225] an important regulator of mitochondrial biogenesis, fatty acid oxidation, and angiogenesis.[227] PGC-1α has shown to be downregulated in skeletal muscle undergoing atrophy, including those of individuals with type 2 diabetes.[228,229] Mice with skeletal-muscle-specific transgenic expression of PGC-1α4, a PGC-1a isoform induced by resistance training, show increased muscle mass and strength and resistance to muscle atrophy, while PGC-1α4 loss-of-function limits myotube hypertrophy in culture.[230] Investigating diabetes-related skeletal muscle fiber-type transition, particularly through mechanisms involving PGC-1α, holds great promise for research. Muscle-specific PGC-1α loss- and gain-of-function experiments in animal models of diabetes (e.g., HFD) and in the context of muscle injury would provide valuable information.

Insulin signaling defects and lipotoxicity

Insulin resistance in peripheral tissues (including skeletal muscle) is characterized by an inability of the target tissue to appropriately modulate glucose disposal or other insulin-mediated effects in response to a specific level of insulin. As a result of insulin resistance, insulin production of beta cells increases, leading to elevated levels of insulin in the blood (hyperinsulinemia). Insulin resistance/compensatory hyperinsulinemia and insulin

deficiency represent the main mechanisms underlying diabetes and are key factors exacerbating loss of muscle mass and function.[238,239] Insulin plays a key regulatory role in autophagy and protein metabolism, which are crucial in the context of muscle regeneration. While insulin levels in individuals with diabetes vary based on the state of the condition, those with type 2 (before complete loss of beta cells)[55] or type 1 diabetes (during treatment) are often exposed to hyperinsulinemia,[240] which can suppress autophagy[55] and limit skeletal muscle regeneration.[241] Full recovery of skeletal muscle after injury/exercise requires elevated rates of mixed muscle and myofibrillar protein synthesis since these undergo extensive degradation.[242,243] The precise function of insulin in human skeletal muscle protein metabolism, however, remains a topic of ongoing debate.[244] Multiple studies have reported opposing conclusions, in part due to the complex interplay between amino acid availability, muscle blood flow, and microvascular recruitment,[245–249] as discussed in more detailed elsewhere.[244,250] Briefly, in the non-diabetic fasted state, muscle protein breakdown exceeds protein synthesis, causing amino acids to move from muscle to the splanchnic tissue, which allows continued synthesis of vital proteins, such as clotting factors.[251,252] In the non-diabetic fed state, the addition of amino acids promotes protein synthesis and reduces protein breakdown in both skeletal muscle and splanchnic tissues, leading to a net gain in protein balance.[250,252] In cases of insulin deficiency, muscle protein breakdown significantly increases while protein synthesis remains unaffected. This results in the transfer of amino acids from muscle to the splanchnic tissue, where both protein synthesis and breakdown increase, but synthesis exceeds breakdown, maintaining a net positive protein balance.[250,253,254] This is likely a mechanism to support the continued synthesis of necessary proteins.[250] Mechanistically, under normal conditions, insulin receptor (IR) and IGF-1 receptor (IGF-1R) promote protein synthesis and inhibit protein degradation by activating the phosphoinositide 3-kinase (PI3K)-AKT-mTOR pathway. During glucose uptake and protein synthesis, AKT phosphorylates FoxO transcription factors, with the resulting phosphorylated FoxO members being exported from the nucleus to the cytoplasm, thereby inhibiting their atrophy-related transcriptional activity. This balance of protein synthesis and degradation is disrupted under conditions with diabetes.[255] Studies have shown that hyperglycemia upregulates Krüppel-like factor 15 (KLF15)[13]—a transcription factor associated with muscle wasting—and atrogenes including muscle RING finger 1 (MuRF1) and muscle atrophy F-box (MAFbx; also termed atrogin-1) in rodent models of diabetes,[255–257] whereas mice with muscle-specific KLF15 deficiency are protected from diabetes-induced muscle atrophy.[13] Simultaneously, insulin defects inhibit the IGF-1-PI3K-AKT-mTOR pathway,[258,259] while stimulating protein degradation via FoxO family members and their downstream E3 ubiquitin ligases and autophagy regulators, resulting in muscle atrophy.[260]

Insulin resistance is highly correlated with ectopic fat deposition,[48,50,261–273] while both are interlinked in a harmful cycle. Ectopic fat is defined as storage of lipids in tissues other than adipose tissue, that normally contain only small amounts of lipids, such as skeletal muscle, liver, and heart. Skeletal muscle fat can be classified as intermuscular adipose tissue (located between muscle fascicles), intramuscular adipose tissue (located between muscle fibers), and intramyocellular lipid droplets. Interestingly, although accumulation of intramyocellular lipids is associated with insulin resistance, endurance-trained athletes, who are highly insulin sensitive, also have increased intramyocellular lipid content.[263] This metabolic paradox suggests that, instead of the magnitude of the intramyocellular lipid reservoir, it is the capacity for intramyocellular lipid oxidation that determines whether these lipids serve a physiological or pathological role.[263] While the terms intermuscular, intramuscular, and intramyocellular fat have often been used interchangeably, they are all associated with decreased muscle strength,[274–280] and regeneration.[274,281–284] In diabetes, as muscle atrophy persists/increases, insulin resistance increases lipolysis and releases free fatty acids (FFAs) from adipose tissue.[259] Increased FFA (referred to as lipotoxicity) further exacerbates proteolysis and impairs the regenerative capacity of skeletal muscle.[282] Mice overexpressing lipoprotein lipase (LPL), which converts triacylglycerol to FFAs and glycerol in skeletal muscle, show increased FFA and impaired muscle regeneration, as evidenced by reduced cross-sectional area of regenerating myofibers after cardiotoxin-induced injury.[282] Further, LPL-expressing myoblasts display lower expression of *Myod* and *Myog*, coupled with a reduced number of myotubes, suggesting impaired differentiation and fusion.[282] Similarly, myoblasts treated with palmitic acid, the most common saturated fatty acid found in the human body, show inhibited proliferation and myogenic differentiation as well as increased mitochondrial ROS levels and mitochondria-mediated apoptosis,[285] while effective muscle regeneration requires proper mitochondrial function.[286,287] Palmitate exposure also causes endoplasmic reticulum (ER) stress in myotubes. This triggers an adaptive mechanism known as the unfolded protein response, leading to the formation of the serine/threonine-protein kinase/endoribonuclease (IREa)–TNF receptor-associated factor 2 (TRAF2)–I kappa B kinase (IKK) complex, which in turn activates nuclear factor κB (NF-κB) to undergo rapid translocation into the nucleus, causing a decrease in *Glut4* gene expression.[288,289] Together, these findings suggest insulin signaling defects and increased FFA as potential mechanisms underlying imbalanced rates of muscle protein synthesis and decreased myogenic potential of MuSCs (Figure 4).

Increased inflammation and excess oxidative stress

Increased inflammation and excess oxidative stress are important mechanisms for limiting effective muscle regeneration and MuSC function in diabetes. Pro-inflammatory cytokines, including IL-6, TNF-α, and C-reactive protein (CRP), are often elevated in patients with diabetes[290–292] and associated with insulin resistance[293,294] and impairments in muscle mass, function, and metabolism.[295,296] Similar to the insulin-mediated pathways previously described, increased levels of IL-6 and TNF-α inhibit the PI3K-AKT-mTOR pathway and activate NFκB and FoxO proteins, which promote the expression of atrogenes (MAFbx and MuRF1) resulting in a negative net protein balance.[259,297] Elevated levels of IL-6 have also been observed in denervation-activated FAPs and are associated with muscle atrophy and fibrosis.[298] Interestingly, IL-6 has both pro-inflammatory and anti-inflammatory properties. Macrophages produce pro-inflammatory IL-6, whereas skeletal muscle produces anti-inflammatory IL-6.[299] In human skeletal

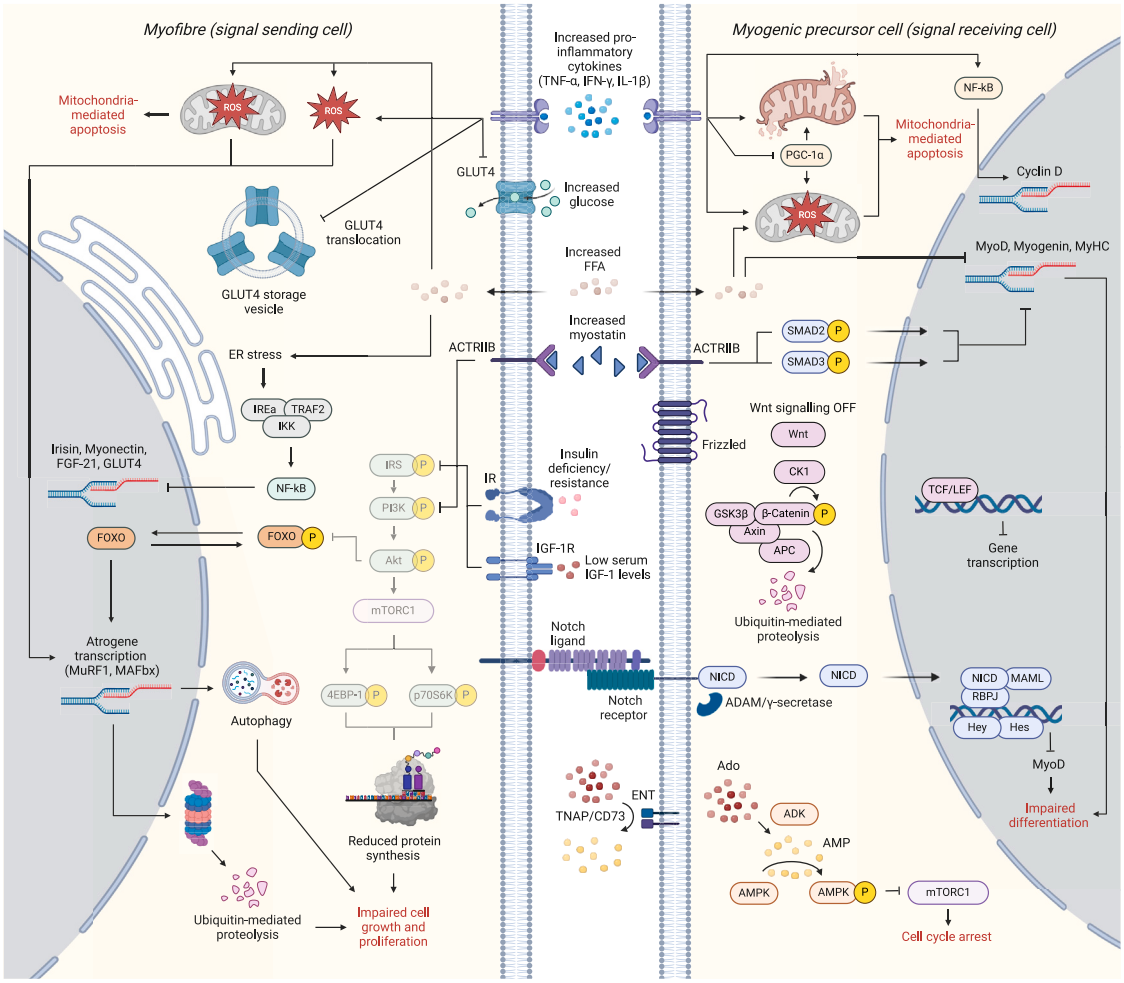

Figure 4. Molecular mechanisms underlying impaired skeletal muscle regeneration in diabetes

Diabetic myopathy is characterized by impairments in both mature muscle fibers and myogenic precursor cells, which limits muscle regeneration when injured. These impairments include MuSC dysfunction, mitochondria-mediated apoptosis, and diminished cell growth and proliferation, which are regulated by multiple pathways such the PI3K-AKT-mTOR pathway, myostatin-SMAD2/SMAD3 signaling, NOTCH and WNT signaling, and the ENT-ADK-AMPK signaling axis.

muscle, IL-6 release increases after prolonged exercise and is therefore considered as a myokine/exerkine.[300] Exercise-induced IL-6 release improves nutrient utilization and muscle hypertrophy.[135] Conversely, however, local IL-6 administration causes muscle atrophy in rats.[301] This dual action is thought to be regulated by two distinct IL-6 receptors: IL-6R and sIL-6R.[11] In this context, NF-κB, an important downstream target of IL-6R, has shown to inhibit myogenic differentiation by upregulating cyclin D1 (*Ccnd1*) expression[302] and downregulating *Myod* expression.[303] Additionally, pro-inflammatory NF-κB signaling promotes the generation of ROS, which induces decreased expression of PGC-1α and disturbances in mitochondrial function and morphology in skeletal muscle.[287,304,305] This has important implications for muscle regeneration, since increased mitochondrial ROS production can limit myogenic progression.[306] For example, overexpression of dual oxidase maturation factor 1 (DUOXA1), a ROS-producing enzyme, in myoblasts leads to increased H_2O_2 levels, fusion defects, reduced expression of myogenin and myosin heavy chain (MyHC), and increased apoptosis, while DUOXA1 knockdown results in a contrary phenotype.[307] Furthermore, depletion of glutathione (an essential non-enzymatic antioxidant in mammalian cells) in myoblasts limits myogenesis as reflected by lower protein levels of MYOD and MyHC as well as reduced myotubes formation, a phenotype that can be reversed by glutathione replenishment via glutathione ethyl ester.[308] Of note, glutathione also induces persistent activation of NF-κB, while glutathione ethyl ester prevents it.[308] Overall, increased inflammation and excess oxidative stress, as occurs in diabetes, share signaling pathways that result in impaired myogenesis (Figure 4). Yet, other cellular responses that have shown important roles on inflammation, such as fibroblast subsets with distinct functions and morphology,[309,310] remain to be explored in the context of muscle regeneration in diabetes.

Dysregulation of myostatin activity

Myostatin represents an important therapeutic target due to its vital involvement in several disorders including diabetes and obesity.[311] Various clinical trials using myostatin-neutralizing compounds/antibodies have been shown to improve muscle

homeostasis in muscle and metabolic diseases.[312,313] Myostatin is a member of the TGF family that works as a negative regulator of muscle growth.[311] Studies have shown that myostatin protein levels are increased in skeletal muscle and plasma from obese insulin-resistant individuals,[314] whereas absence of myostatin improves insulin sensitivity and reduces obesity.[315,316] Of note, aerobic exercise training reduces muscle and plasma myostatin protein levels in insulin-resistant subjects.[317] In addition, subcutaneous administration of myostatin attenuates insulin-stimulated phosphorylation of AKT in muscle and liver of mice with insulin resistance.[317] From a myogenic perspective, myostatin negatively regulates the proliferation[318,319] and differentiation[320] of MuSCs by upregulating cyclin-dependent kinase 2 (CDK2) in myoblasts, which limits the G1 to S phase transition, thus causing cell-cycle arrest.[318,321,322] Overexpression of myostatin reduces protein levels of MyoD and myogenin and inhibits the activation of myoblast differentiation.[321] In contrast, inhibition of myostatin leads to improved cell-cycle withdrawal, thus stimulating myoblast differentiation.[321] In accordance with this, myostatin-deficient mice subjected to cardiotoxin injury express MyoD and regenerate myofibers earlier than controls.[323] Similarly, after cardiotoxin injury, transgenic mice expressing a dominant-negative form of myostatin show greater muscle weights and fiber cross-sectional area (FCSA) and more PAX7-positive nuclei than WT mice.[324] Interestingly, myostatin possess concentration-dependent effects on MuSC proliferation; while high concentrations (80–400 nM) of myostatin inhibit MuSC proliferation,[319,320] low concentrations trigger an opposite response.[325] Binding of myostatin to the activin receptor type 2B (ACTRIIB) leads to activation of small mothers against decapentaplegic (SMAD)2 and SMAD3, promoting their interaction with SMAD4 and translocation of the complex to the nucleus to modulate the expression of genes regulating muscle growth and differentiation.[311] Biopsies taken from the rectus abdominis muscle of people with insulin resistance and obesity show increases in SMAD2, SMAD3, and SMAD4 proteins with reduced transcription of *MYOD* and *MYOG*, as compared with lean age-matched controls.[326] Moreover, mice with streptozotocin-induced diabetes display increased levels of myostatin, TGF-β receptor 1, and SMAD3 in MuSCs as well as impaired muscle regeneration (reduced number of eMHC$^+$ *de novo* myofibers) and MuSC dysfunction after cardiotoxin injury.[149] Furthermore, treatment with insulin or FST (a myostatin antagonist) rescue muscle regenerative capacity and myostatin-TGF-β receptor1-SMAD3 signaling in mice with diabetes.[149] Yet, although SMAD3 is required for the inhibition of myoblast differentiation by myostatin,[320] SMAD3 is essential for normal skeletal muscle growth. SMAD3-null mice exhibit muscle atrophy, increased protein ubiquitination, elevated levels of MuRF1,[327] decreased oxidative enzyme activity, impaired mitochondrial biogenesis, and incomplete recovery of muscle weight and myofiber size after muscle injury.[328] Additionally, *in vitro* experiments show that SMAD3-null myoblasts have impaired proliferation, differentiation, and fusion, resulting in atrophied myotubes.[327] Indeed, retinoic acid treatment, which promotes myogenic differentiation, can increase SMAD3 expression and rescue differentiation in TGF-β-treated cells.[329] SMAD2 also possess pro-myogenic actions. Knockout of *Smad2* expression produces smaller myotubes with lower *Myog* expression, whereas overexpression of *Smad2* increases the expression of *Myog*, thus improving cell differentiation and fusion.[330] Taken together these findings suggest that myostatin represents a mechanism that promotes muscle atrophy and insulin resistance, while limiting effective muscle regeneration (Figure 4). However, more research is needed to better understand its downstream signaling pathways.

Impaired NOTCH and WNT signaling

Diabetes-induced impairments in muscle regeneration and MuSC activity are caused, at least in part, by alterations in NOTCH and WNT signaling pathways. NOTCH signaling is known to inhibit differentiation and contribute to maintaining the quiescence of MuSCs.[331,332] Notably, however, decreased NOTCH signaling has been observed in primary proliferating myoblasts, suggesting that NOTCH's activity may be contextual or not essential for MuSC proliferation.[333] Upon muscle injury, NOTCH receptors bind to δ/jagged, serrate, or lag2 (DSL) ligands from neighboring cells. This causes NOTCH receptors to undergo proteolytic cleavage by enzymes such as ADAM (a disintegrin and metalloproteinase) and γ-secretase, releasing the Notch intracellular domain (NICD),[334] which then translocates into the nucleus, associates with recombining binding protein-Jk (RBPJ),[335,336] and recruits transcriptional coactivators, including mastermind-like (MAML) and histone acetyltransferases (HATs). This complex promotes Hes and Hey transcription,[331,337,338] which suppress MyoD, thus inhibiting differentiation, while stimulating MuSC proliferation and self-renewal in order to maintain the MuSC pool.[339] Under normal conditions (WT mice), NOTCH activity in MuSCs is downregulated upon conversion from quiescent to activated state.[150] In contrast, NOTCH signaling remains activated under this transition in Akita mice, leading to impaired myogenic capacity.[150] Similarly, muscle biopsies from patients with type 1 diabetes display increased protein levels of NOTCH ligand DLL1 and reduced MuSC content, suggesting persistent activation of NOTCH signaling and MuSC dysfunction.[150]

NOTCH signaling interacts with other pathways, such as myostatin (previously described)[340] and WNT,[341,342] to coordinate various stages of muscle regeneration. In contrast to NOTCH, WNT signaling promotes MuSC differentiation and fusion to injured myofibers.[343] WNT is an extracellular ligand that binds to Frizzled receptors located in the cell's outer membrane,[344,345] and stabilizes β-catenin, forming a complex with T cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors that translocates into the nucleus to stimulate the transcription of target genes,[346,347] including MyoD.[348] In cells not stimulated by WNT, β-catenin is targeted for ubiquitination through phosphorylation by the adenomatous polyposis coli (APC)-Axin-GSK3β-CK1 complex and further degradation by the 26S proteasome.[349–351] *In vitro* and *in vivo* experiments have shown that myoblasts lacking β-catenin show delayed differentiation, whereas myoblasts with conditional activation of β-catenin undergo premature growth arrest and differentiation, suggesting that a precise level of β-catenin activity is required for proper myogenesis.[352] Various WNT-related signals have been reported to be involved in muscle regeneration. For instance, APC diminishes canonical WNT signaling to allow cell-cycle progression.[353] Conversely, absence of R-spondin 1 impairs muscle regeneration after injury, affects cell differentiation both *in vitro*

and *in vivo*, and is associated with downregulation of WNT/β-catenin signaling.[354] In diabetes (streptozotocin-induced diabetes), WNT components, including WNT ligands and β-catenin, are downregulated but can be normalized by aerobic exercise.[355] Additionally, exercise-induced improvements on insulin sensitivity in type 2 diabetes are regulated, at least in part, by the WNT-β-catenin pathway.[356] Despite these observations, however, the direct role of WNT signaling on muscle regeneration in diabetes remains to be fully elucidated (Figure 4).

Impaired ENT-ADK-AMPK signaling axis

Mice on a HFD have shown fewer regenerating muscle fibers with blunted MuSC activation and proliferation after cardiotoxin injury (as previously described).[124] Mechanistically, AMPK activity is lower in regenerating muscle from HFD-fed mice compared with those from controls.[124] Of note, when AMPKα1 is knocked out in MuSCs of mice subjected to cardiotoxin injury, it results in impaired MuSC proliferation and differentiation,[124] higher number of necrotic myofibers, delayed disappearance of damaged phagocyted myofibers, and reduced cross-sectional area of regenerating myofibers.[357] AMPKα1 has also shown to be essential for phagocytosis-induced macrophage skewing from a pro- to anti-inflammatory phenotype during resolution of inflammation.[357] Moreover, *in vitro*, *ex vivo*, and *in vivo* experiments show that deletion of AMPKα1 in MuSCs results in a high self-renewal rate that impairs muscle regeneration.[358] Furthermore, when MuSCs with an AMPKα1 deficiency are transplanted, there is a severely impaired myogenic capacity in regenerating muscle fibers, but this impairment is rescued by the drug 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), which activates AMPK.[124] These findings are supported by human experiments, which show that people with obesity and type 2 diabetes have reduced AMPK activity after exercise.[359] In line with this, a recent study found that diabetes can lead to increased levels of extracellular adenosine (eAdo) and AMP (eAMP), which prevent the activation of quiescent MuSCs and inhibit injury-induced muscle regeneration.[179] The study showed that eAdo and eAMP work by engaging the Ado transporters (ENTs)-Ado kinase (ADK)-AMPK signaling axis in MuSCs, which blocks the cell growth checkpoint that is dependent on mTORC1. This mechanism also inhibited the early activation of quiescent FAPs and human MuSCs. In addition, an ADK inhibitor partially reversed the activation defects of MuSCs in *db/db* mice.[179] Collectively, AMPK, ADK, and ENTs play a crucial role in connecting diabetes and obesity to impaired muscle regeneration (Figure 4), providing promising drug targets to facilitate muscle regeneration.

DIABETES VS. DIABETES-RELATED COMORBIDITIES

Despite cumulative evidence demonstrating that diabetes is characterized by impaired skeletal muscle regeneration, the underlying cause is still unclear. Indeed, what causes the overall muscle pathology of diabetes remains to be answered. This applies to several skeletal muscle pathologies, except muscular dystrophies (e.g., Duchenne muscular dystrophy, which is caused by a mutation of the dystrophin gene[360]), and is due to the fact that skeletal muscle health (i.e., muscle mass and strength) is affected by several factors including physical activity, genetics, comorbidities, nutritional status, sleep quality, and aging.[361] Studies investigating muscle regeneration in diabetes have been challenged by the difficulties of including proper control groups to be able to rule out or account for the impact of the above-mentioned factors. For example, several preclinical experiments have used mice with obesity and diabetes vs. lean controls, which complicates the identification of causative mechanisms as outcomes may be explained by obesity[124,241,281,362] and not diabetes per se, or both (see Table 1). Deciphering the role of obesity on muscle regeneration in animal models is complicated since most of them are accompanied by comorbidities, such as hyperglycemia and insulin resistance,[363] which can impact muscle regeneration, as discussed before. Obesity, defined by a BMI of 30 or greater, cannot distinguish between fat and lean tissue and does not consider the heterogeneity of body fat distribution. The percentage of fat and muscle to the total body weight is more important than the total body weight itself. Studying people with diabetes and lower or preserved muscle mass vs. individuals without diabetes with lower or preserved muscle mass may encounter challenges in subject recruitment but will allow us to better understand the impact of body composition on muscle regeneration. A similar approach may also help differentiate the impact of sarcopenia on muscle regeneration in diabetes. Based on different classifications, the prevalence of sarcopenia ranges from 10% to 27% among individuals older than 60 years[364–366] and is 2–4 times higher in individuals with diabetes, even after adjusting for age and BMI.[45] In the context of muscle regeneration, people with or without diabetes have been matched by age. However, this does not eliminate the influence of sarcopenia, as participants may or may not have had sarcopenia. Other diabetes-related complications may also impact muscle regeneration but remain to be explored. For example, compared with patients with chronic heart failure or diabetes, patients with both heart failure and diabetes develop a more severe skeletal muscle pathology, characterized by mitochondrial alterations (lower mitochondrial respiration, content, and coupling efficiency), fiber atrophy, and capillary disruptions that are linked to exercise intolerance.[52]

With respect to studying muscle regeneration, there is no gold standard animal model of diabetes. In Akita mice, inactivation of insulin 2 (*Ins2*) can be compensated by activation of insulin 1 (*Ins1*).[367] This may explain, at least in part, why impairments in muscle regeneration in this animal model are less severe than those observed in streptozotocin-treated mice (experimental diabetes), where β cells are rapidly and completely ablated. Of note, *in vitro* and *in vivo* experiments show that myogenicity is rescued by administration of insulin to streptozotocin-treated mice.[149] These observations demonstrate that untreated diabetes per se can significantly inhibit muscle regeneration.

THERAPIES FOR SKELETAL MUSCLE REGENERATION

Effective repair of skeletal muscle after injury requires controlling inflammation, facilitating regeneration, and limiting fibrosis. To achieve this, different therapies have been developed within the last century and particularly during the last two decades. These include physical therapy/exercise, surgical techniques, muscular tissue engineering, cell therapy, myogenic factors, non-steroidal anti-inflammatory drugs, intramuscular corticosteroids, and dietary supplements.[168,368–370] To date, however,

Table 1. Studies investigating skeletal muscle regeneration in diabetes

Disease group	Control group	Injury model	Main findings	Reference
Human studies				
Non-obese subjects with type 1 diabetes	BMI-, physical activity-, age-matched healthy young adults	eccentric exercise	participants with type 1 diabetes showed lower strength recovery, increased serum creatine kinase, lower MuSC content, delayed MuSC proliferation, greater number of myofibers with sarcolemmal damage, and increased ECM content	Dial et al.[116]
Overweight subjects with diabetic peripheral neuropathy	BMI- and age-matched healthy adults	below-knee amputation surgery	participants with diabetes showed signs of muscle degeneration such as myofiber necrosis, myofiber splitting, and hypercontracted myofibers as well as lower MuSC content and reduced fusion in cultured MuSCs	Bohnert et al.[117]
Overweight subjects with type 2 diabetes (more than half of them had chronic ischemic heart disease and hypertension)	BMI- and age-matched adults without diabetes (half of them had chronic ischemic heart disease and one third had hypertension)	–	skeletal muscle of patients with diabetes showed degenerative remodeling of the ECM that was associated with an increase of a subpopulation of FAPs ($CD90^+$)	Farup et al.[165]
Animal studies				
Akita mice (hyperglycemia, hypoinsulinemia, and increased non-esterified fatty acids)	wild-type mice (increased body mass compared with Akita mice)	cardiotoxin injury	Akita *tibialis anterior* and *gastrocnemius* muscles showed reduced regenerating myofiber area, increased collagen levels, and reduced macrophage and MuSC infiltration	Krause et al.[22]
Akita mice (hyperglycemia)	wild-type mice	cardiotoxin injury	Akita mice exhibited reduced formation of *de novo* myotubes and increased expression of myostatin	Jeong et al.[149]
Akita mice (hyperglycemia)	wild-type mice	cardiotoxin injury	Akita mice had decreased muscle weight and absolute maximal force in both regenerating and uninjured muscles	Vignaud et al.[178]
HFD (8 months)-fed mice (hyperglycemia, hyperinsulinemia, obesity, and higher plasma FFA concentrations)	normal diet-fed wild-type mice	cardiotoxin injury	HFD-fed mice showed impaired growth of regenerating myofibers, delayed myofiber maturation, and increased collagen deposition without impairments in MuSC proliferation	Hu et al.[122]
HFD (2 months)-fed mice (metabolic phenotype was not reported)	normal diet-fed wild-type mice	cardiotoxin injury	HFD-fed mice showed greater area of necrosis and collagen, and reduced area of newly regenerating myofibers ($eMHC^+$ cells); MuSC proliferation (*ex vivo*) was also impaired in HFD-fed mice	D'Souza et al.[152]
HFD (3 months)-fed mice (hyperglycemia and obesity)	normal-diet-fed wild-type mice	cardiotoxin injury	number of regenerating muscle fibers and activation and proliferation of MuSCs were similar in HFD- and normal-diet-fed mice	Nguyen et al.[123]

(*Continued on next page*)

Table 1. *Continued*

Disease group	Control group	Injury model	Main findings	Reference
HFD (3 months)-fed mice (obesity and impaired glucose tolerance and insulin sensitivity)	normal-diet-fed wild-type mice	cardiotoxin injury	HFD-fed mice showed reduced AMPK activation in MuSCs and lower expression of genes important for myogenesis (Pax7 and Myf5, MyoD, and myogenin)	Fu et al.[124]
HFD-fed mice (hyperglycemia, hyperinsulinemia, and obesity)	normal diet-fed wild-type mice	cardiotoxin injury	HFD-fed mice showed a reduction of cardiotoxin-treated lower limb weight and increased ectopic fat deposition	Mogi et al.[166]
HFD-fed mice (metabolic phenotype was not reported)	normal diet-fed wild-type mice	cardiotoxin injury	HFD-fed mice showed fewer regenerating myofibers	Han et al.[179]
ob/*ob* mice (metabolic phenotype was not reported)	wild-type mice	cardiotoxin injury	*ob*/*ob* mice had lower regenerating muscle fibers, impaired proliferation of MuSCs, reduced accumulation of macrophages, and impaired angiogenesis	Nguyen et al.[123]
db/*db* mice (metabolic phenotype was not reported)	wild-type mice	cardiotoxin injury	*db*/*db* mice had lower regenerating muscle fibers, impaired proliferation of MuSCs, reduced accumulation of macrophages, and impaired angiogenesis	Nguyen et al.[123]
db/*db* mice (metabolic phenotype was not reported)	*db*/+ non-diabetic control mice	cardiotoxin injury	muscle sections from *db*/*db* mice showed smaller eMHC^{+} myofibers; MuSCs from *db*/*db* mice were defective in cell cycle re-entry *in vivo* but not *in vitro*	Han et al.[179]
Streptozotocin-treated mice (hyperglycemia and hypoinsulinemia)	young (2–4 months) and old (20–24 months) wild-type mice	cardiotoxin injury	streptozotocin-treated mice showed lower regenerated myofibers; MuSCs from streptozotocin-treated mice failed to generate proliferating fusion-competent myoblasts *ex vivo*	Jeong et al.[149]
Streptozotocin-treated mice (hyperglycemia)	Swiss mice	cardiotoxin injury	streptozotocin-treated mice showed reduced muscle weight, lower absolute maximal force, and increased specific maximal force in both regenerating and uninjured muscles	Vignaud et al.[178]
Streptozotocin-treated mice (metabolic phenotype was not reported)	wild-type mice	cardiotoxin injury	streptozotocin-treated mice showed fewer regenerating myofibers	Han et al.[179]
Young (8 weeks old) and old (26 weeks old) KKAy mice (metabolic phenotype was not reported)	young (8 weeks old) and old (26 weeks old) wild-type mice	cardiotoxin injury	KKAy showed impaired muscle regeneration and ectopic fat deposition; such impairments were more severe in older KKAy mice	Mogi et al.[166]

therapies have shown limited efficacy in preventing or treating the formation of muscle fibrosis.[371–374] As such, muscle injuries represent an ongoing challenge in clinical work.[375] Here, we summarize current methods for muscle regeneration and discuss challenges for their future clinical implementation in diabetes. Notably, when muscle loss is greater than 20%, intrinsic muscle healing mechanisms usually fail to repair the damage,[376] and surgery may be the only therapy capable of restoring partial or full function.

Exercise training

Exercise is widely recognized as a fundamental element to promote health and longevity. It represents a candidate approach of alleviating several diseases, including obesity and diabetes,[377–382] and plays a vital role in maintaining neuromuscular junction stability, even in inactive older adults.[176,383] Exercise has also been shown to have a positive effect on the number of MuSCs.[384–389] Scientists and clinicians have recently become interested in the ability of exercise to support muscle regeneration, which appears to offer a new strategy in combating muscle injury, establishing a theoretical basis for the development of muscle-targeted "exercise mimetics."[390–392] Strength training has proven effective in mitigating muscle atrophy in patients undergoing anterior cruciate ligament reconstruction by increasing FCSA and proportion of type I fibers.[393] Preclinical experiments using notexin-induced muscle injury show that running exercise facilitates the complete restoration of muscle mass by improving the proliferative capacity of myogenic cells and increasing mTOR signaling.[394,395] Interestingly, exercise prior to injury also improves muscle regeneration. Voluntary wheel running before barium chloride-induced muscle damage accelerates muscle repair and improves MuSC function in old mice by restoring cyclin D1 back toward youthful levels.[392] Moreover, it has been reported that after volumetric muscle loss, high-intensity interval training (HIIT) improves muscle regeneration by enhancing innervation and vascularization.[396] A synergistic effect of HIIT and stem cell transplantation has also been observed.[396] Mechanistically, exercise induces a macrophage shift toward an anti-inflammatory phenotype, which regulates the proliferation and differentiation of MuSCs at the injury sites.[397–399] It also promotes the activation of MuSCs by inducing FAPs senescence in mouse models of acute muscle injury and chronic inflammatory myopathy.[400]

Because of the increased prevalence of type 2 diabetes with aging, coupled with age- and diabetes-related decline in muscle mass and strength, resistance exercise training represents one of the cornerstones in type 2 diabetes treatment and care. Exercise represents the link between muscle mass maintenance and muscle regeneration. Contractile activity promotes MuSC fusion and myonuclear accretion.[401] When muscles undergo stress or injury, such as during resistance training, microdamage to the architecture of the muscle occurs, which in turns stimulates the activity of MuSCs and inflammatory cells (i.e., muscle regeneration). This is accompanied by an increase in protein synthesis and concomitant activation of autophagy which are essential for muscle maintenance and growth. Exercise and muscle mass maintenance (as discussed in more detail elsewhere[297,402]) and regeneration therefore represent major research fields in the context of diabetes. Exercise training (endurance, resistance, and HIIT) has shown multiple benefits on skeletal muscle in people with type 2 diabetes. These include increased muscle mass and strength,[379,403–408] increased mitochondrial function[409–412] and content,[404,410,413,414] enhanced insulin sensitivity (clamp, oral glucose tolerance test, glycated hemoglobin, or fasting glucose and insulin concentrations)[410,411,415,416] and activation of autophagy.[417] Preclinical studies in various models of diabetes have extended these findings by demonstrating that exercise prevents muscle atrophy, improves resistance to fatigue, reduces inflammation (IL-6 levels),[418] inhibits atrogene expression[419] and increases MuSC activity ($PAX7^+$ cells) and myonuclear accretion.[420,421] However, despite these observations, the effect of exercise in muscle regeneration after injury has never been directly examined in people with diabetes or animal models of diabetes. Studies implementing injury models (e.g., myotoxic- and eccentric-contraction-induced injury) and exercise training as therapy to improve muscle regeneration are needed before any definitive conclusions can be drawn. This is also the case in type 1 diabetes, where there is poor evidence for a beneficial effect of exercise training on skeletal muscle metabolism and glycemic control.[422]

Cell therapy

Cell therapy represents the most commonly used approach to improve skeletal muscle regeneration. Different cell types including MuSCs, myoblasts, muscle-derived stem cells, pericytes, bone-marrow-derived MSCs (BM-MSCs), adipose-tissue-derived stem cells (ADSCs), and induced pluripotent stem cells (iPSCs) have been investigated as potential options for repairing muscle injuries.[368,423,424] The efficiency of cell therapies relies on how well rejection is managed and how well cells integrate with the host tissue both structurally and functionally, while preserving their myogenic potential and replenishing stem cell niches.[370]

Cell therapies have shown promising results in the treatment of type 2 diabetes and obesity.[425–427] For instance, transplantation of human skeletal muscle myoblasts into limb muscles of mice with type 2 diabetes attenuated hyperglycemia and hyperinsulinemia and improved glucose tolerance[428] by regulating the transcription of genes involved in insulin signaling pathways and mitochondrial biogenesis.[428,429] Intramuscular injections of BM-MSCs improved diabetic polyneuropathy on skeletal muscle in rats with streptozotocin-induced diabetes.[430] Notably, BM-MSCs did not incorporate into tissue structures of recipient animals but stimulated the production of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), thus improving nerve conduction velocity, nerve blood flow, and capillarization.[430] BM-MSCs have also shown promising results when administrated systemically. Tail-vein injections of BM-MSCs reduced losses of muscle mass and strength, fiber atrophy, and fiber-type transitions in HFD mice. This was accompanied by reductions in the ubiquitin proteasome pathway activation, oxidative stress, and myonuclear apoptosis.[431] Notably, these anti-atrophic effects were independent of incorporation of MSCs and changes in body weight.[431] In another study, injections of epidermal growth factor (EGF)-stimulated MSCs improved angiogenesis and blood flow in ischemic hind-limb muscles of mice with type 2 diabetes (*db/db*) via modulation of AKT, VEGF, and hypoxia-inducible factor (HIF) pathways.[432]

Furthermore, a recent study showed that intramuscular injections of human placental mesenchymal stromal cells (P-MSCs) restored glucose uptake by upregulating PI3K-AKT signaling and GLUT4 expression in skeletal muscle of rats with obesity and diabetes. Additionally, P-MSCs re-established dysregulated pro-inflammatory and anti-inflammatory cytokines including IL-1β, IL-6, IFN-γ, TNF-α, and IL-18 and IL-10, IL-13, IL-4, and TGF-β, respectively. These findings have important implications for muscle regeneration, as cytokines modulate the proportion of pro-inflammatory and anti-inflammatory macrophages at the injury site, which directly impacts the early stages of muscle regeneration.[25,29,127,140] Collectively, most cell therapies are more likely acting in a paracrine manner to modulate the muscle microenvironment and promote tissue remodeling. In diabetes, however, the effect of cell therapy in muscle regeneration after injury remains to be directly examined. Moreover, the heterogeneity of MSCs and MuSCs and the difficulties in isolation remain as challenges.[433] When isolated MuSCs are grown *in vitro*, their myogenic potential *in vivo* is greatly reduced, which limits their ability to promote muscle regeneration.[434,435] Furthermore, gene expression, proliferation rate, myogenic differentiation capacity, and self-renewal ability of MuSCs have shown to vary within and between muscles,[436,437] which warrants further research. For example, the masseter muscle—the strongest and most important masticatory muscle—has a poor regenerative capacity in comparison with limb muscles.[438] Furthermore, the method by which cells are administered may be an important factor in their reaching their intended destination, which remains a cause of concern for the establishment of cell therapies in metabolic disorders.

Dietary supplementation

Several dietary supplements have been investigated to improve muscle mass and function in diabetes. However, how these treatments impact muscle regeneration in this disease remains poorly explored, although experiments in other cohorts suggest that beneficial effects are likely to occur. For example, several systematic reviews conclude that branched-chain amino acids (BCAAs) supplementation can be efficacious on outcomes of exercise-induced muscle damage or muscle injury[439–441]; although, there is also contradictory evidence.[442] In rats subjected to eccentric exercise, BCAAs supplementation promotes muscle regeneration via enhancing macrophage polarization, which in turn modulates proliferation and differentiation of MuSCs.[443] BCAAs, mainly leucine, improve protein synthesis via insulin-dependent and -independent mechanisms, which help counteract "anabolic resistance" in people with diabetes.[259,444] Leucine poses strong insulinotropic properties that enhance glucose disposal, reduce protein degradation, and increase amino acid availability.[444] Preclinical experiments using different models of muscle injury, such as cryolesion and exercise, demonstrate that leucine supplementation improves muscle regeneration by attenuating inflammation, protein ubiquitination, and collagen deposition, while increasing protein synthesis, fiber size, and maximum tetanic strength.[445–447] Whether these also occur in conditions with diabetes remains to be determined. Other supplements, including omega-3s and vitamin D, have shown beneficial effects on muscle regeneration in different cohorts. Omega-3s are polyunsaturated fatty acids mainly derived from seafood and vegetable oils. Numerous clinical trials demonstrate that omega-3s induce faster recovery of muscle function and muscle soreness after exercise-induced muscle damage.[448–452] This has been corroborated by systematic reviews and meta-analyses.[453,454] Moreover, animal studies show that omega-3s improve muscle regeneration by increasing MYOD expression,[455] promote pro- to anti-inflammatory macrophage phenotype transition,[456,457] reduce systemic inflammation by modulating IFN-γ and IL-10 cytokines,[456] and reduce muscle oxidative stress.[456,458] Notably, obese mice supplemented with omega-3s gain less weight and fat mass, and show skeletal muscle transcriptional changes related to fibrosis, fatty acid catabolism, and inflammation.[459] Furthermore, *in vitro* experiments show that omega-3s and their derived metabolites (specifically the oxylipins) improve myogenesis during inflammatory conditions, at least in part via activation of the AKT-mTOR pathway and inhibition of pro-inflammatory pathways.[460–462] Vitamin D, on the other hand, improves muscle mass and function in patients with muscle wasting[463] and is currently recommended for people with diabetes, especially those with muscle deficits.[464] Interestingly, the combination of vitamin D, protein/amino acids, and exercise has a synergistic effect on muscle mass and strength, IGF-1, and inflammation.[465] Whey protein drink enriched with vitamin D and leucine in combination with resistance exercise and HIIT improves muscle mass and glycemic control in older adults with obesity and type 2 diabetes.[466,467] Similarly, a combination of resistance exercise and a high-protein diet improves weight loss, body composition, and muscle strength in individuals with type 2 diabetes and obesity.[468] However, further research is needed to determine whether these combinations yield additive effects on muscle regeneration. Probiotics also represent a promising approach to improve muscle health. A recent meta-analysis of randomized controlled trials showed that probiotics supplementation improves muscle mass and strength.[469] Similar analyses have shown that probiotics also possess anti-obesity effects[470] and reduce fasting blood glucose and insulin resistance in patients with diabetes.[471,472] Moreover, probiotics supplementation reduces muscle strength loss and blood biomarkers of muscle damage and inflammation and accelerate recovery after exercise-induced muscle damage.[473] Altogether, dietary supplements, including BCAAs, omega-3s, vitamin D, and probiotics, represent a promising strategy to ameliorate diabetes- and obesity-induced impairments in muscle regeneration. Other supplements that impact MuSC activity and muscle regeneration remain to be tested in the context of diabetes but may have beneficial effects. For instance, treatment with the nicotinamide adenine dinucleotide (NAD) precursor nicotinamide riboside (NR) rejuvenates MuSCs in aged mice, accelerate muscle regeneration after cardiotoxin-induced muscle damage in aged and young mice, prevent MuSC senescence in dystrophic mice, and increase muscle function and mouse life span.[474] Mechanisms underlying NAD-induced benefits on muscle remodeling include the mitochondrial unfolded protein response and synthesis of prohibitins, a family of stress-response proteins that sense mitochondrial stress and control cellular senescence in mammals.[475] Despite these observations, however, we have previously shown that supplementation with NR and PT (i.e., the combination of NR and pterostilbene) does not improve muscle

recovery (e.g., MuSC content, proliferation, and fiber size) after eccentric contraction-induced injury in elderly individuals.[476] Therefore, the role of NAD precursors in muscle regeneration requires further research before drawing strong conclusions.

Pharmacotherapy

Numerous antidiabetic drugs may impact muscle structure, function and/or metabolism, although their regenerative potential is still poorly understood. Insulin represents one of the most potent hypoglycemic drugs available, but its long-term effects on skeletal muscle health have been questioned.[259,477] Additionally, insulin-treated elderly people with diabetes have a higher risk of severe hypoglycemia, falls, and fractures.[477–479] Metformin is another drug widely used in the treatment of type 2 diabetes, and evidence suggests that it may improve muscle mass and strength.[480,481] Moreover, some, but not others,[482] have found that metformin attenuates necrosis[483] and muscle catabolism, preserves myofiber size, and increases MuSC proliferation and AMPK activation after injury.[484] Discrepancies between studies may be related to the nature of the injury (cardiotoxin injury vs. burn injury) and its impact on mobility.[74] Notably, negative side effects, including digestive intolerance, dysgeusia, hyperoxia, and vitamin B12 deficiency, have been reported in metformin-treated elderly people with diabetes.[259,485] Sodium-glucose cotransporter 2 inhibitors (SGLT-2is) have been shown to be good therapeutic options for the treatment of cardiometabolic disorders.[486] SGLT-2is inhibit the Na^+/glucose transporter SGLT2, responsible for glucose reabsorption in proximal renal tubules, thus exerting a hypoglycemic effect. SGLT-2is trigger adaptive changes in skeletal muscle substrate metabolism favoring metabolism of fatty acids.[487] SGLT-2is have also been shown to improve muscle mass and strength, reduce muscle-atrophy-associated transcripts (*Foxo1*, *Mstn*, *Murf1*, and *Fbxo32*) in obese mice with diabetes (*db/db* mice),[488,489] and improve skeletal muscle contractility and mitochondrial function in obese-hyperglycemic rats.[490] Furthermore, SGLT-2is improve vascular remodeling after injury,[491] which may have important implications on skeletal muscle regeneration. On the other hand, inhibition of atrogenes also represents a promising strategy to improve muscle regeneration. MuRF1 and MAFbx (also termed atrogin-1) were identified more than 20 years ago as two muscle-specific E3 ubiquitin ligases that are increased transcriptionally in skeletal muscle under atrophic conditions,[257,492] such as diabetes and obesity,[256] making them important markers of muscle atrophy. MuRF1 and MuRF2 play an important cooperative role in skeletal muscle regeneration and myogenesis by modulating the chromatin remodeling complex.[493] Small-molecule chemical knockdown of MuRF1 increases muscle performance and attenuates muscle weight loss in cancer cachexia[494] and improves skeletal muscle contractility in obese-hyperglycemic rats.[495] Other drugs, including thiazolidinediones,[496] transdermal testosterone gels,[497,498] myostatin/ACTRIIB inhibitors,[312,313,499] selective androgen receptor modulators (SARMs),[500,501] dipeptidyl peptidase 4 (DPP4) inhibitors, and glucagon-like peptide-1 receptor agonists (GLP-1RAs), have been investigated as treatments to ameliorate diabetes-induced muscle wasting and/or weakness (as discussed in greater detail in other reviews[502,503]), but their impact on muscle regeneration remains to be explored.

KNOWLEDGE GAPS, CLINICAL TRANSLATION, AND FUTURE PERSPECTIVES

Diabetes is characterized by a severe skeletal muscle pathology. Increasing evidence indicates that conditions with obesity and diabetes impact the ability of skeletal muscle to repair itself when injured. Muscle regeneration is a complex process orchestrated by multiple myogenic and non-myogenic cell types. While studies have provided important insights into the impact of diabetes in MuSCs and FAPs, there is still a need to investigate other regulators and cell populations, such as the complement system, mast cells and T cells, all of which can impact different stages of muscle regeneration. Multi-omics technologies are currently being used in this field and will hopefully enable the identification of novel cell subpopulations and cell-cell interactions associated with muscle regeneration, including their regulatory mechanisms. Conducting multi-omics analyses, along with functional and histological assessments, in both animal models and individuals with diabetes, will provide a more comprehensive characterization of skeletal muscle pathology in diabetes. This should be addressed in different diabetic cohorts (e.g., people with type 1 or type 2 diabetes with or without obesity) including appropriate control groups (e.g., weight-, sex-, age-, and physical activity-matched individuals) to better understand and differentiate the role of obesity, sex, aging, and physical activity in skeletal muscle health. In parallel, similar multi-level analyses should be performed in the context of muscle regeneration, using physiologically relevant injury models, such as eccentric contraction-induced injury, which has already been used in both healthy humans[476] and animals (mice).[103] This approach will allow us to confirm whether mice and humans with diabetes have a similar regenerative response after injury, thus directing future experiments and therapeutic development. Genome-wide associations studies (GWASs) would also help discover novel therapeutic targets. For instance, a recent GWAS in participants with chronic obstructive pulmonary disease identified genetic variations related to myogenic differentiation and muscle regeneration.[504] This unbiased hypothesis-free approach has identified sets of genetic loci associated with lean body mass,[505] muscle strength,[506–508] muscle metabolism,[509] and insulin-stimulated glucose uptake[510] but remains to be applied to diabetes-related muscle defects. Similarly, depletion of specific cell populations (e.g., stem cell depletion) and gain- and loss-of-function experiments in animal models of diabetes (e.g., HFD-fed mice) are still missing and will elucidate causal relationships between cells and genes and processes involved in muscle regeneration.

Muscle-organ crosstalk has shown to play an important role in several biological processes[511]; however, its role in muscle regeneration in diabetes remains to be explored and alterations may exist. For example, the gut microbiome is known to play an important role in the progression of insulin resistance and diabetes,[512–518] while recent evidence suggests that microbiota-dependent Treg cells regulate MuSC function and promote skeletal muscle regeneration.[519] Similarly, the influence of sex on muscle regeneration in the context of diabetes remains to be examined, while differences are likely to occur. Various aspects of energy balance and glucose metabolism differ between men and women and influence their predisposition to type 2

diabetes.[520,521] In almost all animal models, males are more likely to develop obesity, hyperglycemia, and insulin resistance than females in response to dietary changes.[520] In the context of muscle regeneration, some human studies[522,523] but not others[524] have reported sex-based differences in response to exercise-induced muscle damage. Compared with males, females may be relatively protected against muscle damage, in part due to higher concentrations of estradiol.[525,526] Yet, it has also been reported that following exercise-induced muscle damage, men have a greater myogenic and inflammatory response compared with women,[527] which highlights the need for more research.

Exercise training (endurance, strength, and HIIT), cell therapy, dietary supplements, and pharmacological treatments represent promising therapeutic modalities to improve muscle regeneration in diabetes. However, exercise-induced regenerative medicine is still an emerging discipline, while effective and safe cell therapies remain to be identified, in part due to difficulties in isolation, administration, and immune rejection. Effective repair of skeletal muscle after injury is unlikely to be achieved with a single treatment. A multidisciplinary approach including the most effective combination of exercise training regimes, dietary supplements, and cell therapy or drugs may be the most effective approach to stimulate regeneration, control inflammation, and limit fibrosis. Yet, further research is needed to validate preliminary studies. Clinical trials using injury models that mimic physiological conditions, as previously conducted in healthy individuals (eccentric-contraction-induced injury),[476] remain to be performed in patients with diabetes. Notably, most studies investigating muscle regeneration in diabetes lack functional assessments of skeletal muscle. An in-depth characterization of skeletal muscle contractile properties, including *in vivo*, *in situ*, and *in vitro* measurements, will provide important information on how diabetes and treatments impact skeletal muscle's capacity for generating force, which is the most reliable indicator of successful muscle recovery after injury.

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AUTHOR CONTRIBUTIONS

E.E.-G. wrote the initial draft of the manuscript through discussion with J.T.T. All authors reviewed, commented on, and approved the final version of this manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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