Cell

Reversing Cachexia

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Muscle atrophy (cachexia) in cancer patients is a life-threatening condition for which therapeutic options are limited. Zhou et al. (2010) now identify a new target for treating cachexia, the activin type-2 receptor (ActRIIB). In several mouse models of cachexia, the authors reversed wasting of skeletal and cardiac muscle and increased life span by blocking ActRIIB with a decoy receptor.

Wasting of skeletal muscle is common in a number of diseases, including sepsis, severe injury, renal failure, diabetes, and cancer. Muscle atrophy leads to general muscle weakness (asthenia), impairment of normal activities, and eventually death through respiratory failure. Muscle loss is part of the syndrome of cachexia and arises through a combination of hypoanabolism, together with increased catabolism of myofibrillar proteins, particularly myosin. Cachexia affects ~80% of patients with advanced cancers and accounts for ~25% of deaths, but current treatments for muscle atrophy are limited. Many studies show that the ubiquitin-proteasome proteolytic pathway plays a major role in the degradation of muscle proteins during cachexia (Lecker et al., 1999). Expression of two muscle-specific ubiquitin ligases is essential for ubiquitination and subsequent degradation of myofibrillar proteins. These are MuRF1, whose substrates include myosin in muscle and troponin 1 in heart (Clarke et al., 2007), and atrogin-1/MAFbx, which targets the eukaryotic initiation factor 3 subunit 5 that induces expression of muscle structural proteins and boosts muscle growth (hypertrophy) (Lagirand-Cantaloube, et al., 2008). Apoptosis may also be involved in muscle wasting, and depression of protein synthesis and stem cell quiescence are also known to lead to hypoanabolism. In this issue, Zhou et al. (2010) report the identity of a new potential therapeutic target, the activin type-2 receptor (ActRIIB), for treating muscle wasting. They show in several mouse models of cachexia that blocking ActRIIB with a decoy receptor not only counters the wasting process in skeletal muscle and heart but also is associated with increased survival.

A number of factors have been implicated in muscle wasting, including cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and IL-6, and interferon-γ, as well as tumor factors such as proteolysis-inducing factor and glucocorticoids (Tisdale, 2009). Myostatin, a member of the TGF-β superfamily, plays an important role in glucocorticoid-induced muscle atrophy (Gilson et al., 2007). Myostatin is a negative regulator of muscle growth and, together with activin, another member of the TGF-β family, is thought to be responsible for the development of cachexia in mice lacking the hormone inhibin (which antagonizes activin action) (Matzuk et al., 1994). Both myostatin and activin bind to ActRIIB, a high-affinity activin type-2 receptor in muscle, to initiate a signaling cascade leading to increased expression of atrogin-1 and MuRF1 and increased degradation of myofibrillar proteins through the ubiquitin-proteasome pathway (Figure 1).

In the Zhou et al. (2010) study, the authors examined the therapeutic potential of blocking the ActRIIB pathway on muscle wasting and survival by using an ActRIIB decoy receptor (sActRIIB) in several mouse models of cachexia (Figure 1). The results obtained in these models—which included mice transplanted with murine colon-26 carcinoma cells, nude mice transplanted with human G361 melanoma or human TOV-21G ovarian carcinoma xenografts, and inhibin-deficient animals—show that this treatment not only prevents further skeletal muscle wasting, but also restores previous muscle loss, although it had no effect on fat mass. Treatment with the sActRIIB decoy receptor also completely blocked the atrophy of cardiac muscle, without any change in expression of the atrophy-specific ubiquitin ligases, MuRF1 or atrogin-1, or stimulation of stem cell proliferation. There was an increase in the survival time of the treated animals even though tumor growth was not inhibited, reflecting the importance of cachexia, in particular the loss of skeletal muscle, in determining the survival time of cancer patients. Treatment with sActRIIB had no effect on the production of TNF-α, IL-1β, or IL-6, although it stimulated food intake. Treatment attenuated activation of the ubiquitin-proteasome system, decreasing expression of both atrogin-1 and MuRF1, as well as ubiquitin, and increasing levels of myosin. In the muscles of mice lacking inhibin-α, expression of phosphorylated Smad2 is markedly increased above levels in wild-type animals; treatment with sActRIIB completely blocked Smad2 phosphorylation and activation. Smad2 is a transcription factor that stimulates activation of FOXO3a, which is then dephosphorylated and moves to the nucleus, where it induces expression of both atrogin-1 and MuRF1 (Figure 1). Treatment with sActRIIB decreased the total FOXO3a content and increased the amount of phosphorylated FOXO3a in the gastrocnemius muscle of mice lacking inhibin-α, resulting in decreased expression of both atrogin-1 and MuRF1. In addition, sActRIIB markedly stimulated proliferation of muscle satellite stem cells, suggesting that even in severely atrophied muscles, some satellite cells with proliferative potential are present. Thus, muscle wasting is counteracted by administration of the sActRIIB decoy receptor through a decrease in protein degradation together with hypertrophy of the satellite

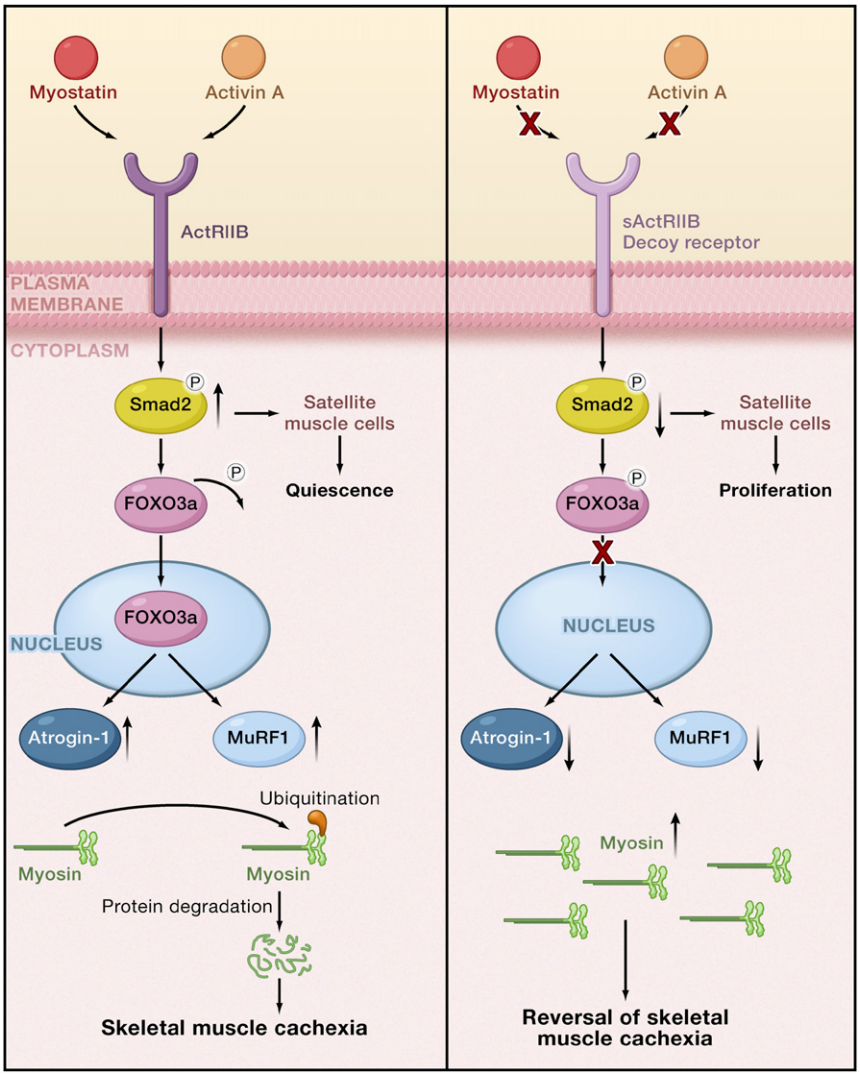

Figure 1. Reversing Muscle Wasting in Mice

Shown is the intracellular signaling pathway activated by the TGF-β ligands myostatin and activin A (left) and the blocking of this pathway by a decoy receptor (right).

(Left) Myostatin and activin A bind to the activin type-2 receptor (ActRIIB), resulting in phosphorylation of Smad2, which dephosphorylates the transcription factor FOXO3a and keeps muscle satellite stem cells quiescent. Dephosphorylated FOXO3a then moves to the nucleus and switches on expression of the muscle-specific ubiquitin ligases MuRF1 and atrogin-1. These ubiquitin ligases stimulate degradation of myofibrillar proteins such as myosin by the ubiquitin-proteasome system, resulting in muscle wasting (cachexia).

(Right) A decoy receptor, sActRIIB, blocks the action of myostatin and activin A, resulting in a decrease in phosphorylated Smad2, an increase in satellite cell proliferation, and a decrease in MuRF1 and atrogin-1. This results in an increase in myosin and production of new muscle, resulting in a reversal of skeletal and cardiac muscle wasting (Zhou et al., 2010).

cell population, leading to the production of new muscle.

This approach—blocking myostatin, activin and other myostatin family proteins—shows more promise than previous attempts to treat muscle wasting. Thus, treatment of mice bearing colon-26 tumor cells with valproic acid, a histone deacetylase inhibitor that increases chromatin compaction and decreases gene expression, decreased myostatin levels and increased expression of follistatin, an inhibitor of myostatin. However, there was no effect on muscle atrophy or expression of the ubiquitin ligases MuRF1 and atrogin-1 (Bonetto et al., 2009). Another study (Benny Klimek et al., 2010), also in the colon-26 mouse model, found that the histone deacetylase inhibitor trichostatin A, which also induces follistatin production, failed to preserve muscle mass. However, it did increase muscle mass in normal mice and in mice with muscular dystrophy. Surprisingly, mice lacking myostatin implanted with the Lewis lung carcinoma lost more muscle mass than did wild-type mice (Benny Klimek et al., 2010), suggesting that a lack of myostatin signaling from early stages of development might make muscle more susceptible to atrophy. Despite these disappointing initial results, administration of the activin receptor extracellular domain/Fc fusion protein (ACVR2B-Fc) profoundly inhibited muscle wasting and protected adipose stores in mice bearing both colon-26 and Lewis lung carcinoma cells (Benny Klimek et al., 2010). These results suggest that blocking ligands of the myostatin family from binding to their receptors is more successful than other approaches. Together with the encouraging results of Zhou et al., these data suggest that this may be a new therapeutic strategy for reversing cachexia-induced muscle wasting and prolonging survival in cancer and other diseases.

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