Muscle performance is influenced by turnover of contractile proteins. Production of new myofibrils and degradation of existing proteins is a delicate balance, which, depending on the condition, can promote muscle growth or loss. Protein synthesis and protein degradation are coordinately regulated by pathways that are influenced by mechanical stress, physical activity, availability of nutrients, and growth factors. Understanding the signaling that regulates muscle mass may provide potential therapeutic targets for the prevention and treatment of muscle wasting in metabolic and neuromuscular diseases.

Cell size is determined by a balance between new protein accumulation and degradation of existing proteins. Genetic studies in both drosophila and mammals have shown that pathways controlling protein synthesis and protein breakdown have an important role to determine cell size. The two processes are tightly regulated and interrelated. The first level of connection occurs during protein synthesis when the quality control of the cell degrades proteins that are not correctly folded. At a further level, protein degradation systems determine the half-life of protein and, in muscle, are required to replace sarcomeric proteins as a consequence of changes in muscle activity. Both systems need ATP, and muscle energy level is one of the cellular check points that decide either to promote growth and hypertrophy or activate protein breakdown and atrophy. Importantly, the proteolytic systems can produce alternative energy substrates that are used by the cell to maintain internal homeostasis in conditions of energy stress. Recent findings provide a new view, which considers the growth-promoting pathways and the proteolytic systems coordinately regulated. The following short review will focus mainly on in vivo studies and will be schematically divided into two parts: the first part will describe pathways controlling muscle hypertrophy, and the second part will be focused on signaling involved in muscle atrophy.

Muscle Hypertrophy

The growth of skeletal muscle mass, like the mass of any other tissue, depends on protein turnover and cell turnover (83). Cellular turnover plays a major role during muscle development in embryos. Moreover, satellite cell incorporation into the growing fibers takes place during postnatal muscle growth (63) concomitantly with increased protein synthesis. The activation of satellite cells is important for maintaining a constant size of each nuclear domain (quantity of cytoplasm/nuclei of nuclei within that cytoplasm). Unlike young muscle, the contribution of cellular turnover to homeostasis of adult fibers is minor, and its role in hypertrophy has even been recently debated (56, 73). In adult muscle, the physiological conditions promoting muscle growth, therefore, do so mainly by increasing protein synthesis and decreasing protein degradation. However, satellite cells are activated in compensatory hypertrophy (65, 85), and addition of new nuclei to the growing fiber seems to be required for extreme hypertrophy. The pathways controlling cellular and protein turnover are different, and their contribution to muscle hypertrophy has to be considered during the interpretation of data resulting from studies with transgenic animals. Loss- and gain-of-function studies in which the transgene is perturbed early during postnatal growth might affect cellular turnover significantly more than protein synthesis. Results could be completely different if the same pathway is acutely perturbed in adult muscle age when the role of protein turnover is dominant (Figure 1).

IGF1-AKT signaling and the control of muscle growth

IGF1. IGF1 is among the best characterized muscle growth-promoting factors. In addition to circulating IGF1, mainly synthesized by the liver under GH control, local production by skeletal muscle of distinct IGF1 splicing products has recently raised considerable interest. A specific IGF1 splice product is important for load- and stretch-induced adaptations in skeletal muscle (25). Increased IGF1 gene expression has been demonstrated following functional overload induced by elimination of synaptic muscles (55). Muscle-specific overexpression in transgenic mice of an IGF1 isoform locally expressed in skeletal muscle results in muscle hypertrophy (60) and, importantly, the growth of muscle mass matches with a physiological increase of muscle strength. Moreover even acute ectopic expression of IGF1 in adult muscles by electroporation is sufficient to promote muscle hypertrophy (6). Although these results suggest an autocrine/paracrine role for local IGF1 in activity-dependent muscle plasticity, direct evidence from transgenic animals, has no been obtained so far. The activity of Akt is controlled through the generation of phosphatidylinositol triphosphates (PI3P) directly (99). Akt activation, which promotes muscle growth and hypertrophy, is selectively observed in the signal transduction pathway of IGF1, whereas Akt2 is not induced in skeletal muscles (79). How Akt2, which is specific for PI3P, contributes to muscle hypertrophy remains to be determined (99).

Exercise in vivo also results in muscle growth in the absence of IGF1 (56). The exercise-induced increase of Akt activity regulates the growth-promoting signaling pathways, as demonstrated by the negative impact of Akt inhibition on the improvement of performance (99). In small animals, muscle hypertrophy induced by exercise is specifically associated with Akt activation (56, 73). In adult muscle, the physiological conditions promoting muscle growth, therefore, do so mainly by increasing protein synthesis and decreasing protein degradation. However, satellite cells are activated in compensatory hypertrophy (65, 85), and addition of new nuclei to the growing fiber seems to be required for extreme hypertrophy. The pathways controlling cellular and protein turnover are different, and their contribution to muscle hypertrophy has to be considered during the interpretation of data resulting from studies with transgenic animals. Loss- and gain-of-function studies in which the transgene is perturbed early during postnatal growth might affect cellular turnover significantly more than protein synthesis. Results could be completely different if the same pathway is acutely perturbed in adult muscle age when the role of protein turnover is dominant (Figure 1).

IGF1-AKT signaling and the control of muscle growth

IGF1. IGF1 is among the best characterized muscle growth-promoting factors. In addition to circulating IGF1, mainly synthesized by the liver under GH control, local production by skeletal muscle of distinct IGF1 splicing products has recently raised considerable interest. A specific IGF1 splice product is important for load- and stretch-induced adaptations in skeletal muscle (25). Increased IGF1 gene expression has been demonstrated following functional overload induced by elimination of synaptic muscles (55). Muscle-specific overexpression in transgenic mice of an IGF1 isoform locally expressed in skeletal muscle results in muscle hypertrophy (60) and, importantly, the growth of muscle mass matches with a physiological increase of muscle strength. Moreover even acute ectopic expression of IGF1 in adult muscles by electroporation is sufficient to promote muscle hypertrophy (6). Although these results suggest an autocrine/paracrine role for local IGF1 in activity-dependent muscle plasticity,
Akt activation is induced by IGF1 and insulin through the generation of phosphatidylinositol-3,4,5-triphosphates produced by PDK1, which is opposed by the activity of the phosphatase PTEN and SHIP2. Phosphatidylinositol-3,4,5-triphosphates recruit Akt to the plasma membrane by binding to its NH2-terminal pleckstrin homology domain. At the membrane, Akt is phosphorylated on separate residues by at least two distinct kinases, PDK1 and the mTOR-Rictor complex. The role of Akt in muscle growth was first suggested by the finding that an active Ras double mutant (RasV12C40) that selectively activates the Akt pathway through the phosphatidylinositol 3 kinase (PI3K) promotes muscle growth, thus opening new perspectives in the signaling of fiber size (67) (FIGURE 2). This observation was subsequently confirmed by overexpressing a constitutively active form of Akt in adult skeletal muscle (10, 72). Similar results were obtained by the generation of conditional transgenic mice in which Akt is expressed in adult skeletal muscles only after tamoxifen (41) or tetracycline (37) treatment.

In mammals, there are three Akt genes, Akt1 (PKBα), Akt2 (PKBβ), and Akt3 (PKBγ), which appear to have distinct functions. In skeletal muscle, Akt1 and Akt2 are expressed at higher levels compared with Akt3, which is mainly expressed in the brain. Targeted deletion experiments have shown that Akt1-null mice display growth retardation and muscle atrophy, whereas Akt2-null mice differ from a Type 2 diabetes-like syndrome, and Akt3-null mice have impaired brain development (111).

Exercise in vivo is associated with activation of Akt1 but not Akt2 and Akt3 kinases in contracting muscles (98). Akt activity is increased in the rat plantaris after functional overload induced by elimination of synergistic muscles (10). Subsequent studies both in rats and humans confirmed that Akt activity is increased in response to muscle contractile activity (69, 78–80). Surprisingly, this effect was observed only in the fast EDL but not in the slow soleus muscle (78, 79). The finding that passive stretch of the fast rat EDL muscle can also induce Akt activation has suggested that mechanical tension may be a part of the mechanism by which contraction activates Akt in fast-twitch muscles (79). However, it remains to be established how mechanical stress is converted to Akt activation. Akt activity is also increased in response to hormonal and growth factor stimulation, in particular insulin is known to activate Akt2, whereas IGF1 activates primarily Akt1. Taken together with other observations, these results suggest that Akt1 is a major mediator of skeletal muscle hypertrophy. Although it has been established that Akt plays a crucial role in muscle growth, the downstream targets involved in muscle hypertrophy remain to be defined.

FIGURE 1
Schematic description of spectrum of developmental stages and the different contribution of cellular turnover and protein turnover to muscle growth
The principal pathways controlling cell and protein turnover are schematically depicted.
protein Rheb that in turn activates mTOR in complex with the raptor adapter protein (mTOR-raptor or TORC1). Transgenic mice overexpressing TSC1 specifically in skeletal muscle show a defect in muscle growth (103).

**S6K1.** mTOR is part of two multiprotein complexes: mTORC1, which contains raptor and is rapamycin sensitive, is required for signaling to S6K and 4E-BP1, whereas mTORC2, which contains rictor, is required for signaling to Akt-FoxO (FIGURE 2). The effect of mTOR on the translation machinery and protein synthesis is mediated by TORC1-dependent phosphorylation of the ribosomal protein S6 kinases (S6K1 and 2) and of 4E-BP1, a repressor of the cap-binding protein eIF4E. S6K1 appears to be an important effector of the Akt pathway, since muscle fibers are smaller in S6K1-null mice, and their hypertrophic response to IGF1 and to activated Akt is blunted (71). However S6K1 knockout mice show no impairment in polysome formation, in protein synthesis, and in protein degradation (60). TORC1 complex also negatively regulates the IGF1 pathway via S6K1 (4, 100). Thus the two mTOR complexes, mTORC1 and mTORC2, may have opposite effects on Akt activity: TORC1 negatively regulates IGF1 signaling, whereas TORC2 enhances Akt activity (FIGURE 2). An additional factor that complicates the pathway is that long-term rapamycin treatment in vitro can inhibit not only TORC1 but also the mTORC2 complex and thus potentially affect, in some cell types, the Akt-FoxO signaling. This raises the possibility that, under certain circumstances, rapamycin may induce transcriptional regulation not through a direct effect, e.g., by blocking mTOR phosphorylation of downstream targets, but through an indirect transcriptional effect by inhibiting Akt and thus derepressing FoxO. It is therefore suggested that FoxO activity/localization should always be monitored in studies involving rapamycin treatment (44).

**Myostatin and the cellular turnover**

Myostatin, a member of the TGF-β family, is expressed and secreted predominantly by skeletal muscle and functions as a negative regulator of muscle growth. Mutations of the myostatin gene lead to a hypertrophic phenotype in mice, sheep, and cattle, and a loss-of-function mutation in the human myostatin gene was also found to induce increased muscle mass (14, 47, 59, 87). The increase in muscle mass is a consequence of hyperplasia, which is an increase in cell number, and hypertrophy, which is an increase in cell size. The hyperplasia suggests an activation of muscle stem cells, and, in fact, the myostatin pathway influences Pax 7, MyoD, and myogenin expression inhibiting satellite cell activation and differentiation (36, 57, 58). Only a few studies explore the effect of myostatin inhibition in adult muscle. Treating 24-wk-old mice with an anti-myostatin antibody for 5 wk induces a 12% increase in muscle mass (109). Furthermore, when tamoxifen-inducible Cre recombinase mice (108), next 3 mo mass, the specific proteins in these two studies and conduct studies and confirm these two rounds of regeneration.}

**Beta adrenergic signal transduction**

Among the hormones that control muscle protein Rheb that in turn activates mTOR in complex with the raptor adapter protein (mTOR-raptor or TORC1). Transgenic mice overexpressing TSC1 specifically in skeletal muscle show a defect in muscle growth (103).

**S6K1.** mTOR is part of two multiprotein complexes: mTORC1, which contains raptor and is rapamycin sensitive, is required for signaling to S6K and 4E-BP1, whereas mTORC2, which contains rictor, is required for signaling to Akt-FoxO (FIGURE 2). The effect of mTOR on the translation machinery and protein synthesis is mediated by TORC1-dependent phosphorylation of the ribosomal protein S6 kinases (S6K1 and 2) and of 4E-BP1, a repressor of the cap-binding protein eIF4E. S6K1 appears to be an important effector of the Akt pathway, since muscle fibers are smaller in S6K1-null mice, and their hypertrophic response to IGF1 and to activated Akt is blunted (71). However S6K1 knockout mice show no impairment in polysome formation, in protein synthesis, and in protein degradation (60). TORC1 complex also negatively regulates the IGF1 pathway via S6K1 (4, 100). Thus the two mTOR complexes, mTORC1 and mTORC2, may have opposite effects on Akt activity: TORC1 negatively regulates IGF1 signaling, whereas TORC2 enhances Akt activity (FIGURE 2). An additional factor that complicates the pathway is that long-term rapamycin treatment in vitro can inhibit not only TORC1 but also the mTORC2 complex and thus potentially affect, in some cell types, the Akt-FoxO signaling. This raises the possibility that, under certain circumstances, rapamycin may induce transcriptional regulation not through a direct effect, e.g., by blocking mTOR phosphorylation of downstream targets, but through an indirect transcriptional effect by inhibiting Akt and thus derepressing FoxO. It is therefore suggested that FoxO activity/localization should always be monitored in studies involving rapamycin treatment (44).

**Myostatin and the cellular turnover**

Myostatin, a member of the TGF-β family, is expressed and secreted predominantly by skeletal muscle and functions as a negative regulator of muscle growth. Mutations of the myostatin gene lead to a hypertrophic phenotype in mice, sheep, and cattle, and a loss-of-function mutation in the human myostatin gene was also found to induce increased muscle mass (14, 47, 59, 87). The increase in muscle mass is a consequence of hyperplasia, which is an increase in cell number, and hypertrophy, which is an increase in cell size. The hyperplasia suggests an activation of muscle stem cells, and, in fact, the myostatin pathway influences Pax 7, MyoD, and myogenin expression inhibiting satellite cell activation and differentiation (36, 57, 58). Only a few studies explore the effect of myostatin inhibition in adult muscle. Treating 24-wk-old mice with an anti-myostatin antibody for 5 wk induces a 12% increase in muscle mass (109). Furthermore, when tamoxifen-inducible Cre recombinase mice (108), next 3 mo mass, the specific proteins in these two studies and conduct studies and confirm these two rounds of regeneration.}
recombinase removes the floxed myostatin gene in 4-mo-old mice, muscle mass increases 25% during the next 3 mo (108). However, despite the effect on muscle mass, the specific muscle force has not been measured in these two studies. Overexpression of follistatin, an inhibitor of myostatin (47), promotes a great increase in muscle size. Interestingly, mice resulting from follistatin transgenic and myostatin knockout mice show tremendous increases in muscle mass supporting the concept that other myostatin-like molecules are present and relevant for muscle growth (46). There are few studies and conflicting results on the effect of exercise on myostatin gene expression in skeletal muscle (15). Furthermore, the increase of muscle mass of myostatin-null mice does not correlate with an increase in muscle force (7). Ultrastructural observations reveal an accumulation of tubular aggregates in type IIB fibers. This evidence is also supported by the decrease in specific force generation of hyperthyroidic ski transgenic mice (12). Ski negatively regulates Smad phosphorylation, thereby inhibiting signaling of TGF-β-like factors, such as myostatin. These findings contrast with muscle-specific overexpression of insulin-like growth factor 1, where fiber hypertrophy is accompanied by increased maximum force generation and maintained specific force levels. Myostatin binds to activin receptor IIB (48), a type II TGF-β receptor, and muscle hypertrophy is induced in transgenic mice expressing a truncated and inactive activin receptor (ActRIIB) (47). The downstream targets of the myostatin pathway and their role in protein synthesis as well as protein degradation (see below) are still to be determined. However, myostatin inhibition is beneficial for maintaining muscle mass in animal models of Duchenne muscular dystrophy in which the contribution of satellite cells to regeneration is important (61, 102).

Beta adrenergic and mechanical sensors

Among the hormonal responses increased by exercise, the acute elevations in catecholamines are especially interesting with respect to changes in muscle phenotype. Beta-agonists such as clenbuterol, acting through β2 adrenoreceptors, are known to cause muscle hypertrophy and a slow-to-fast fiber-type switch. Interestingly, some effects of catecholamines could be mediated by local production of IGF-I and IGF-II by skeletal muscle (8, 90). Indeed the growth effect of beta-agonists is, at least partially, mediated by AKT-mTOR pathway since rapamycin almost completely blunted the hypertrophic effects of clenbuterol (40). Activation of AKT pathway has not been explored in contracting muscle. An attractive emerging concept in muscle biology is that signals dependent on muscle activity, and specifically on mechanical load, may arise in the sarcomere, the basic unit of the contractile machinery of striated muscles, and from there transmitted to the nucleus to affect gene expression (43). The giant elastic protein titin, which spans half the sarcomere extending from the Z disk to the M band and interacts with a large number of muscle proteins, provides an exciting example of a sarcomeric activity-dependent signaling complex (signalosomes) (42). A unique property of titin is the presence in the M-band region of a serine/threonine kinase domain that can be induced to acquire an open active conformation by stretch and contraction (28). In active muscle cells, the titin kinase domain (TK) is linked through two zinc-finger scaffolding proteins, nhr1 and p60, to a member of the muscle-specific RING-finger proteins, MURF2 (43). In the absence of mechanical activity, the signalosome is dissociated, and MURF2 translocates to the nucleus where it can interact with the serum response transcription factor SRE, leading to nuclear export of SRE and loss of SRE-dependent gene expression. This pathway may thus control muscle growth because SRE is known to regulate muscle gene expression, and conditional deletion of the SRE gene causes severe skeletal muscle hypoplasia during the perinatal period (51). SRE regulates muscle gene expression by binding serum response elements (SRE) in target genes and seems to integrate different growth promoting pathways: for example, SRE is a target of Akt signaling in Hela cells (107) and can recruit the androgen receptor to muscle gene promoters (101). The titin kinase-SRF pathway described above is probably just one of several links between the sarcomere and the nucleus that are only now beginning to emerge (43).

Muscle Atrophy

Atrophy is a decrease in cell size mainly caused by loss of organelles, cytoplasm, and proteins. This concept is important when a genetic approach is used to dissect the contribution of certain pathways to muscle loss. As mentioned above, the mass of a tissue is controlled by cellular turnover and protein turnover (FIGURES 1 AND 2). Genetic modifications that interfere with embryonic and postnatal growth result in smaller muscles in adults. This reduction in muscle size is caused by failure/inhibition of growth and not by a real atrophy process. Keeping in mind the above definition, another important concept is that protein turnover is dominant over cellular turnover during acute phases of muscle wasting when sarcomeric proteins are rapidly lost such as during fasting, disease, and denervation. Evidence that blocking satellite cells is sufficient to trigger muscle atrophy in adult muscle has never been determined. Furthermore, myonuclei are normally reduced during muscle atrophy to keep rather constant the size of the nuclear domain (16, 22). Thus the current understanding suggests that inhibiting cellular turnover would not influence protein
breakdown and muscle weakness and would not affect nuclear domain maintenance, but it might be important for the replacement of damaged myofibers or myonuclei. The importance of cellular turnover for long-term muscle atrophy, e.g., long-term denervation, has yet to be addressed.

**Atrophy: an active process that requires transcriptional regulation**

A major contribution in understanding muscle atrophy comes from the pioneering studies on gene expression profiling performed independently by group members Goldberg and Glass (9, 26). The idea to compare gene expression in different models of muscle atrophy leads to the identification of a subset of genes that are commonly up- or downregulated in atrophying muscle. Since all the diseases used for the experiments of microarray (i.e., diabetes, cancer cachexia, chronic renal failure, fasting, and denervation) have muscle atrophy in common, the commonly up or down genes are believed to regulate the loss of muscle components and are called atrophy-related genes or atrogens (76).

Together, these findings indicate that muscle atrophy is an active process controlled by specific signaling pathways and transcriptional programs. Furthermore, the two most induced genes are two novel muscle-specific ubiquitin ligases, atrogin-1/MAFbx and MuRF1, that are upregulated in different models of muscle atrophy and are responsible for the increased protein degradation through the ubiquitin-proteasome system (9, 26).

In fact, knockout mice for either atrogin-1/MAFbx or MuRF1 are partially resistant to denervation atrophy (9). Importantly, recent findings suggest that myostatin, a member of TGF-β superfamily that inhibits myogenesis, is able to suppress protein breakdown in muscle and is resistant to muscle atrophy in common, the commonly up or down genes are believed to regulate the loss of muscle components and are called atrophy-related genes or atrogens (76).

**IGF1-AKT-FoxO signaling**

A subsequent crucial step was the identification of the signaling pathways that regulate the expression of the two muscle-specific ubiquitin ligases. Previous studies have shown that IGF1-insulin signaling, while promoting muscle growth, is able to suppress protein breakdown (77). Furthermore, IGFBP transgenic mice are resistant to muscle atrophy induced either by atrophy-related genes such as atrogin-1 (58) and MuRF1, but not atrophy-related genes such as IGF1/insulin signaling, while promoting muscle growth, is able to suppress protein breakdown in muscle and is resistant to muscle atrophy in common, the commonly up or down genes are believed to regulate the loss of muscle components and are called atrophy-related genes or atrogens (76).

**Inflammatory cytokines and NF-κB signaling**

The NF-κB transcription factors, which play a major role as mediators of immunity and inflammation, are also expressed in skeletal muscle and appear to mediate the effect of inflammatory cytokines, in particular TNF-α, on muscle wasting and catabolism. In the inactive state, NF-κB is sequestered in the cytoplasm by a family of inhibitory proteins called IkB. In response to TNF-α, the IkB kinase (IKK) complex phosphorylates IkB, resulting in its ubiquitination and proteasomal degradation; this leads to nuclear translocation of NF-κB and activation of NF-κB-mediated gene transcription. Muscle-specific overexpression of IKKα in transgenic mice leads to severe muscle wasting mediated, at least in part, by the ubiquitin-ligase MuRF1, but not by MuRF2. The NF-κB-mediated inflammatory response is activated in different diseases and stresses, such as diabetes, cancer cachexia, chronic renal failure, fasting, and denervation. A subsequent crucial step was the identification of the signaling pathways that regulate the expression of the two muscle-specific ubiquitin ligases. Previous studies have shown that IGF1-insulin signaling, while promoting muscle growth, is able to suppress protein breakdown in muscle and is resistant to muscle atrophy in common, the commonly up or down genes are believed to regulate the loss of muscle components and are called atrophy-related genes or atrogens (76).

**Myostatin: a downstream mediator of muscle atrophy**

Despite the high expression of myostatin in the skeletal muscle of healthy and diseased animals, the physiological role of myostatin in muscle wasting still remains to be elucidated. Myostatin expression and serum myostatin levels are increased in many chronic diseases, such as cancer cachexia, diabetes, and chronic renal failure. In fact, a significant increase in serum myostatin levels has been observed in cancer patients, and animals with myostatin gene deletion have increased muscle mass. Moreover, myostatin knockout mice have increased muscle mass and reduced muscle atrophy in response to denervation and other catabolic stimuli. The overexpression of myostatin in mice results in severe muscle wasting and atrophy, whereas the deletion of myostatin leads to increased muscle mass and reduced muscle atrophy. The exact mechanism by which myostatin regulates muscle mass and atrophy remains to be elucidated.

**Conclusion**

In summary, muscle atrophy is an active process that requires transcriptional regulation. The identification of atrophy-related genes and the role of specific signaling pathways, such as IGF1-AKT-FoxO and NF-κB, have provided valuable insights into the molecular mechanisms underlying muscle wasting. Further research is needed to understand the complex interplay between these pathways and to develop effective strategies for the prevention and treatment of muscle wasting.
Muscle atrophy and muscle wasting are hallmarks of multiple chronic conditions, including denervation atrophy, muscle wasting associated with Duchenne muscular dystrophy, and muscle atrophy resulting from aging, sepsis, or cancer cachexia. 

Muscle atrophy results from a decreased balance between protein synthesis and breakdown. This is generally due to a decreased activity of Akt signaling, which is mediated by the phosphatidylinositol 3-kinase (PI3K)/Akt pathway. Akt is a serine/threonine kinase that is crucial for muscle growth and survival. It phosphorylates and activates multiple downstream targets, including the translational activator 4E-BP1, the stress-activated protein kinase/mammalian target of rapamycin (S6K1), and FoxO transcription factors. 

In the absence of Akt signaling, muscle atrophy occurs through the activation of the FoxO transcription factors, which leads to the upregulation of atrogenes (atrogin-1/MAFbx and MuRF1). These atrogenes promote protein breakdown in muscle tissues. The upregulation of atrogenes is mediated by the Akt-dependent inactivation of FoxO, which is achieved through a series of post-translational modifications, including phosphorylation, ubiquitination, and proteasomal degradation. 

Akt pathway activity is crucial for muscle mass maintenance. Mice with Akt deficiency display muscle atrophy and a reduced ability to compensate for muscle loss. Conversely, Akt activation through genetic or pharmacological means results in muscle hypertrophy and increased muscle mass. 

Research has shown that Akt inhibition can result in muscle atrophy, and Akt activation can prevent muscle atrophy. The Akt pathway plays a critical role in muscle regeneration and repair, as Akt inhibition has been shown to inhibit muscle regeneration in models of muscle injury. 

The Akt pathway is regulated by multiple upstream signals, including insulin, growth factors, and the AMP-activated protein kinase (AMPK). AMPK activation can inhibit Akt through phosphorylation, leading to muscle atrophy. Conversely, Akt activation can inhibit AMPK through PKBα-dependent inhibition of the glycogen synthase kinase 3 (GSK3). This cross-talk between the Akt and AMPK pathways is crucial for muscle mass maintenance. 

In summary, the Akt pathway is a key regulator of muscle mass, and its deregulation can lead to muscle atrophy. Understanding the mechanisms by which Akt signaling is regulated and its role in muscle mass maintenance is essential for the development of therapeutic strategies to prevent muscle atrophy in conditions such as muscular dystrophy, denervation atrophy, and cancer cachexia. 

References: 
induction is still unclear, but recent evidence suggests that the autophagy-lysosome system is activated during atrophy. Mizushima et al. (62) generated transgenic mice expressing LC3 fused with GFP. LC3 is the mammalian homolog of Atg8 gene and is critical for membrane commitment and growth to engulf organelles, cytoplasm, glycogen, and protein aggregates. Morphological analyses documented the activation of the autophagy system during fasting in skeletal muscle (62). Indeed, muscle cell culture confirmed that the autophagy-lysosome system is the major proteolytic pathway implicated in nutrient-dependent proteolysis (63). Further experiments lend insight into the signaling pathways involved and identified an mTOR-independent but PI3KIII-beclin-dependent control of the autophagic system in myotubes (96). Furthermore, electron microscopic and biochemical studies have shown that autophagy is activated also in denervation atrophy (24, 86). However, denervation-induced atrophy shows a slower pace of autophagy when compared with fasted-mediating atrophy. This effect is mediated by Runx1, which is upregulated during denervation and is required to preserve muscle mass. Lack of Runx1 resulted in myofibrillar disorganization and excessive autophagy in denervated muscles (105). Runx1 knockout mice show double-or triple-headed sarcomeres, which disrupt the sarcomere and actin-cytoskeleton (49). Furthermore, Runx1 is essential for the catabolic events that lead to muscle atrophy. It is known that the dystrophin-glycoprotein complex (DGC) is required for muscle integrity and that its disruption induces muscle degeneration (111). Within the DGC, titin, myotilin, nebulin, and dystrophin act as molecular bridges that connect the cytoskeleton to the contractile filaments and therefore are crucial for the maintenance of muscle integrity (4). Within the sarcomere, dystrophin disrupts actin cleavage and XIAP overexpression promotes myofibrillogenesis and ATP production in denervated muscle (117). XIAP overexpression confers resistance to TNFα-mediated muscle wasting (117). Although the role of XIAP in the dystrophin-glycoprotein complex (DGC) is still unclear, current evidence suggests that XIAP overexpression is critical for muscle regeneration (117). The dystrophin-glycoprotein complex (DGC) is required for muscle integrity and function. However, the contribution of the autophagy-lysosome system to dystrophinopathies remains to be investigated.
muscles are protected from the atrophy induced by denerervation, fasting, or expression of FoxO3 (81). Treatment with statins induces FoxO3-mediated atrogin-1 activation and related muscle alterations. In cell culture and in zebrafish, statins cause muscle atrophy, disorganization of myofibrils, and mitochondrial dysfunctions (31). These changes are completely aborted by either the deletion of atrogin-1 or by PGC-1α overexpression. These results may explain why oxidative fibers tend to be resistant to atrophy compared with glycolytic fibers and suggest that metabolic changes are crucial for muscle atrophy (50). Among the different energy-dependent pathways, AMPK acts as the cellular sensor of energy balance. Indeed, stressing energy in muscle cell culture either by oligomycin treatment or by replacing glucose with 2-deoxyglucose triggers myotube atrophy (4). Interestingly, increased levels of AMPK activation of AMPK, lipid consumption, and smaller muscles have all been observed in S6K1 and S6K2 knockout mice. Importantly, AMPK inhibition rescues skeletal muscle growth in these mice, confirming that S6K1/2 deletion alters energy balance (4) and suggesting that AMPK activity is a key factor for myotube size. Interestingly, these mice show normal methionine incorporation and polysomal profiles as well as autophagy and upregulation of atrogin-1/MAFbx and MuRF1 (60). Altogether, these findings describe a connection between AMPK and FoxO3. AMPK phosphorylates several AKT-independent sites of FoxO3, stimulating its transcriptional activity on target genes (29, 30). Indeed, treating muscle cell culture with AICAR, an activator of AMPK, causes an increase of protein breakdown and atrogin-1/MAFbx expression via the FoxO3 family (70). The physiological relevance of such important control over protein breakdown and muscle atrophy in vivo remains to be explored.

Within the myotube, mitochondria are crucial in regulating metabolism and might be a potential source of catalytic signals. Insulin resistance and diabetes have been reported to trigger caspase-3-mediated actin cleavage, which would release myofibrils from the sarcomere for subsequent degradation via the prosome (20). Caspase-3 activation is mediated by Bax, which disrupts the mitochondrial external membrane, causing cytochrome-c release and apoptosis formation (49). Furthermore, inhibition of caspases by XIAP overexpression protects adult skeletal muscle from atrophy in an animal model of diabetes (106). However, the contribution of caspases to muscle atrophy should be further investigated using loss of function approaches.

**Mechanical sensor of inactivity**

The dystrophin glycoprotein complex (DGC) anchors the muscle cytoskeleton to the cell membrane via dystrophin and its binding partners. This complex is important for correct transduction of myosin movements on actin to the extracellular matrix. Indeed, lack of dystrophin exacerbates mechanical stress on the myotube plasma membrane, causing muscle damage and degeneration. This classical view considers a purely structural function of DGC proteins. However, an attractive role of dystrophin in transduction of mechanical signals to the nucleus has recently been proposed. In fact, dystrophin is lost from the cell membrane under atrophic conditions, causing a loss of continuity between the cell membrane of the myotube and the extracellular matrix (1). This decreased interaction between membrane and matrix is required for muscle loss since forced dystrophin expression in transgenic mice counteracts both cachexia-induced muscle wasting and upregulation of atrogin-1/MAFbx and MuRF1. Further support for the DGC acting as a mechanical sensor has recently been published. Neuronal NOS (nNOS) is normally bound to the DGC, but when the DGC is disrupted, as occurs in dystrophic muscle, its localization is disturbed and it is no longer at the sarcolemma. A similar nNOS dysregulation has recently been described during disuse-induced muscle atrophy. Free nNOS dissociates to the cytoplasm where it enhances FoxO3-mediated transcription and upregulation of atrogin-1 and MuRF1 (95). Interestingly, the NF-κB pathway is not involved in nNOS-mediated muscle atrophy (95). Since nNOS generates NO, an important player in protein nitrosylation and in reactive oxygen species generation, the role of oxidative stress in muscle atrophy is an important aspect to be analyzed in future studies.

**Glucocorticoids-induced muscle atrophy**

Glucocorticoids are elevated in many pathological conditions associated with muscle loss. Moreover glucocorticoid treatment induces atrogin-1 and MuRF1 expression and muscle wasting both in cell culture and in vivo (10, 13, 77, 82, 84). Importantly, adrenalectomy or treatment with a glucocorticoid receptor antagonist (RU-486) attenuates muscle loss in some diseases (84). However, the mechanisms of glucocorticoid-mediated muscle atrophy are unclear. In fact, none of the atrophy-related genes have been found to be directly regulated by glucocorticoids, and no glucocorticoid response elements on atrogenes promoters have been identified as critical for their expression (45). Thus most of the glucocorticoid effects are indirect, mainly affecting pathways previously described to be crucial for muscle growth or loss. Glucocorticoids are reported to decrease IGF1 production and increase myostatin secretion. Other effects like downregulation of the anabolic transcription factor ATF4, activation of p38β/ERK, or upregulation of REE3D1, an inhibitor of mTORC signaling, are described, but no obvious mechanism can explain the...
direct involvement of corticosteroids in regulation of atrophy-related genes [3, 84, 104, 110]. Even less clear is the recent description of deamethasone-dependent
• MutZ and M1 degradation by NUF, terminal ubiqui-
tinilation pathway, especially if we consider that
MyoD is described to be atrogin-1 substrate (94, 95). The recent description of dexamethasone-dependent
function experiments on glucocorticoid receptor
muscle protein breakdown is unclear. Loss and gain of
MyoD is described to be atrogin-1 substrate (94, 95).

Conclusions
Over the last few years, the mechanisms controlling muscle loss have attracted the attention of the scientif-
ic community due to their relevance in various fields of
study such as aging, prognosis of many diseases, quality
of life, and sports medicine. From the recent findings,
this new scenario emerges that considers the
size of the myofiber and muscle performance a result
findings, a new scenario emerges that considers the
community, setting the base for future studies, which
should enable us to identify new therapeutic targets
and drugs.

The critical reading of Kenneth Day is gratefully acknowledged. I apologize to colleagues whose works were not cited owing to space limitations.

Our work is supported by grants from ASI (OSMA proj-
et), Telethon-Italy (TFC04009), and Compagnia San Ga-
lorenzo.

References
tion: a regulatory link between muscle dystrophy and can-
3. Adams CM. Role of the transcription factor ATF4 in the ana-
bolic actions of insulin and the anti-anabolic actions of gluco-
5. Allen DL, Unterman TG. Regulation of myostatin expression

6. Aligholizadeh MB, Gerrard D, Watkins BA, Hancock K. Ectopic expression of IGF-I and Shh by skeletal muscle inhibits disea-
12. Charge SB, Brack AS, Hughes SM. Aging-related satellite cell proliferation is the recent description of dexamethasone-depend-
dent involvement of corticosteroids in regulation of
muscle protein breakdown is unclear. Loss and gain of
MyoD is described to be atrogin-1 substrate (94, 95).

Conclusions
Over the last few years, the mechanisms controlling muscle loss have attracted the attention of the scientif-
ic community due to their relevance in various fields of
study such as aging, prognosis of many diseases, quality
of life, and sports medicine. From the recent findings,
this new scenario emerges that considers the
size of the myofiber and muscle performance a result
findings, a new scenario emerges that considers the
community, setting the base for future studies, which
should enable us to identify new therapeutic targets
and drugs.

The critical reading of Kenneth Day is gratefully acknowledged. I apologize to colleagues whose works were not cited owing to space limitations.

Our work is supported by grants from ASI (OSMA proj-
et), Telethon-Italy (TFC04009), and Compagnia San Ga-
lorenzo.

References
tion: a regulatory link between muscle dystrophy and can-
3. Adams CM. Role of the transcription factor ATF4 in the ana-
bolic actions of insulin and the anti-anabolic actions of gluco-
...


