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STAT3 signaling as a potential target to treat muscle-wasting diseases

David Sala¹ and Alessandra Sacco^{1,*}

¹ Development, Aging and Regeneration Program (DARe), Sanford Burnham Prebys Medical Discovery Institute, 10901 North Torrey Pines Rd, La Jolla, CA 92037, USA.

Abstract

Purpose of review—This review summarizes our current knowledge of the role of STAT3 signaling in skeletal muscle regeneration and the maintenance of muscle mass.

Recent findings—STAT3 signaling plays a pivotal role in regulating the function of multiple cell types in skeletal muscle. This includes muscle stem cells, myofibers and macrophages. It regulates muscle stem cell function by antagonizing self-renewal. STAT3 also functions in myofibers to regulate skeletal muscle mass. This is highly relevant under pathological conditions where STAT3 activation promotes protein degradation and muscle atrophy. Transient pharmacological inhibition of STAT3 partially prevents muscle wasting. However, the mechanisms responsible for the improvement of muscle condition is not currently well understood. This is due to the complexity of the system, as STAT3 has a critical role in regulating the function of several cell types residing in skeletal muscle.

Summary—Muscle wasting is associated with several human diseases such as muscle dystrophies or cancer cachexia. However, currently there are no effective treatments for this condition, and there is a critical need to identify new potential targets for the development of efficient therapeutic approaches.

Keywords

STAT3; skeletal muscle; muscle wasting; muscle stem cells

Introduction

Adult skeletal muscle is a highly specialized tissue responsible for the performance of voluntary movements, and it is essential for the maintenance of metabolic homeostasis. This is due to the structure and organization of the most abundant cell type in this tissue, the myofiber. Myofibers are elongated and multinucleated cells that contain protein filaments named myofibrils. The main components of these myofibrils are actin and myosin filaments, which are organized in sarcomeres. Sarcomeres give skeletal muscle its striated appearance

*Corresponding author: Alessandra Sacco, Ph.D., Development, Aging and Regeneration Program, Sanford Children's Health Research Center, Sanford Burnham Prebys Medical Discovery Institute, 10901 North Torrey Pines Rd, La Jolla, CA 92037, USA, Tel: 858-597-5337, asacco@sbpdiscovery.org.

Conflicts of interest

The authors have no conflicts of interest.

and allow this tissue to perform contraction. However, several other cell types reside in skeletal muscle (reviewed in (1, 2)). Among these cells types, there are muscle stem cells (MuSCs), macrophages and fibroadipogenic progenitors (FAPs). Although their role in the maintenance of skeletal muscle in basal conditions is not still well defined, they have a significant impact in muscle repair in both acute and chronic pathological conditions (1-3). In fact, skeletal muscle has a remarkable capacity to regenerate that mainly relies on the temporal coordination of these residing mononucleated cell types.

MuSCs are essential for the postnatal muscle growth and required for muscle regeneration. These cells reside in their anatomical niche under the basal lamina surrounding the myofibers in a quiescent state in adult skeletal muscle in basal conditions. Upon injury, MuSCs become activated, proliferate and differentiate to form the new myofibers. However, pathological conditions such as muscle dystrophies or accelerated muscle wasting alter MuSC function and this impairment contributes to the progression of the disease (4). In the case of muscle dystrophies, chronic damage in skeletal muscle is associated with the functional exhaustion of MuSCs, which significantly contribute to disease progression (5). Similarly, aging has also been associated with a functional exhaustion of MuSCs, together with their loss of quiescence (6, 7).

Macrophages are resident cells in skeletal muscle and they play an essential role in regeneration (1, 3). Upon muscle injury, leucocytes are recruited to the injured area and this causes an initial inflammatory response (1, 3). Among these leucocytes, there are proinflammatory M1 macrophages (1, 3). Accumulating evidence indicate that macrophages coordinate skeletal muscle regeneration by providing soluble factors to stimulate proliferation of FAPs and MuSCs (1, 3). One example is IL-6 (Interleukin-6), which is secreted by macrophages and acts both in a paracrine and autocrine manner. Indeed, in mice lacking IL-6, upon skeletal muscle injury there was impaired macrophage infiltration and this was associated with decreased expression levels of inflammatory cytokines as well as CCL2 and CCL3 (8). IL-6 activates STAT3 (Signal transducer and activator of transcription 3), a recently characterized regulator of myogenic lineage progression in MuSCs (9, 10). Indeed, in vitro assays have shown that macrophages from IL-6^{-/-} mice or with STAT3 knockdown were impaired in their ability to promote myoblast proliferation, suggesting a critical role of this pathway in the communication among the different cell types involved in tissue repair (8). As tissue regeneration progresses M1 macrophages transition to M2 anti-inflammatory macrophages that promote myogenic differentiation (1, 3). This transition from an inflammatory to an anti-inflammatory state is crucial for proper muscle repair (1, 3). In fact, muscle dystrophies and other pathological conditions characterized by chronic muscle damage alter this transition leading to the development of fibrotic and fat deposition (1, 3, 11).

FAPs are a recently identified population of mesenchymal multipotent stem cells that reside in the interstitial space in skeletal muscle (12-14). Upon injury, FAPs rapidly proliferate and promote the differentiation of MuSCs through the secretion of different cytokines (13, 15). Similar to macrophages, IL-6 is among the most relevant ones. After this initial wave of proliferation, there is a reduction in the number of FAPs (2, 13). It has been recently reported that macrophages have a central role in regulating FAP numbers during the

regenerative process (11). Under dystrophic conditions, FAP numbers are aberrantly high and this contributes to the fibroadipogenic deposition (11, 16). In fact, one of the hallmarks of several muscle wasting conditions (such as muscle dystrophy, cancer cachexia, or aging) is the ectopic deposition of fat in this tissue that negatively affects its function (15). Myosteatorsis has been recently associated with poor prognosis and systemic inflammation in cancer cachexia (17, 18). The pathological differentiation of FAPs into adipocytes is starting to be considered one of the causes of this detrimental intramuscular fat infiltration (12, 14-16). Overall, available data indicates that temporal coordination between the different cell types residing in skeletal muscle is essential for a successful regenerative process. Thus, it is crucial to further define the molecular effectors mediating the communication between these different cell types for the development of effective treatments for muscle pathologies. STAT3 has been described as a key regulator of the function of macrophages, MuSCs and myofibers in both healthy and pathological conditions (Figure 1).

In this review, we will focus in the role of STAT3 in MuSCs and myofibers, and in its potential as a target to treat muscle-wasting diseases.

STAT3: regulation and function

STAT3 is a transcription factor that mediates the intracellular signaling of several cytokines (reviewed in (19, 20)). Among them, STAT3 is especially relevant for the signaling of IL-6 and other cytokines of the same family including IL-10, IL-11, leukemia inhibitory factor (LIF) or oncostatin M (20, 21). Upon activation of this signaling pathway, STAT3 is phosphorylated in tyrosine 705 (Y705), and this induces STAT3 dimerization (both homodimerization or heterodimerization with other STATs) and translocation to the nucleus where it regulates gene transcription (19, 20). Several kinases are able to phosphorylate STAT3 at Y705, such as JAKs (Janus Kinases), receptor tyrosine kinases (RTKs) or SRC. However, JAKs are the main mediators of this phosphorylation event on STAT3 (19, 20).

Other posttranslational modifications have been described to regulate STAT3 function. One example is the phosphorylation on serine 727, which enhances STAT3 transcriptional activity (19, 20). mTOR (mammalian Target of Rapamycin) and several MAPKs (Mitogen-Activated-Protein-Kinases) can phosphorylate STAT3 in this position (19, 20). In addition, STAT3 is also acetylated on lysine 685. STAT3 acetylation is necessary for STAT3 dimerization and this modification has been linked to the methylation and repression of different promoters (through STAT3 interaction with DNA methyltransferase 1 –DNMT1) (20, 22). Direct methylation of STAT3 is also able to regulate its transcriptional activity. Indeed, STAT3 methylation by EZH2 (Histone-lysine N-methyltransferase enhancer of zeste homolog 2) at K180 and K49 promotes its Y705 phosphorylation and activation (20, 23, 24). In contrast, methylation of STAT3 in lysine K140 reduces its transcriptional activity (24). Finally, unphosphorylated STAT3 can also regulate gene transcription by interacting with other transcription factors such as NFκB, FoxO1 or FoxO3 (19). Overall, this suggests that STAT3 regulation through PTMs (post-translational modifications) is quite complex and not completely understood.

Another level of STAT3 regulation is the existence of different isoforms. The full-length STAT3 is known as STAT3α. However, a shorter isoform is generated by alternative splicing

of the mRNA, STAT3 β . STAT3 β is able to bind the DNA and interact with other STAT3 α partners. However, the transactivation domain is absent and does not have the S727 that promotes transcriptional activity of STAT3 α (19). Finally, the isoform STAT3 γ (generated by proteolytic cleavage of STAT3 α , and also lacks the transactivation domain) and the putative isoform STAT3 δ have also been described, but their existence has been only reported in granulocytes (19, 25).

Although STAT3 has been classically characterized as a transcription factor, recent reports show that STAT3 has also highly relevant non-transcriptional roles. It is of special interest its role as autophagy regulator. STAT3 can activate or inhibit autophagy depending on the cell type and the intracellular localization (reviewed in (19)). For example, cytosolic STAT3 can inhibit autophagy by interacting and sequestering FoxO1 and FoxO3 in the cytosol (FoxO1 and FoxO3 induce autophagy thorough the upregulation of autophagy-related genes), and by interacting and inhibiting PKR (PKR phosphorylates and activates eIF2A, which in turn activates autophagy) (19). Moreover, nuclear STAT3 can repress the expression of proautophagy genes (such as Beclin1) and increase the expression of genes that inhibit autophagy (such as Bcl2) (19). In contrast, STAT3 can activate autophagy by increasing the expression of HIF1 α and Bnip3 (both are autophagy activators), and also by direct binding and stabilization of HIF1 α (19). Thus, STAT3 role as autophagy regulator will require further study.

Finally, recent studies have identified a role of phosphorylated STAT3 (S727) in mitochondria, in which it promotes electron transport chain (ETC) function in both transformed and untransformed cells (26, 27). In contrast, phosphorylation of STAT3 at Y705 in the nucleus activates the transcription of several genes to promote aerobic glycolysis and reduce mitochondrial function (28). Thus, specific posttranslational modifications may drive selective roles of STAT3 in cellular metabolic switch. Recently, Sartorelli group has shown that upon activation MuSCs undergo a metabolic switch from oxidative to glycolytic metabolism (29). It will be interesting to evaluate whether STAT3 mediates this critical transition.

STAT3 in MuSCs

In skeletal muscle, two recent reports provided further evidence that STAT3 plays a major role in the regulation of cell fate choices in MuSCs (9, 10). Our study provide evidence that STAT3 is phosphorylated on tyrosine 705 upon MuSC activation and promotes the progression from MuSCs to committed myogenic progenitors by upregulating MyoD, thus antagonizing self-renewal. We have recently shown that deletion of STAT3 specifically in MuSCs utilizing the Pax7-CreER STAT3^{flox/flox} mouse model leads to expansion of MuSCs and impairment of muscle regeneration upon injury, as STAT3 is required for proper myogenic differentiation (9). Furthermore, transient delivery of a STAT3 inhibitor in vivo, which promotes expansion of MuSCs that are later competent for differentiation, efficiently accelerated tissue repair in both young and aged muscles (9). The same effect was observed in severely dystrophic mdx/mTR muscles. A parallel study from Rudnicki group showed that inhibition of STAT3 signaling promotes symmetric expansion of MuSCs (10). However,

the mechanisms through which STAT3 regulates myogenic lineage progression and symmetric division are not well understood.

Interestingly, it has also been reported that STAT3 signaling is upregulated in aged MuSCs (10). In fact, STAT3 promotes cellular senescence by upregulating p19 in prostate cancer (30), and it will be interesting to assess whether this mechanism is conserved also in MuSCs. These findings suggest that pharmacological manipulation of STAT3 could provide therapeutic approaches for muscle maintenance and repair. Understanding the causes of the detrimental activation of STAT3 signaling in MuSCs in aged and dystrophic conditions, i.e. whether there are elevated levels of activating cytokines in the microenvironment, such as IL-6, or whether there are also contributing intrinsic components, will improve our understanding of the process. Consistent with these findings, delivery of an IL-6 receptor neutralizing antibody to dystrophic mice improved muscle condition (31). Finally, the identification of the relevant downstream targets will provide critical insights in the transcriptional output of STAT3 signaling in MuSCs.

STAT3 in myofibers

Several reports have shown that STAT3 is a major regulator of skeletal muscle mass and metabolism. STAT3 activation has been directly linked to the loss of muscle mass in several murine models of muscle wasting, such as streptozotocin-induced diabetes, chronic kidney disease (CKD) and cancer cachexia (32-35). In some of these studies, authors utilized the MCK-Cre STAT3^{flx/flx} mouse model, which abrogates STAT3 expression specifically in myofibers (32, 33). Induction of diabetes, CKD or cancer cachexia in control mice increases pSTAT3 (Y705) levels in whole muscle extracts, indicating an activation of this transcription factor (32). However, STAT3 ablation in myofibers only partially prevents muscle loss under these conditions (32, 33). Further analysis revealed that STAT3 promotes muscle wasting by two different mechanisms: by increasing myostatin expression through C/EBP δ upregulation, which leads to increased expression of genes involved in protein degradation such as MuRF1 or atrogin 1 (32, 33); by the increase in expression and activity of caspase 3 (33). Both mechanisms lead to increased protein degradation in muscle by stimulating the UPS (Ubiquitin Proteasome System) activity (32, 33).

In addition to STAT3 genetic ablation in myofibers, several reports have shown that pharmacological inhibition of STAT3 (both direct and indirect) is able to ameliorate muscle wasting in mice (32-35). Most of these studies have been done in murine models of cancer cachexia (33-35). The treatment of cachectic mice with C188-9 (STAT3 inhibitor), AG490 (JAK2 inhibitor), sunitinib (tyrosine kinase inhibitor) or sorafenib (tyrosine kinase inhibitor) partially prevented loss of muscle mass (33-35). Moreover, inhibition of STAT3 with C188-9 also ameliorated muscle wasting in CKD and streptozotocin-induced diabetes (32). However, most of the used drugs indirectly inhibit STAT3 by affecting upstream kinases. These kinases regulate the activity of additional proteins different from STAT3 and this may also contribute to improvement observed in pathological conditions. Moreover, these drugs were delivered by subcutaneous injection, intraperitoneal injection, or oral gavage. Thus, other cell types in skeletal muscle different from myofibers, as well as other tissues, could also mediate the effects observed on muscle mass.

It has also been shown that STAT3 can regulate autophagy in skeletal muscle (36). Briefly, Fyn promotes the phosphorylation of STAT3 (Y705), and pSTAT3 causes a reduction in Vps34 protein levels that inhibits autophagy (36). This mechanism is specific to glycolytic fibers, and was not observed in an oxidative muscle as soleus (36). This data suggests a differential role of STAT3 depending on the myofiber type.

Based on studies performed in cultured myotubes, it was suggested that STAT3 has a central role in regulating muscle insulin sensitivity (37, 38). However, a recent report shows that this may not be the case in myofibers in vivo (39). In this study, authors used MCK-Cre STAT3^{flox/flox} mice fed with high fat diet for three weeks (39). Under these conditions, STAT3 ablation in myofibers did not prevent the development of insulin resistance and glucose intolerance in these mice (39). This data suggests that the environment in skeletal muscle causes a different effect in myofibers than in myotubes in culture and that likely the interaction of myofibers with the other cell types resident in skeletal muscle modulates STAT3 signaling in vivo.

STAT3 signaling in human pathology

Some of the findings described above in mouse models were also validated in humans. IL-6 circulating levels are elevated in several human pathologies that cause accelerated muscle wasting, including Duchene muscular dystrophy, CKD, cancer cachexia and diabetes (31, 32, 40, 41). Analysis of muscle biopsies from patients with CKD revealed increased content of IL-6 and pSTAT3 (Y705) in this tissue (32). Overall, available data suggest that STAT3 signaling pathway is involved in the muscle wasting observed in different human pathologies. Pharmacological inhibition of STAT3 ameliorates muscle wasting in murine models of accelerated muscle loss (9, 10, 31-35), suggesting that pharmacological manipulation of STAT3 signaling pathway in humans could be a promising approach for the treatment of muscle-wasting associated diseases. In fact, JAK-STAT inhibitors are currently being used in the clinic to treat inflammatory diseases such as rheumatoid arthritis or psoriasis. Moreover, other STAT3 inhibitors are currently under clinical trials for the treatment of several human cancers (such as head and neck cancer, lymphoma or hepatoma). Some examples of drugs used in clinical trials are STAT3 DECOY, IONIS-STAT3Rx, AZD9150 or OPB-31121 (the respective clinicaltrials.gov identifiers are: NCT00696176, NCT01563302, NCT02417753, NCT01839604, NCT00955812). Thus, potential therapeutic applications targeting STAT3 to ameliorate muscle wasting would have an accelerated translation to the clinic.

Conclusion

STAT3 signaling is emerging as a critical regulator of skeletal muscle maintenance and regeneration, and as a nodal point of integration of extracellular cues emanating from the microenvironment. It is currently being tested as target in multiple therapeutic approaches. Future efforts will focus on further understanding the underlying molecular mechanisms, including the downstream STAT3 targets as well as its critical role in mediating the communication among the different cell types involved in tissue repair. Overall, this could potentially lead to the development of more targeted and efficient therapeutic approaches.

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Key points

- STAT3 is a key regulator of multiple muscle resident cell types, including MuSCs, myofibers and macrophages.
- STAT3 is emerging as a nodal point in integrating multiple signaling pathways in skeletal muscle.
- STAT3 promotes myogenic lineage progression in MuSCs, and its inhibition promotes their symmetric expansion.
- STAT3 chronic activation in myofibers enhances protein degradation and promotes muscle atrophy.
- Transient STAT3 pharmacological inhibition has been proven to ameliorate muscle wasting in several pathological conditions.

Figure 1.
STAT3 major roles in the different cell types residing in skeletal muscle.