Molecular Pathways: Cachexia Signaling—A Targeted Approach to Cancer Treatment

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Abstract

Cancer cachexia is a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass, which negatively affects quality of life and portends a poor prognosis. Numerous molecular substrates and mechanisms underlie the dysregulation of skeletal muscle synthesis and degradation observed in cancer cachexia, including proinflammatory cytokines (TNFα, IL1, and IL6), and the NF-kB, IGF1/AKT/mTOR, and myostatin/activin–SMAD pathways. Recent preclinical and clinical studies have demonstrated that anti-cachexia drugs (such as MABp1 and soluble receptor antagonist of myostatin/activin) not only prevent muscle wasting but also may prolong overall survival. In this review, we focus on the significance of cachexia signaling in patients with cancer and highlight promising drugs targeting tumor cachexia in clinical development.

Background

Cancer cachexia is a complex metabolic syndrome characterized by an irreversible loss of skeletal muscle mass, which leads to progressive functional impairment (1). Cachexia is a significant cause of morbidity and mortality, affecting 60% to 80% of patients with cancer, and is particularly common in individuals with pancreatic cancer (2, 3). In addition to functional impairment, cachexia is associated with increased fatigue and emotional distress, all of which considerably compromise quality of life. Moreover, patients with cancer and cachexia are less likely to respond to chemotherapy and radiation and are more likely to endure treatment toxicities (4). Importantly, cachexia may be a direct result of malignancy as well as the chemotherapeutics (e.g., bevacizumab or sorafenib) used to treat it. Sarcopenia, a related but distinct condition, also results in loss of muscle mass but is attributable to aging and inactivity, rather than anorexia, a feature of cachexia marked by decreased energy expenditure and reduced fat accumulation (5). The definition of cachexia has evolved in recent years (1), and much remains to be understood regarding the interplay between cachexia, anorexia, and sarcopenia and how these entities affect cancer development, treatment resistance, and patient outcomes.

Studies evaluating the metabolic alterations inducing cancer cachexia have revealed several tumor-derived cytokines and pathways implicated in skeletal muscle degradation (6) and have led to the development of promising therapies for the prevention of muscle wasting (7). However, advances in this field have been impeded by a lack of consensus regarding the clinical assessment of cancer cachexia as well as the heterogeneity of disease presentation (8). A better understanding of the molecular mechanisms underlying tumor cachexia has the potential to identify novel therapeutic targets and inform the development of successful interventions. In this review, we critically summarize cachexia signaling in patients with cancer and highlight recent preclinical and clinical advances in the management of this paraneoplastic syndrome.

Cachexia pathways in muscle tissue

Cancer cachexia ultimately results from an imbalance in the regulation of muscle protein synthesis and degradation. Such muscle wasting is orchestrated by extracellular ligands which activate several intersecting intracellular signaling pathways (Fig. 1). In particular, proinflammatory cytokines derived from immune or tumor cells, including TNFα, IL1, and IL6, have been shown to trigger muscle wasting through activation of NF-kB and JAK/STAT pathways, respectively. Accumulating evidence also suggests that the IGF1 pathway induces skeletal myogenesis, while myostatin and activin serve as negative regulators of IGF1 signaling to inhibit muscle growth and promote degradation. Other major skeletal muscle proteolytic pathways include the ubiquitin/proteasome system (UPS), as well as the autophagy/lysosomal, calpain, and the caspase pathways (9–11). The UPS has received the most attention, through which the ubiquitin E3 ligases, muscle ring finger protein 1 (MuRF-1), and atrophy gene 1/muscle atrophy F-box (Atrogin-1/MAFbx), act as the two main regulators of muscle protein breakdown.

Cytokines activate protein degradation in cancer cachexia

Multiple cytokines, including TNFα, IL1, and IL6, have been implicated in facilitating a cachectic state (12), and their expression or upregulation is prompted by both tumor- and host-derived factors. High serum levels of these cytokines are present in many patients with cancer with cachexia.

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doi: 10.1158/1078-0432.CCR-16-0495

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Figure 1.
Cachexia signaling regulating protein synthesis and degradation in muscle and anti-cachexia drugs in development. IGF1/Akt/mTOR signaling: Binding of IGF1 to IGF1R results in phosphorylation of the insulin receptor substrate (IRS). IRS activates PI3K/Akt signaling, which then stimulates protein synthesis by activating mTOR. mTOR activates the ribosomal S6K and eukaryotic initiation factor 4E-BP-1, leading to protein synthesis. Akt also phosphorylates and inhibits FoxOs, which is a negative regulator of myogenesis. Myostatin/activin signaling: Myostatin/activin binds to type II receptor (ActRIIB) and induces its dimerization with the activin type I receptor. Subsequent phosphorylation of Smad2/3 recruits Smad4. The Smad complex is translocated into the nucleus to induce transcriptional changes, which result in muscle wasting. Simultaneously, myostatin/activin reduces Akt activity and suppresses FoxO phosphorylation. Dephosphorylated FoxOs are translocated into the nucleus and induce the transcription of target genes, which regulate the ubiquitin/proteasome and autophagy/lysosome systems. IL6 signaling: The binding of IL6 to its receptors induces homodimerization of gp130 and its complex, which activate JAK/STAT3 signaling. Phosphorylated STAT3 forms a dimer and translocates into the nucleus, leading to increased protein degradation. TNFα and IL1 signaling: Binding of TNFα or IL1 to its receptor activates the IKK complex, which phosphorylates IkBa proteins. This signal-induced phosphorylation targets IkBa for polyubiquitination and subsequent degradation by the proteasome, thereby allowing the RelB/p52 complex to translocate to the nucleus to transcribe respective target genes.
TNFα has long been recognized as a mediator of cancer cachexia. Its administration leads to increased protein degradation in cultured muscle cells (13) and in rat muscle (14). In murine models, TNFα and recombinant IL1 act synergistically to reduce muscle protein content (15). Mechanistically, these cytokines increase NF-κB–mediated transcription and subsequent ubiquitination and proteasomal degradation of the NF-κB heterodimers, acting in concert with the ubiquitination and proteolysis associated with higher levels of conjugated ubiquitin (28). FoxO proteins are transcriptional regulators of autophagy, which promote protein ubiquitination and degradation in muscle cells. Myostatin and activin suppress Akt growth, leading to inhibition of FoxO3 (29, 30) and subsequent upregulation of MuRF1–1, Atrogin-1 (or MAFbx), and autophagy genes to induce muscle protein degradation.

**Clinical–Translational Advances**

Nutritional support alone, or in conjunction with anabolic drugs such as enobosarm (an oral, nonsteroidal, selective androgen receptor modulator) or anamorelin (an orally active ghrelin receptor antagonist), has failed to deliver clinical benefit in patients with cancer with cachexia (31). Directly targeting the cachexia pathway may indeed prove to be a more successful endeavor. To this end, recent preclinical and clinical studies have offered a number of drugs with promising activity against cancer-induced muscle wasting (Table 1).

**TNFα**

Administration of TNFα results in increased skeletal muscle proteolysis associated with higher levels of conjugated ubiquitin (32). TNFα is also involved in anorexia associated with tumor growth, as suggested by the use of TNF inhibitors in anorectic tumor-bearing rats. Specifically, the injection of TNF inhibitor in tumor-bearing rats significantly improves food intake and body weight (33). Despite these promising preclinical data, TNFα inhibitors have not demonstrated meaningful clinical benefit. In two phase II studies, which randomized patients with advanced cancer to either etanercept (a recombinant fusion protein of TNFα type II receptor, which blocks TNFα activity) or infliximab (a recombinant anti-TNFα antibody) versus placebo (34, 35), no significant benefit was shown with respect to reducing muscle wasting, restoring lean body mass, or improving quality of life. Likewise, the addition of infliximab to gemcitabine to treat cachexia in patients with advanced pancreatic cancer did not yield any significant benefit when compared with placebo (36). In fact, a phase II/III randomized, placebo-controlled study combining infliximab with docetaxel in patients with non–small cell lung cancer (NSCLC) was terminated early due to significantly worse quality of life in the experimental group. Recent data suggest that a monoclonal antibody against fibroblast growth factor-inducible 14 (Fn14), which is related to the TNF receptor superfamily and is a receptor for the TWEAK cytokine, may help prevent tumor-induced cachexia and prolong survival in C26 tumor–bearing mice (37). Interestingly, TWEAK blockade using an anti-TWEAK antibody had no effect on Fn14-induced cachexia, suggesting the presence of a second, as yet unidentified ligand for Fn14.

**IGF1/Akt/mTOR pathway has anabolic effects on muscle by inhibiting protein degradation and promoting myogenesis**

IGF1 signaling is a major anabolic pathway involved in muscle development and regeneration (25). Several studies have shown that IGF1/Akt signaling suppresses protein breakdown and promotes muscle growth (26, 27). Binding of IGF1 to its receptor triggers the activation of P70S6K/Akt signal transduction, inducing protein synthesis by blocking the repression of mTOR. Activated mTOR phosphorylates its two major targets, S6K1 and 4E-BP1, which play a key role in myogenesis. Akt further phosphorylates and inactivates forkhead box O proteins (FoxO3a, FoxO1, FoxO3b, and FoxO4) by promoting their export from the nucleus to the cytoplasm (28). FoxO proteins are transcriptional regulators of autophagy, which promote protein ubiquitination and degradation in muscle cells. Myostatin and activin suppress Akt activity, leading to disinhibition of FoxO3 (29, 30) and subsequent upregulation of MuRF1–1, Atrogin-1 (or MAFbx), and autophagy genes to induce muscle protein degradation.
potential antitumor effects in the response analysis. The most common adverse event in this study was proteinuria (all grade, n = 11; 21%). Subsequently, a phase III randomized study comparing MABp1 monotherapy to megestrol acetate was performed in patients with advanced colorectal cancer with cachexia (39). In this study, MABp1-treated patients had a trend toward improved median overall survival without worsening physical function, compared with patients receiving megestrol acetate. A placebo-controlled, double-blind phase III study in refractory patients with colorectal cancer is ongoing.

IL6

ALD518, a humanized monoclonal antibody that binds with high affinity to human IL6, is being developed for the treatment of anemia, cachexia, and fatigue (12). A phase I study of 9 patients with advanced cancer has reported statistically significant differences in hand grip strength and fatigue after ALD518 administration (40). In a phase II randomized placebo-controlled study in 124 patients with advanced NSCLC, ALD518 resulted in less lean body mass reduction, improved lung symptom scores, and reversed fatigue and anemia (41, 42). ALD518 is well tolerated, with minimal adverse effects and has the potential to improve anemia and fatigue, as well as reduce cancer-related cachexia.

Myostatin/activin pathway

Several studies have suggested that serum levels of activin (43, 44) and myostatin (43) are increased in patients with cancer cachexia. In mouse models, inhibition of myostatin/activin signaling has been shown to increase muscle mass and improve physical performance and muscle function (45, 46). A recombinant decoy ActRIIB antagonist, which inhibits both myostatin and activin-mediated Smad2/3 signal transduction, dramatically prevented muscle wasting and prolonged survival in multiple mouse models without affecting inflammatory cytokine levels (47). A myostatin-specific antibody (PF-354) has also been shown to suppress tumor-induced muscle wasting and loss of muscle function, even in mildly cachectic mice (48). Unfortunately, clinical trials testing the ActRIIB decoy were stopped because of gum and nose bleeding events in healthy adults and boys with Duchenne muscular dystrophy. Another myostatin-specific antibody (LY2495655) and its receptor ActRIIB-specific antibody (bimagrumab or BYM338) showed promising results in clinical trials. A phase I study of LY2495655 in patients with advanced cancer not receiving chemotherapy showed that LY2495655 was well tolerated and provided durable improvement in hand grip strength and functional tests (49). A phase II study of LY2495655 in patients with advanced pancreatic cancer receiving standard chemotherapy is ongoing, with overall survival as the primary endpoint (NCT1505530). Similarly, BYM338 has previously shown an improvement in thigh muscle volume at 8 weeks in patients with inclusion body myositis (50) and is now being tested in a randomized, double-blind, placebo-controlled phase II trial in patients with lung and pancreatic cancer (NCT01433263). Interestingly, this pathway may also play an important role in prevention strategies. For example, in a study of patients with early-stage gastric cancer, myostatin expression was found to be upregulated in muscle tissue before the onset of significant weight loss (51), suggesting that early intervention to prevent cancer cachexia may delay tumor recurrence or progression and improve outcomes.

Little is known regarding how modulation of cachexia signaling influences tumor biology. However, studies suggest that activation of cachexia signaling may contribute to tumor progression. Gallot and colleagues reported on the effect of myostatin...
signaling on cancer biology using LLC tumor-bearing mice. In this study (32), tumor weight was significantly lower in Mstn-/- mice than in wild-type mice. In addition, gene expression analysis in tumor tissue showed this phenotype to be associated with reduced expression of genes involved in angiogenesis, tumor metabolism, activin signaling, and apoptosis. These results are consistent with studies showing that the soluble type II receptor antagonist of myostatin and activin (sActRIIB) reduced tumor weight and incidence of lung metastases (45, 53). Taken together, myostatin/activin signaling has a critical role not only in muscle cell degradation but also in cancer progression, although it should be noted that these data have not been reproduced in other studies. Interestingly, myostatin/activin signaling has been associated with activation of angiogenesis. For instance, ALK5 overexpression promotes tumor angiogenesis, invasion, and metastatic potential by upregulating matrix metalloproteinase-9 in tumor cells (54). Conversely, an inhibitor of the type I activin-like receptor (SB431542) has been shown to decrease VEGF expression and inhibit angiogenesis. These data warrant further investigation and may lead to novel drug combinations with inhibitors of cachexia signaling.

Conclusions

The mechanisms of cancer cachexia are heterogeneous and multifactorial. Targeting the cachexia signaling pathway has shown promising results in preclinical and early clinical trials but primarily to prevent muscle wasting rather than prolong survival. Ongoing phase III clinical trials are testing the clinical efficacy of these novel compounds. Improving the classification, objective assessment, and monitoring of patients with cancer with cachexia remain challenges to the clinical development of agents targeting this pathway. A refined understanding of how cancer cachexia affects oncogenic signaling in different cancer types and host status is critically needed to develop more successful therapeutic interventions. Identifying predictive biomarkers for these compounds, based on the precise mechanism of cachexia affected, will be essential to bringing these compounds into the clinic.

Disclosure of Potential Conflicts of Interest

H.-J. Lenz is a consultant/advisory board member for Bayer, Boehringer Ingelheim, Celgene, Merck Serono, and Roche. No potential conflicts of interest were disclosed by the other authors.

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Grant Support

H.-J. Lenz was supported by the NIH under award number P30CA014089, Wunder Project, Call to Cure, and Danny Butler Memorial Fund.

Received April 27, 2016; revised June 9, 2016; accepted June 9, 2016. Published OnlineFirst June 23, 2016, in Clin Cancer Res; 22(16) August 15, 2016.
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