Published in final edited form as:

Curr Opin Clin Nutr Metab Care. 2008 May ; 11(3): 233–241. doi:10.1097/MCO.0b013e3282fa1810.

Epigenetic drugs in the treatment of skeletal muscle atrophy

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Abstract

Purpose of review—A dynamic network of anabolic and catabolic pathways regulates skeletal muscle mass in adult organisms. Muscle atrophy is the detrimental outcome of an imbalance of this network. The purpose of this review is to provide a critical evaluation of different forms of muscle atrophy from a mechanistic and therapeutic point of view.

Recent findings—The identification and molecular characterization of distinct pathways implicated in the pathogenesis of muscle atrophy have revealed potential targets for therapeutic interventions. However, an effective application of these therapies requires a better understanding of the relative contribution of these pathways to the development of muscle atrophy in distinct pathological conditions.

Summary—We propose that the decline in anabolic signals ('passive atrophy') and activation of catabolic pathways ('active atrophy') contribute differently to the pathogenesis of muscle atrophy associated with distinct diseases or unfavorable conditions. Interestingly, these pathways might converge on common transcriptional effectors, suggesting that an optimal intervention should be directed to targets at the chromatin level. We provide the rationale for the use of epigenetic drugs such as deacetylase inhibitors, which target multiple signaling pathways implicated in the pathogenesis of muscle atrophy.

Keywords

autophagy; cachexia; chromatin; deacetylase inhibitors; muscle atrophy; sarcopenia

Introduction

Mass and fiber size of adult skeletal muscles is continuously regulated in response to changes in workload, tension, hormones and nutrition, by a dynamic balance between anabolic and catabolic signaling pathways [1,2]. Fine-tuning of these pathways and possibly their reciprocal controls ensure a constant adaptation of skeletal myofibers to physiological cues, leading to transitory hypertrophy or atrophy. However, deregulation of these pathways might result in dramatic changes of muscle mass that are associated with systemic diseases or unfavorable events. Although no specific pathological conditions correlate with muscle hypertrophy – which is rather associated with an increased performance – muscle atrophy develops in coincidence with a number of diseases (cancer cachexia, muscle wasting during chronic inflammatory disorders), or represents one detrimental outcome of aging (sarcopenia), chronic disuse and starvation.

Although it is difficult to establish the criteria that distinguish the muscle atrophy as an adaptive and beneficial response from the pathological muscle atrophy, a schematic distinction can be made between the atrophy of myofibers that occurs in consequence of the decline of anabolic signals (passive atrophy) and the muscle atrophy caused by the activation of catabolic pathways (active atrophy). The value of this definition is purely didactic and indicates the first event that initiates the atrophic process following specific stimuli. This definition is complicated by the evidence that anabolic pathways can suppress catabolic pathways; thus, the term 'passive-active atrophy' might indicate the activation of muscle catabolism in consequence of the release of the inhibitory control of anabolic signals (see Fig. 1). Likewise, catabolic pathways can suppress anabolic pathways. Overall, an overlap of these mechanisms is typically observed during the progression of most of the pathological forms of muscle atrophy.

In the following paragraphs, we will summarize the current knowledge on the pathways that regulate muscle mass and will illustrate the rationale supporting the ability of deacetylase inhibitors to interfere with multiple pathways implicated in the pathogenesis of muscle atrophy.

Dynamic network of signaling regulating skeletal muscle mass

In adult organisms, skeletal muscles constantly adjust the rate of protein synthesis and undergo myonuclear turnover, via regenerative events, in response to pathways elicited by local and systemic cues.

The IGF1 signaling is the prototypical pathway that promotes myofiber hypertrophy by stimulating both protein synthesis and muscle regeneration [3,4]. Local increase in IGF1 is stimulated following muscle exercise [5], whereas systemic IGF1 is released in response to endocrine changes and mediates the effect of anabolic hormones [6]. Furthermore, the IGF1 pathway is activated by nutrients and insulin. Upon IGF1 binding to its membrane receptor (IGFR), the phosphorylation of the insulin receptor substrate 1 (IRS-1) and the engagement of the PI3K-Akt signaling stimulate a number of distinct downstream events [7,8]. Activation of mTOR [9] results in an increase in protein translation via the activation of the positive regulator of protein translation p70S6K, and the inhibition of PHAS-1, a negative regulator of translation [10,11]. Simultaneous inhibition of glycogen synthase kinase 3 beta (GSK3 β) and forkhead box, subgroup O (FOXO) transcription factors by Akt-mediated phosphorylation also promotes hypertrophy by preventing the activation of atrophic or catabolic signals [12–14]. Furthermore, conflicting data exist regarding the contribution of calcineurin – a serine/threonine protein phosphatase that activates nuclear factor of activated T cells (NFAT) transcription factors by dephosphorylation [15] – in IGF1-mediated hypertrophy [16,17].

The ability of the IGF1 pathway to stimulate proliferation of muscle progenitors (e.g. satellite cells) appears to rely on the parallel activation of the Ras-Raf-MEK-ERK pathway, which promotes proliferation and survival [18–20]. Furthermore, a unique property of the IGF1 pathway resides in its ability to promote both proliferation and differentiation. We have recently reported on the mechanism by which IGF1-activated Akt1 and 2 stimulate the recruitment of the acetyltransferases p300 and PCAF to the chromatin of muscle loci, an event necessary to initiate the transcription of muscle specific genes in response to regeneration cues [21•].

Myostatin is a member of the TGF β family of signal transduction proteins that negatively regulates muscle mass in the adults by inhibiting muscle regeneration [22,23]. Indeed, the increase in muscle mass observed in myostatin-null animals predominantly results from an increase in the number of muscle fibers (hyperplasia). Myostatin has been isolated as the

gene mutated in cattle characterized by abnormal hypertrophy of the skeletal muscle [24]. Similarly, myostatin-null mice display an increase in muscle mass relative to control animals [22], and gene mutation that precludes myostatin expression has been identified in humans and dogs showing a hyper-muscular phenotype [25,26•]. Myostatin effect on muscles is opposed by other members of the TGF β family such as follistatin and follistatin-related gene [27]. Consistently, systemic overexpression of myostatin in mice causes significant loss in muscle mass, and the effect is reversed by follistatin administration [28]. Thus, factors that interfere with myostatin activity can be considered anabolic signals.

Other important regulators of muscle regeneration are the Notch signaling, which negatively control the fate of muscle stem cells, their recruitment and fusion into myofibers [29,30] and IL4, which is induced in myotubes in response to the calcineurin–NFAT signaling and stimulates myoblast fusion into preexisting myotubes [31].

Steroid hormones, and in particular, androgens, are potent anabolic factors which exert their effect by directly regulating gene transcription [32]. However, it is unclear if their anabolic activity relies more on increased protein synthesis or an enhanced regeneration-mediated myonuclear turnover.

Different mechanisms leading to distinct forms of muscle atrophy

An imbalance in the signaling network described above can cause muscle atrophy. In principle, muscle atrophy is an adaptive response of the organism to maintain the metabolic and energy homeostasis in adverse conditions, such as prolonged muscle disuse or starvation. Thus, it is important to define the conditions in which this response might turn into a pathological or unfavorable event. In the following paragraphs, we distinguish different forms of muscle atrophy on the basis of leading mechanisms and specific pathways implicated.

‘Passive’ muscle atrophy

Passive muscle atrophy defines the interruption or decline of anabolic pathways that is typically observed during muscle disuse or starvation. In these circumstances, the rate of protein synthesis and muscle growth decreases as a consequence of the reduced availability of nutrients and anabolic signaling pathways. This is possibly an adaptive response, which is transient and fully reversible when the anabolic pathways are restored. However, this form of atrophy can turn into a more severe condition when muscle catabolism is activated – a passive–active muscle atrophy.

Muscle catabolism occurs through an acceleration of protein degradation, which is largely caused by increased activity of the ATP-dependent ubiquitin–proteasome pathway [33–35]. Expression-screening studies [36,37] aimed at characterizing atrophy markers identified two genes whose expression increased significantly in multiple models of muscle atrophy: muscle ring finger 1 (MuRF1) and muscle atrophy f-box (MAFbx), also indicated as Atrogin-1. Both MuRF1 and Atrogin-1 encode E3 ubiquitin ligases that mediate the degradation of components of the contractile apparatus [38,39,40•]. Mice in which MuRF1 or MAFbx were deleted show a partial resistance to muscle atrophy in experimental conditions [36]. MuRF1 and Atrogin-1 are upregulated in myotubes treated with the cachectic glucocorticoid dexamethasone, and this upregulation is antagonized by the activation of the IGF-1/Akt pathway [13,14,41]. Thus, the interruption of the IGF1 signaling can simultaneously affect the protein synthesis, regeneration ability and catabolic activities of muscles. The release of the catabolic pathway by decreased IGF1 signaling is an extreme solution to provide energy supply in the form of amino acids derived from the protein breakdown.

Akt-mediated suppression of Atrogin-1 and MuRF1 transcription occurs via functional inhibition of the FOXO family of transcription factors [13,14]. Akt-mediated phosphorylation of FOXOs prevents their nuclear translocation and the activation of MuRF1 and Atrogin-1 transcription. Activation of FOXO3 is sufficient to induce atrophy [13], and transgenic expression of FOXO1 results in the atrophic phenotype [42].

Additional events that regulate FOXO activity include other posttranslational modifications such as ubiquitination and acetylation [43••]. The multifaceted mechanism of FOXO regulation suggests that other signaling pathways can actively induce muscle catabolism by promoting FOXO activity.

‘Active’ muscle atrophy

Muscle-specific ubiquitin ligases can be directly activated via induction of NFκB by proinflammatory cytokines. Several cytokines show a muscle wasting potential, among them TNFα, which was originally named ‘cachectin’ [44]. TNFα is a potent activator of NFκB [45], and chronic activation of NFκB has been associated with muscle wasting and cachexia [46]. Consequently, genetic interference of the NFκB signaling attenuates muscle wasting [47]. TNFα-mediated activation of NFκB downregulates MyoD by promoting mRNA decay [48]. Furthermore, activation of NFκB in transgenic mice causes muscle wasting through accelerated protein breakdown via selective expression of MuRF1 and consequent ubiquitin-dependent proteolysis [46]. Collectively, these data support the evidence that cytokine-induced NFκB is a key component of the signaling leading to active muscle atrophy. However, the finding that Atrogin-1 is not activated upon NFκB activation suggests that an independent pathway induces active atrophy. TNFα has been shown to stimulate Atrogin-1 expression via the p38 pathway, possibly through FOXO activation [49]. Thus, it appears that muscle wasting can be induced by at least two distinct mechanisms, FOXO/Atrogin-1 and NFκB/MuRF1 signaling. It is currently unknown if FOXO can participate in NFκB signaling to MuRF1. However, one NFκB downstream signaling target – the nitric oxide synthase – might regulate FOXO activity, suggesting a potential indirect link between NFκB and FOXO [50,51••].

Active muscle atrophy can also be induced by myostatin. Interestingly, the myostatin promoter contains multiple glucocorticoid response elements [52]. Thus, myostatin upregulation can be an important event in dexamethasone-induced muscle atrophy. Consistently, myostatin-null mice are protected from glucocorticoid-induced atrophy [53•]. Furthermore, several FOXO-responsive elements are present in the murine myostatin promoter, and FOXO1-mediated activation of myostatin has been reported [54•]. Thus, myostatin upregulation might integrate different signaling pathways leading to active atrophy, and is therefore a valuable candidate target for interventions toward countering muscle atrophy.

Distinct mechanisms of muscle atrophy in pathological conditions

Involuntary weight loss by muscle atrophy can be categorized into four primary etiologies: starvation, disuse, sarcopenia and cachexia. Although these different types of muscle atrophy share common characteristics, they represent distinct pathological entities, regulated, at least in part, by different signaling pathways.

In the next paragraphs, we illustrate the relative contribution by the different forms of atrophy described above to these pathological conditions.

Muscle atrophy following starvation

During starvation, a number of metabolic and endocrine responses are activated to maintain the glucose and energy homeostasis. Nutrient withdrawal results in the decline of growth factor-mediated anabolic pathways in muscles, leading to progressive reduction of the myofiber size [55]. This initial response is conceivably one typical example of 'passive' atrophy, which is reversible by the resumption of growth factor-activated signaling. A catabolic pathway might be triggered by a passive-active mechanism, along with the disorder progression (i.e. prolonged starvation or malnutrition), as an extreme response to provide nutrients from muscles.

Muscle atrophy following disuse

Prolonged periods of skeletal muscle inactivity due to denervation, unloading, and immobilization invariably result in significant muscle atrophy [56]. Unlike the muscle wasting caused by systemic diseases, disuse-associated muscle atrophy is initiated by a reduction in contractile activity and muscle tension, and is therefore another example of 'passive' form of atrophy. However, an activation of the ubiquitin-proteasome pathway has been reported in disuse muscle atrophy, possibly by a passive-active mechanism [57]. Furthermore, the activation of the noncanonical NFkB pathway, which involves p50 and Bcl-3, and is not induced by inflammatory cytokines, has also been reported in experimental models of disuse atrophy [58,59]. It is possible that reactive oxygen species (ROS) activate NFkB directly. ROS can also stimulate FOXO activity. This evidence link the oxidative stress produced in the muscles during unloading and immobilization with the activation of the ubiquitin-proteasome pathway [60,61].

Whether the relative contribution of different forms of muscle atrophy – passive and active – determines the severity of muscle atrophy during disuse and could determine the therapy responsiveness will be an interesting matter to look into.

Age-associated muscle atrophy: sarcopenia

Sarcopenia is the reduction of muscle mass and strength occurring during normal aging [62]. Multiple factors contribute to the development and progression of sarcopenia, in particular neuromuscular and hormonal changes, poor nutrition, chronic inflammation and reduced physical activity. In this regard, both passive and active muscle atrophy seem to be equally implicated in sarcopenia.

The decline in the IGF1 signaling plays a pivotal role in sarcopenia, as IGF1 levels decrease steadily with age [63]. IGF1 administration ameliorates the senescent muscle phenotype in mice [4,64], and recombinant IGF1 supplemented to elderly women was reported to improve protein synthesis [65]. Hormonal changes also strongly correlate with sarcopenia, with epidemiological and experimental data supporting the relationship between reduced testosterone levels and the decline in muscle mass [66,67].

Defective muscle regeneration is another major contributor to the loss of muscle mass in sarcopenia [68]. One of the mechanisms responsible for the reduced regenerative potential in muscles of aged mice consists in the decline of Notch signaling [69,70]. The regenerative potential of old muscles can be experimentally restored by forced activation of Notch signaling [71].

Muscle wasting in sarcopenia also results from the loss of muscle fibers via apoptosis, and the atrophy of the remaining fibers. In particular, type II glycolytic fibers seem to be preferentially affected by atrophy [72,73], resulting in muscles showing increased characteristics of type I oxidative fibers, with reduced rate of force development, and this is

likely to contribute to muscle weakness. An important modulator of fiber type is the peroxisome proliferator-activated receptor- γ coactivator-1 α (PGC-1 α), a factor implicated in the regulation of muscle oxidative capacity and mitochondrial biogenesis [74]. Increased activity stimulates the expression of PGC-1 α , promoting fiber type switching from glycolytic toward more oxidative fibers [75]. PGC-1 α protects skeletal muscle from atrophy, opposing the effects of FOXO on muscle mass [76]. PGC-1 α is preferentially expressed in type I fibers, and the great sensitivity to atrophy of type II muscle fibers can be explained by their low content of PGC-1 α .

PGC-1 α is a coactivator of MEF2-dependent transcription of oxidative genes in slow fibers. Class II histone deacetylases (HDACs) also contribute to the determination of skeletal muscle fiber type, by inhibiting the transcription factor MEF2 [77]. Thus, epigenetic drugs that target MEF2 coregulators at the chromatin level have the potential of modulating muscle fiber type.

Elevated levels of ROS are also detectable in muscles during sarcopenia, leading to mitochondrial dysfunction and reduced cellular ATP content [78]. The progressive decline in mitochondrial function, and the resulting energy depletion within the cell, might account for the increased apoptosis observed in aging skeletal muscles [79].

Finally, increased levels of circulating inflammatory cytokines and the activation of calcium-dependent proteolytic system have been described in aging skeletal muscles [80•].

Muscle wasting in chronic diseases: cachexia

An example of prevalently active muscle atrophy is provided by cachexia – a wasting syndrome which entails the progressive loss of both adipose and skeletal muscle tissues in concert with severe injury, chronic or end-stage malignant and infectious diseases such as cancer and AIDS [81].

A number of immune and tumor-derived cytokines such as TNF α , interleukin 1 (IL1), IL6 and IFN γ as well as tumor-specific factors such as the proteolysis-inducing factor (PIF) are associated with cachexia [82,83]. Apart from stimulating NF κ B-mediated upregulation of components of the ubiquitin–proteasome system [49,84], these cytokines can interfere with muscle differentiation by parallel mechanisms, such as TNF α -mediated induction of PW-1, a transcription factor implicated in p53-induced apoptosis [85,86].

Cellular mechanisms underlying cachexia include impaired satellite cell function [87]. Elevated levels of TNF α inhibit muscle regeneration [88]. A direct link between cachexia and the maintenance of muscle integrity through dystrophin function in mdx mice has also been recently discovered [89]. The dystrophin glycoprotein complex (DGC), whose components are mutated in Duchenne–Becker dystrophy, forms a mechanical link between the extracellular matrix to the cytoskeleton [90] and plays a role in signaling to downstream effectors (i.e. iNOS). Disruption of dystroglycan binding to laminin inhibits activation of Akt signaling [91]. In cachectic muscle fibers, the myofibrillar membrane is altered, and dystrophin level is reduced [89]. Transgenic animals overexpressing dystrophin are more resistant than wild-type littermates to atrophic conditions, and restoration of DGC is sufficient to decrease ubiquitin ligase expression [89]. Since Akt blocks the upregulation of MuRF1 and Atrogin-1, and DGC disruption inhibits Akt, a signaling initiated by dystrophin can counter skeletal muscle atrophy. Thus, boosting dystrophin levels or downstream signaling may be equally used as an intervention against muscle wasting in dystrophies and cancer [89,92]. The relationship between atrophy and dystrophin signaling is further supported by recent studies showing that neuronal NOS (nNOS), which is normally bound to the DGC complex and deregulated in muscular dystrophy, is also deregulated in muscle

atrophy [51•,93,94]. When untethered from DGC, nNOS is able to activate FOXO-mediated transcription, thus contributing to the upregulation of MuRF1 and Atrogin-1 [50].

During late stages of cachexia a number of other concurrent conditions (inactivity, malnutrition and often aging) contribute to muscle atrophy and catabolism.

Muscle wasting and autophagy: a pathological or adaptive response?

Autophagy is an intracellular degradation system that delivers cytoplasmic components to the lysosomes and play a critical role in starvation adaptation, intracellular protein and organelles clearance, development, cell death and tumor suppression [95•,96]. Autophagy is activated by depletion of nutrients or lack of growth factors, whose main sensor is the kinase mTOR [97]. The process is mediated by a unique organelle called the autophagosome, which engulfs the portion of the cytoplasm to be degraded, to produce amino acids that are required for the cell to counter starvation. Autophagy is thought to be a nonselective degradation system, in contrast to the ubiquitin–proteasome system, which specifically targets only ubiquitinated proteins for proteasomal degradation.

Impaired autophagy is involved in the development of muscle diseases, named autophagic vacuolar myopathies (AVMs), such as Pompe disease and Danon disease [98–100]. Autophagy is likely to contribute to muscle wasting. The lysosomal proteolytic system is stimulated in different conditions leading to muscle atrophy [101,102•]. Furthermore, genetic screening in *Drosophila* suggested a role for FOXO in modulating autophagy [103•]. Recent studies show that FOXO3 is required for the induction of autophagy in skeletal muscles [104•,105•]. Constitutively active FOXO3 induces autophagosome formation and upregulation of the autophagy genes in skeletal muscle. Hence, suppression of FOXO3 activity by Akt reverts this effect. FOXO3 directly controls the expression of autophagy genes by binding to their promoters; in particular, Bnip3 seems to mediate the effects of FOXO3 on autophagy [104•]. It is important to note that the inhibition of the ubiquitin–proteasome system does not impair autophagy. Thus, FOXO3 controls independently the two major pathways of protein breakdown in skeletal muscle – the ubiquitin–proteasome and autophagy–lysosome pathways – that control the degradation of myofibrillar proteins and of organelle membranes, respectively. The simultaneous activation of these two pathways by FOXO3 ensures that the loss of different cell components is coordinated in atrophy conditions, resulting in a functional muscle, albeit with reduced strength and endurance (see Fig. 2).

In addition to the induction of muscle atrophy, alterations in the IGF1 pathway have been suggested to play a role in increasing longevity by affecting FOXO activity [106–108]. Interestingly, FOXO-induced autophagy may be important in the extension of lifespan [109]. These data suggest an overlap in the pathways mediating longevity and atrophy/autophagy in skeletal muscle, and raise interesting issues on the beneficial or detrimental role of muscle atrophy during aging.

A rationale for using deacetylase inhibitors in the treatment of muscle atrophy

The participation of multiple pathways in the development of muscle atrophy poses the question of whether blocking only one pathway is sufficient to counter atrophy, and suggests that interventions able to simultaneously target distinct pathways would provide the optimal therapeutic option. Furthermore, the central role of FOXO-dependent gene transcription in regulating different events within the atrophic program indicates that drugs interfering with FOXO activity and the downstream chromatin signaling might be particularly effective.

These considerations prompted an interest toward epigenetic drugs as potential therapeutic agents in muscle atrophy (see Fig. 3).

Deacetylase inhibitors represent a prototype of epigenetic drugs [110]. Their action relies on the ability to block the enzymatic function of histone deacetylases (HDACs). The therapeutic versatility of these compounds is demonstrated by their use in the experimental treatment of different diseases, including cancer, genetic diseases (i.e. muscular dystrophy) and degenerative disorders [111,112,113••,114,115]. Recent evidence demonstrates that deacetylase inhibitors promote an increase in skeletal muscle mass by targeting multiple pathways [116,117], thereby suggesting the potential effectiveness of these compounds in the treatment of muscle atrophy. This possibility is supported by the reported analogies existing between dystrophic and cachectic muscles [89]. In both cases, the complete absence or the reduced levels of dystrophin impair the activation of downstream signaling regulating muscle mass, that is, nitric oxide pathway and Akt. The reported ability of deacetylase inhibitors to protect dystrophic muscles from degeneration in mouse models of Duchenne muscular dystrophy [114] suggests, in principle, the potential efficacy of these compounds in countering muscle atrophy. This conceptual extension is substantiated by studies that have elucidated the molecular mechanism by which deacetylase inhibitors promote muscle growth and increase myofiber size. Another study [116] revealed that muscle-specific upregulation of the myostatin inhibitor, follistatin, is a key event underlying the effect of deacetylase inhibitors on muscle size. Thus, deacetylase inhibitors can have an indirect anabolic effect that is equivalent to myostatin inactivation. However, other independent effects might contribute to the anti-atrophic action of deacetylase inhibitors. First, class II HDACs negatively control MEF2-dependent transcription of slow fiber genes, and HDAC inhibition can promote fiber II switch into fiber I type, which appear to be more resistant to atrophy. Second, the regulation of FOXO activity by posttranslational events, such as acetylation, indicates that agents that affect the acetylation pattern (i.e. deacetylase inhibitors) can pharmacologically modulate FOXO-dependent transcription. Indeed, the mammalian Sir2 homologue, SIRT1, regulates FOXO activity [43••]; however, the role of HDAC in this regulation has not been reported. Third, there is evidence that deacetylase inhibitors activate, possibly by indirect mechanisms, the IGF1 pathway. Gene profiling of muscle cells exposed to deacetylase inhibitors showed changes in the pattern of IGF1 binding proteins [116]. Akt activation was reported in deacetylase inhibitor-treated cells [117], and increased levels of activated Akt correlate with the downregulation of E3 ubiquitin ligases in dystrophic muscles that were exposed to deacetylase inhibitors (our unpublished data).

Conclusion

Given the availability of deacetylase inhibitors in clinical practice [110], it will be interesting to study the effect of these compounds in experimental models of muscle atrophy. It should be noted that deacetylase inhibitors seem to promote muscle hypertrophy only in a regenerative environment [116]. Thus, future studies need to establish whether deacetylase inhibitors can promote muscle hypertrophy in the absence of regeneration, and whether atrophic muscles are able to regenerate in response to appropriate stimuli.

Acknowledgments

Pier Lorenzo Puri is supported by Telethon career grant, AIRC, Compagnia San Paolo di Torino, AFM and Parent Project.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

1. Glass DJ. Signalling pathways that mediate skeletal muscle hypertrophy and atrophy. *Nat Cell Biol.* 2003; 5:87–90. [PubMed: 12563267]
2. Jagoe RT, Goldberg AL. What do we really know about the ubiquitin-proteasome pathway in muscle atrophy? *Curr Opin Clin Nutr Metab Care.* 2001; 4:183–190. [PubMed: 11517350]
3. Goldspink DF, Garlick PJ, McNurlan MA. Protein turnover measured in vivo and in vitro in muscles undergoing compensatory growth and subsequent denervation atrophy. *Biochem J.* 1983; 210:89–98. [PubMed: 6189483]
4. Musarò A, McCullagh K, Paul A, et al. Localized Igf-1 transgene expression sustains hypertrophy and regeneration in senescent skeletal muscle. *Nat Genet.* 2001; 27:195–200. [PubMed: 11175789]
5. DeVol DL, Rotwein P, Sadow JL, et al. Activation of insulin-like growth factor gene expression during work-induced skeletal muscle growth. *Am J Physiol.* 1990; 259(1 Pt 1):E89–95. [PubMed: 2372054]
6. Philippou A, Maridaki M, Halapas A, Koutsilieris M. The role of the insulin-like growth factor 1 (IGF-1) in skeletal muscle physiology. *In Vivo.* 2007; 21:45–54. [PubMed: 17354613]
7. Bodine SC, Stitt TN, Gonzalez M, et al. Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. *Nat Cell Biol.* 2001; 3:1014–1019. [PubMed: 11715023]
8. Rommel C, Bodine SC, Clarke BA, et al. Mediation of IGF-1-induced skeletal myotube hypertrophy by PI(3)K/Akt/mTOR and PI(3)K/Akt/GSK3 pathways. *Nat Cell Biol.* 2001; 3:1009–1013. [PubMed: 11715022]
9. Scott PH, Brunn GJ, Kohn AD, et al. Evidence of insulin-stimulated phosphorylation and activation of the mammalian target of rapamycin mediated by a protein kinase B signaling pathway. *Proc Natl Acad Sci U S A.* 1998; 95:7772–7777. [PubMed: 9636226]
10. von Manteuffel SR, Gingras AC, Ming XF, et al. 4E-BP1 phosphorylation is mediated by the FRAP-p70s6k pathway and is independent of mitogen-activated protein kinase. *Proc Natl Acad Sci U S A.* 1996; 93:4076–4080. [PubMed: 8633019]
11. Hara K, Yonezawa K, Kozlowski MT, et al. Regulation of eIF-4E BP1 phosphorylation by mTOR. *J Biol Chem.* 1997; 272:26457–26463. [PubMed: 9334222]
12. Cross DA, Alessi DR, Cohen P, et al. Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. *Nature.* 1995; 378:785–789. [PubMed: 8524413]
13. Sandri M, Sandri C, Gilbert A, et al. Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. *Cell.* 2004; 117:399–412. [PubMed: 15109499]
14. Stitt TN, Drujan D, Clarke BA, et al. The IGF-1/PI3K/Akt pathway prevents expression of muscle atrophy-induced ubiquitin ligases by inhibiting FOXO transcription factors. *Mol Cell.* 2004; 14:395–403. [PubMed: 15125842]
15. Horsley V, Pavlath GK. NFAT: ubiquitous regulator of cell differentiation and adaptation. *J Cell Biol.* 2002; 156:771–774. [PubMed: 11877454]
16. Musarò A, McCullagh KJ, Naya FJ, et al. IGF-1 induces skeletal myocyte hypertrophy through calcineurin in association with GATA-2 and NF-ATc1. *Nature.* 1999; 400:581–585. [PubMed: 10448862]
17. Semsarian C, Wu MJ, Ju YK, et al. Skeletal muscle hypertrophy is mediated by a Ca²⁺-dependent calcineurin signalling pathway. *Nature.* 1999; 400:576–581. [PubMed: 10448861]

18. Moelling K, Schad K, Bosse M, et al. Regulation of Raf-Akt cross-talk. *J Biol Chem.* 2002; 277:31099–31106. [PubMed: 12048182]
19. Rommel C, Clarke BA, Zimmermann S, et al. Differentiation stage-specific inhibition of the Raf-MEK-ERK pathway by Akt. *Science.* 1999; 286:1738–1741. [PubMed: 10576741]
20. Zimmermann S, Moelling K. Phosphorylation and regulation of Raf by Akt (protein kinase B). *Science.* 1999; 286:1741–1744. [PubMed: 10576742]
21. Serra C, Palacios D, Mozzetta C, et al. Functional interdependence at the chromatin level between the MKK6/p38 and IGF1/PI3K/AKT pathways during muscle differentiation. *Mol Cell.* 2007; 28:200–213. [PubMed: 17964260] This manuscript reveal an essential role of inflammation-activated MKK6-p38 and the IGF1-induced PI3K/AKT pathways in the assembly of the muscle transcriptosome, by targeting distinct components at the chromatin level.
22. McPherron AC, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. *Nature.* 1997; 387:83–90. [PubMed: 9139826]
23. Langley B, Thomas M, Bishop A, et al. Myostatin inhibits myoblast differentiation by down-regulating MyoD expression. *J Biol Chem.* 2002; 277:49831–49840. [PubMed: 12244043]
24. Grobet L, Martin LJ, Poncelet D, et al. A deletion in the bovine myostatin gene causes the double-muscling phenotype in cattle. *Nat Genet.* 1997; 17:71–74. [PubMed: 9288100]
25. Schuelke M, Wagner KR, Stolz LE, et al. Myostatin mutation associated with gross muscle hypertrophy in a child. *N Engl J Med.* 2004; 350:2682–2688. [PubMed: 15215484]
26. Mosher DS, Quignon P, Bustamante CD, et al. A mutation in the myostatin gene increases muscle mass and enhances racing performance in heterozygote dogs. *PLoS Genet.* 2007; 3:e79. [PubMed: 17530926] This paper describes a myostatin mutation found in a dog breed resulting in a double-muscling phenotype.
27. Amthor H, Nicholas G, McKinnell I, et al. Follistatin complexes myostatin and antagonises myostatin-mediated inhibition of myogenesis. *Dev Biol.* 2004; 270:19–30. [PubMed: 15136138]
28. Zimmers TA, Davies MV, Koniaris LG, et al. Induction of cachexia in mice by systemically administered myostatin. *Science.* 2002; 296:1486–1488. [PubMed: 12029139]
29. Luo D, Renault VM, Rando TA. The regulation of Notch signaling in muscle stem cell activation and postnatal myogenesis. *Semin Cell Dev Biol.* 2005; 16:612–622. [PubMed: 16087370]
30. Kitzmann M, Bonniue A, Duret C, et al. Inhibition of Notch signaling induces myotube hypertrophy by recruiting a subpopulation of reserve cells. *J Cell Physiol.* 2006; 208:538–548. [PubMed: 16741964]
31. Horsley V, Jansen KM, Mills ST, Pavlath GK. IL-4 acts as a myoblast recruitment factor during mammalian muscle growth. *Cell.* 2003; 113:483–494. [PubMed: 12757709]
32. Solomon AM, Bouloux PM. Modifying muscle mass: the endocrine perspective. *J Endocrinol.* 2006; 2:349–360. [PubMed: 17088404]
33. Attaix D, Ventadour S, Codran A, et al. The ubiquitin-proteasome system and skeletal muscle wasting. *Essays Biochem.* 2005; 41:173–186. [PubMed: 16250905]
34. Tawa NE Jr, Odessey R, Goldberg AL. Inhibitors of the proteasome reduce the accelerated proteolysis in atrophying rat skeletal muscles. *J Clin Invest.* 1997; 100:197–203. [PubMed: 9202072]
35. Lecker SH, Jagoe RT, Gilbert A, et al. Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression. *FASEB J.* 2004; 18:39–51. [PubMed: 14718385]
36. Bodine SC, Latres E, Baumhueter S, et al. Identification of ubiquitin ligases required for skeletal muscle atrophy. *Science.* 2001; 294:1704–1708. [PubMed: 11679633]
37. Gomes MD, Lecker SH, Jagoe RT, et al. Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy. *Proc Natl Acad Sci U S A.* 2001; 98:14440–14445. [PubMed: 11717410]
38. Centner T, Yano J, Kimura E, et al. Identification of muscle specific ring finger proteins as potential regulators of the titin kinase domain. *J Mol Biol.* 2001; 306:717–726. [PubMed: 11243782]
39. Kedar V, McDonough H, Arya R, et al. Muscle-specific RING finger 1 is a bona fide ubiquitin ligase that degrades cardiac troponin I. *Proc Natl Acad Sci U S A.* 2004; 101:18135–18140. [PubMed: 15601779]

- 40••. Clarke BA, Drujan D, Willis MS, et al. The E3 ligase MuRF1 degrades myosin heavy chain protein in dexamethasone-treated skeletal muscle. *Cell Metab.* 2007; 6:376–385. [PubMed: 17983583] Identification of the mechanism by which myosin heavy chain is degraded under atrophy conditions.
41. Satchek JM, Ohtsuka A, McLary SC, Goldberg AL. IGF-I stimulates muscle growth by suppressing protein breakdown and expression of atrophy-related ubiquitin ligases, atrogin-1 and MuRF1. *Am J Physiol Endocrinol Metab.* 2004; 287:E591–E601. [PubMed: 15100091]
42. Kamei Y, Miura S, Suzuki M, et al. Skeletal muscle FOXO1 (FKHR) transgenic mice have less skeletal muscle mass, down-regulated Type I (slow twitch/red muscle) fiber genes, and impaired glycemic control. *J Biol Chem.* 2004; 279:41114–41123. [PubMed: 15272020]
- 43••. Hasselgren P. Ubiquitination, phosphorylation, and acetylation: triple threat in muscle wasting. *J Cell Physiol.* 2007; 213:679–689. [PubMed: 17657723] Interesting review underscoring the role of posttranslational modifications of proteins involved in muscle atrophy and the modulation of their activity.
44. Beutler BA, Milsark IW, Cerami A. Cachectin/tumor necrosis factor: production, distribution, and metabolic fate in vivo. *J Immunol.* 1985; 135:3972–3977. [PubMed: 2999236]
45. Langen RC, Schols AM, Kelders MC, et al. Inflammatory cytokines inhibit myogenic differentiation through activation of nuclear factor-kappaB. *FASEB J.* 2001; 15:1169–1180. [PubMed: 11344085]
46. Cai D, Frantz JD, Tawa NE Jr, et al. IKKbeta/NF-kappaB activation causes severe muscle wasting in mice. *Cell.* 2004; 119:285–298. [PubMed: 15479644]
47. Mourkioti F, Kratsios P, Luedde T, et al. Targeted ablation of IKK2 improves skeletal muscle strength, maintains mass, and promotes regeneration. *J Clin Invest.* 2006; 116:2945–2954. [PubMed: 17080195]
48. Guttridge DC, Mayo MW, Madrid LV, et al. NF-kappaB-induced loss of MyoD messenger RNA: possible role in muscle decay and cachexia. *Science.* 2000; 289:2363–2366. [PubMed: 11009425]
49. Li YP, Chen Y, John J, et al. TNF-alpha acts via p38 MAPK to stimulate expression of the ubiquitin ligase atrogin1/MAFbx in skeletal muscle. *FASEB J.* 2005; 19:362–370. [PubMed: 15746179]
50. Agustí A, Morlá M, Sauleda J, et al. NF-kappaB activation and iNOS upregulation in skeletal muscle of patients with COPD and low body weight. *Thorax.* 2004; 59:483–487. [PubMed: 15170030]
- 51••. Suzuki N, Motohashi N, Uezumi A, et al. NO production results in suspension-induced muscle atrophy through dislocation of neuronal NOS. *J Clin Invest.* 2007; 117:2468–2476. [PubMed: 17786240] Involvement of nNOS/NO in the regulation of FOXO in muscle atrophy.
52. Ma K, Mallidis C, Artaza J, et al. Characterization of 5'-regulatory region of human myostatin gene: regulation by dexamethasone in vitro. *Am J Physiol Endocrinol Metab.* 2001; 281:E1128–E1136. [PubMed: 11701425]
- 53•. Gilson H, Schakman O, Combaret L, et al. Myostatin gene deletion prevents glucocorticoid-induced muscle atrophy. *Endocrinology.* 2007; 148:452–460. [PubMed: 17038559] This paper suggests an important role of myostatin in muscle atrophy caused by glucocorticoids.
- 54•. Allen DL, Unterman TG. Regulation of myostatin expression and myoblast differentiation by FoxO and SMAD transcription factors. *Am J Physiol Cell Physiol.* 2007; 292:C188–C199. [PubMed: 16885393] Role of FOXO1 and SMAD transcription factors in the regulation of myostatin the expression.
- 55•. Thomas DR. Loss of skeletal muscle mass in aging: examining the relationship of starvation, sarcopenia and cachexia. *Clin Nutr.* 2007; 26:389–399. [PubMed: 17499396] Review examining how different forms of atrophy are linked.
56. Stevenson EJ, Giresi PG, Koncarevic A, Kandarian SC. Global analysis of gene expression patterns during disuse atrophy in rat skeletal muscle. *J Physiol.* 2003; 551(Pt 1):33–48. [PubMed: 12844509]
57. Reid MB. Response of the ubiquitin-proteasome pathway to changes in muscle activity. *Am J Physiol Regul Integr Comp Physiol.* 2005; 288:R1423–R1431. [PubMed: 15886351]

58. Hunter RB, Stevenson E, Koncarevic A, et al. Activation of an alternative NF-kappaB pathway in skeletal muscle during disuse atrophy. *FASEB J*. 2002; 16:529–538. [PubMed: 11919155]
59. Hunter RB, Kandarian SC. Disruption of either the Nfkb1 or the Bcl3 gene inhibits skeletal muscle atrophy. *J Clin Invest*. 2004; 114:1504–1511. [PubMed: 15546001]
60. Li YP, Schwartz RJ, Waddell ID, et al. Skeletal muscle myocytes undergo protein loss and reactive oxygen-mediated NF-kappaB activation in response to tumor necrosis factor alpha. *FASEB J*. 1998; 12:871–880. [PubMed: 9657527]
61. Furukawa-Hibi Y, Yoshida-Araki K, Ohta T, et al. FOXO forkhead transcription factors induce G(2)-M checkpoint in response to oxidative stress. *J Biol Chem*. 2002; 277:26729–26732. [PubMed: 12048180]
62. Rosenberg IH. Sarcopenia: origins and clinical relevance. *J Nutr*. 1997; 127(Suppl 5):990S–991S. [PubMed: 9164280]
63. Juul A, Main K, Blum WF, et al. The ratio between serum levels of insulin-like growth factor (IGF)-I and the IGF binding proteins (IGFBP-1, 2 and 3) decreases with age in healthy adults and is increased in acromegalic patients. *Clin Endocrinol (Oxf)*. 1994; 41:85–93. [PubMed: 7519529]
64. Barton ER, Morris L, Musaro A, et al. Muscle-specific expression of insulin-like growth factor I counters muscle decline in mdx mice. *J Cell Biol*. 2002; 157:137–148. [PubMed: 11927606]
65. Butterfield GE, Thompson J, Rennie MJ, et al. Effect of rhGH and rhIGF-I treatment on protein utilization in elderly women. *Am J Physiol*. 1997; 272(1 Pt 1):E94–E99. [PubMed: 9038857]
66. Tenover JL. Experience with testosterone replacement in the elderly. *Mayo Clin Proc*. 2000; (Suppl 75):S77–S81. discussion S82. [PubMed: 10959222]
67. Sinha-Hikim I, Cornford M, Gaytan H, et al. Effects of testosterone supplementation on skeletal muscle fiber hypertrophy and satellite cells in community-dwelling older men. *J Clin Endocrinol Metab*. 2006; 91:3024–3033. [PubMed: 16705073]
68. Conboy IM, Rando TA. Aging, stem cells and tissue regeneration: lessons from muscle. *Cell Cycle*. 2005; 4:407–410. [PubMed: 15725724]
69. Conboy IM, Conboy MJ, Smythe GM, Rando TA. Notch-mediated restoration of regenerative potential to aged muscle. *Science*. 2003; 302:1575–1577. [PubMed: 14645852]
70. Conboy IM, Rando TA. The regulation of Notch signaling controls satellite cell activation and cell fate determination in postnatal myogenesis. *Dev Cell*. 2002; 3:397–409. [PubMed: 12361602]
71. Conboy IM, Conboy MJ, Wagers AJ, et al. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. *Nature*. 2005; 433:760–764. [PubMed: 15716955]
72. Lexell J, Taylor CC, Sjöström M. What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. *J Neurol Sci*. 1988; 84:275–294. [PubMed: 3379447]
73. Balagopal P, Schimke JC, Ades P, et al. Age effect on transcript levels and synthesis rate of muscle MHC and response to resistance exercise. *Am J Physiol Endocrinol Metab*. 2001; 280:E203–E208. [PubMed: 11158921]
74. Puigserver P. Tissue-specific regulation of metabolic pathways through the transcriptional coactivator PGC1-alpha. *Int J Obes (Lond)*. 2005; 29(Suppl 1):S5–S9. [PubMed: 15711583]
75. Lin J, Wu H, Tarr PT, et al. Transcriptional co-activator PGC-1 alpha drives the formation of slow-twitch muscle fibres. *Nature*. 2002; 418:797–801. [PubMed: 12181572]
76. Sandri M, Lin J, Handschin C, et al. PGC-1alpha protects skeletal muscle from atrophy by suppressing FoxO3 action and atrophy-specific gene transcription. *Proc Natl Acad Sci U S A*. 2006; 103:16260–16265. [PubMed: 17053067]
77. McKinsey TA, Zhang CL, Olson EN. MEF2: a calcium-dependent regulator of cell division, differentiation and death. *Trends Biochem Sci*. 2002; 27:40–47. [PubMed: 11796223]
78. Dirks AJ, Hofer T, Marzetti E, et al. Mitochondrial DNA mutations, energy metabolism and apoptosis in aging muscle. *Ageing Res Rev*. 2006; 5:179–195. [PubMed: 16647308]
79. Dirks A, Leeuwenburgh C. Apoptosis in skeletal muscle with aging. *Am J Physiol Regul Integr Comp Physiol*. 2002; 282:R519–R527. [PubMed: 11792662]

80. Dargelos E, Brulé C, Combaret L, et al. Involvement of the calcium-dependent proteolytic system in skeletal muscle aging. *Exp Gerontol.* 2007; 42:1088–1098. [PubMed: 17937979] This paper presents evidence of implication of calpains in sarcopenia.
81. Tisdale MJ. Cachexia in cancer patients. *Nat Rev Cancer.* 2002; 2:862–871. [PubMed: 12415256]
82. Frost RA, Lang CH. Skeletal muscle cytokines: regulation by pathogen-associated molecules and catabolic hormones. *Curr Opin Clin Nutr Metab Care.* 2005; 8:255–263. [PubMed: 15809527]
83. Li YP, Reid MB. Effect of tumor necrosis factor-alpha on skeletal muscle metabolism. *Curr Opin Rheumatol.* 2001; 13:483–487. [PubMed: 11698724]
84. Hasselgren PO, Wray C, Mammen J. Molecular regulation of muscle cachexia: it may be more than the proteasome. *Biochem Biophys Res Commun.* 2002; 290:1–10. [PubMed: 11779124]
85. Coletti D, Yang E, Marazzi G, Sassoon D. TNFalpha inhibits skeletal myogenesis through a PW1-dependent pathway by recruitment of caspase pathways. *EMBO J.* 2002; 21:631–642. [PubMed: 11847111]
86. Schwarzkopf M, Coletti D, Sassoon D, Marazzi G. Muscle cachexia is regulated by a p53-PW1/Peg3-dependent pathway. *Genes Dev.* 2006; 20:3440–3452. [PubMed: 17182869]
87. Dasarathy S, Dodig M, Muc SM, et al. Skeletal muscle atrophy is associated with an increased expression of myostatin and impaired satellite cell function in the portacaval anastomosis rat. *Am J Physiol Gastrointest Liver Physiol.* 2004; 287:G1124–G1130. [PubMed: 15256363]
88. Coletti D, Moresi V, Adamo S, et al. Tumor necrosis factor-alpha gene transfer induces cachexia and inhibits muscle regeneration. *Genesis.* 2005; 43:120–128. [PubMed: 16158413]
89. Acharyya S, Butchbach ME, Sahenk Z, et al. Dystrophin glycoprotein complex dysfunction: a regulatory link between muscular dystrophy and cancer cachexia. *Cancer Cell.* 2005; 8:421–432. [PubMed: 16286249]
90. Durbecq M, Campbell KP. Muscular dystrophies involving the dystrophin-glycoprotein complex: an overview of current mouse models. *Curr Opin Genet Dev.* 2002; 12:349–361. [PubMed: 12076680]
91. Langenbach KJ, Rando TA. Inhibition of dystroglycan binding to laminin disrupts the PI3K/AKT pathway and survival signaling in muscle cells. *Muscle Nerve.* 2002; 26:644–653. [PubMed: 12402286]
92. Gregorevic P, Allen JM, Minami E, et al. rAAV6-microdystrophin preserves muscle function and extends lifespan in severely dystrophic mice. *Nat Med.* 2006; 12:787–789. [PubMed: 16819550]
93. Grozdanovic Z, Gosztonyi G, Gossrau R. Nitric oxide synthase I (NOS-I) is deficient in the sarcolemma of striated muscle fibers in patients with Duchenne muscular dystrophy, suggesting an association with dystrophin. *Acta Histochem.* 1996; 98:61–69. [PubMed: 9054190]
94. Crosbie RH, Barresi R, Campbell KP. Loss of sarcolemma nNOS in sarcoglycan-deficient muscle. *FASEB J.* 2002; 16:1786–1791. [PubMed: 12409321]
95. Mizushima N. Autophagy: process and function. *Genes Dev.* 2007; 21:2861–2873. [PubMed: 18006683] Review describing the process of autophagy and its role in cell metabolism.
96. Mizushima N. The pleiotropic role of autophagy: from protein metabolism to bactericide. *Cell Death Differ.* 2005; 12(Suppl 2):1535–1541. [PubMed: 16247501]
97. Lum JJ, DeBerardinis RJ, Thompson CB. Autophagy in metazoans: cell survival in the land of plenty. *Nat Rev Mol Cell Biol.* 2005; 6:439–448. [PubMed: 15928708]
98. Hesselink RP, Wagenmakers AJ, Drost MR, et al. Lysosomal dysfunction in muscle with special reference to glycogen storage disease type II. *Biochim Biophys Acta.* 2003; 1637:164–170. [PubMed: 12633905]
99. Nishino I, Fu J, Tanji K, et al. Primary LAMP-2 deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease). *Nature.* 2000; 406:906–910. [PubMed: 10972294]
100. Nishino I. Autophagic vacuolar myopathy. *Semin Pediatr Neurol.* 2006; 13:90–95. [PubMed: 17027858]
101. Bechet D, Tassa A, Taillandier D, et al. Lysosomal proteolysis in skeletal muscle. *Int J Biochem Cell Biol.* 2005; 37:2098–2114. [PubMed: 16125113]

- 102•. Sacheck JM, Hyatt JP, Raffaello A, et al. Rapid disuse and denervation atrophy involve transcriptional changes similar to those of muscle wasting during systemic diseases. *FASEB J*. 2007; 21:140–155. [PubMed: 17116744] This paper shows that the atrophy associated with systemic catabolic states and following disuse involves the induction of similar transcription patterns.
- 103•. Juhász G, Puskás LG, Komonyi O, et al. Gene expression profiling identifies FKBP39 as an inhibitor of autophagy in larval *Drosophila* fat body. *Cell Death Differ*. 2007; 14:1181–1190. [PubMed: 17363962] Evidence of the role of FOXO in modulating autophagy in *Drosophila*.
- 104••. Mammucari C, Milan G, Romanello V, et al. FoxO3 controls autophagy in skeletal muscle in vivo. *Cell Metab*. 2007; 6:458–471. [PubMed: 18054315]
- 105••. Zhao J, Brault JJ, Schild A, et al. FoxO3 coordinately activates protein degradation by the autophagic/lysosomal and proteasomal pathways in atrophying muscle cells. *Cell Metab*. 2007; 6:472–483. [PubMed: 18054316] These two papers demonstrate the involvement of autophagy in muscle atrophy, and most importantly, define FOXO as a key mediator of both proteolysis and autophagy.
106. Tatar M, Bartke A, Antebi A. The endocrine regulation of aging by insulin-like signals. *Science*. 2003; 299:1346–1351. [PubMed: 12610294]
107. Murphy CT, McCarroll SA, Bargmann CI, et al. Genes that act downstream of DAF-16 to influence the lifespan of *Caenorhabditis elegans*. *Nature*. 2003; 424:277–283. [PubMed: 12845331]
108. Berdichevsky A, Viswanathan M, Horvitz HR, Guarente L. *C. elegans* SIR-2.1 interacts with 14-3-3 proteins to activate DAF-16 and extend life span. *Cell*. 2006; 125:1165–1177. [PubMed: 16777605]
109. Meléndez A, Tallóczy Z, Seaman M, et al. Autophagy genes are essential for dauer development and life-span extension in *C. elegans*. *Science*. 2003; 301:1387–1391. [PubMed: 12958363]
110. Minucci S, Pelicci PG. Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. *Nat Rev Cancer*. 2006; 1:38–45. [PubMed: 16397526]
111. Steffan JS, Bodai L, Pallos J, et al. Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in *Drosophila*. *Nature*. 2001; 413:739–744. [PubMed: 11607033]
112. Minamiyama M, Katsuno M, Adachi H, et al. Sodium butyrate ameliorates phenotypic expression in a transgenic mouse model of spinal and bulbar muscular atrophy. *Hum Mol Genet*. 2004; 11:1183–1192. [PubMed: 15102712]
- 113•. Elaut G, Rogiers V, Vanhaecke T. The pharmaceutical potential of histone deacetylase inhibitors. *Curr Pharm Des*. 2007; 13:2584–2662. [PubMed: 17897003] Review on the pharmacological relevance of the use of histone deacetylase inhibitors in the treatment of human disorders.
114. Minetti GC, Colussi C, Adami R, et al. Functional and morphological recovery of dystrophic muscles in mice treated with deacetylase inhibitors. *Nat Med*. 2006; 10:1147–1155. [PubMed: 16980968]
115. Iezzi S, Cossu G, Nervi C, et al. Stage-specific modulation of skeletal myogenesis by inhibitors of nuclear deacetylases. *Proc Natl Acad Sci U S A*. 2002; 11:7757–7766. [PubMed: 12032356]
116. Iezzi S, Di Padova M, Serra C, et al. Deacetylase inhibitors increase muscle cell size by promoting myoblast recruitment and fusion through induction of follistatin. *Dev Cell*. 2004; 5:673–684. [PubMed: 15130492]
117. Liu Y, Denlinger CE, Rundall BK, et al. Suberoylanilide hydroxamic acid induces Akt-mediated phosphorylation of p300, which promotes acetylation and transcriptional activation of RelA/p65. *J Biol Chem*. 2006; 281:31359–31368. [PubMed: 16926151]

Figure 1. Pathways involved in different mechanisms of muscle atrophy

Interruption of anabolic pathways that promote protein synthesis and regeneration causes a decrease in muscle growth – a passive form of muscle atrophy. Active–passive muscle atrophy is triggered when the interruption of anabolic pathways releases the negative control on E3 ubiquitin ligase transcription. Direct activation of E3 ubiquitin ligase gene transcription by inflammatory pathways causes an active form of muscle atrophy.

Figure 2. A global network of signaling that coordinates different cellular pathways of skeletal muscles in response to environmental cues

Note that the arrow between FOXO and myostatin refers to the FOXO-responsive elements identified on the myostatin promoter and the FOXO-dependent activation of myostatin transcription. FOXO, forkhead box subtype O; ROS, reactive oxygen species. Modified from [6,105••].

Figure 3. Potential targets of deacetylases inhibitors in the treatment of muscle atrophy
FOXO, forkhead box subtype O.