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Inflammatory burden and amino acid metabolism in cancer cachexia

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Abstract

Purpose of review—Cancer cachexia is associated with marked alterations in skeletal muscle protein metabolism that lead to muscle wasting and, in some cases, death. The inflammatory response elicited by cancer is a likely, if not primary, mediator of these alterations. This review focuses on the possible relationship between inflammatory signaling and altered amino acid metabolism in cancer.

Recent findings—Loss of skeletal muscle in cancer patients can potentially be due to anorexia and early satiety, reduced muscle protein synthesis, and/or increased muscle protein breakdown. Inflammation has been associated with each of these mechanisms. Effects on appetite appear to be mediated by the melanocortin system in the hypothalamus. Studies in animal models of cachexia suggest that modulation of orexigenic and anorexigenic pathways in this system may improve nutrient consumption. Inflammatory cytokines such as IL-6 and TNFα likely contribute to the effects of inflammation on muscle protein metabolism through several pathways.

Summary—Limited studies in humans suggest that targeted anti-inflammatory and nutritional interventions may ameliorate the net catabolic effect on skeletal muscle protein metabolism. Future studies of the precise mechanism of muscle protein loss, as well as novel or combination therapies to inhibit inflammation and promote anabolism, are warranted.

Keywords

amino acid; ubiquitin proteasome pathway

Introduction

Cachexia is a multifaceted syndrome describing the loss of body mass as a result of both accelerated catabolism of fat and skeletal muscle and anorexia. Cachexia does not simply refer to a loss of body weight [1•] and can be differentiated from sarcopenia (age-induced loss of skeletal muscle) and starvation (in which body mass loss is caused by nutrient deficiency and preferential loss of adipose tissue occurs) [2]. In cancer cachexia, profound inflammation is both a diagnostic characteristic [3] as well as a possible mechanism for the accompanying anorexia and wasting. In the present review, we focus on the relationship between cancer-induced inflammation and muscle wasting.

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Characteristics of cancer cachexia

Although descriptions vary, weight loss, anorexia, and inflammation are the cardinal characteristics of cancer cachexia and are correlated with adverse outcomes [3]. Although muscle weakness and fatigue are often present (e.g. 70–100% of cancer patients experience fatigue [4]) in cancer patients and significantly impact quality of life, they are also common in noncachectic cancer patients and thus may not be predictive of cancer cachexia [3]. Elevated resting energy expenditure has also been associated with cachexia and is thought to be at least partially due to the acute-phase inflammatory response (as indicated, for example, by increased circulating levels of C-reactive protein, fibrinogen, and white blood cells) present in these patients [5•].

Although weight loss occurs in roughly half of cancer patients [5•], in cachexia, the weight loss represents a marked loss of skeletal muscle and fat. Strictly speaking, cachexia describes the manifestations (e.g. excessive loss of body weight, lean body mass, and adipose tissue) of a process that was initiated at some point in the past. Accordingly, patients who exhibit characteristics (e.g. systemic inflammation, anorexia) that are associated with the state of cachexia as well as 5% or greater weight loss may be considered ‘precachectic’ [1•]. When the loss of body weight reaches 15% or greater the patient is in a frank cachectic state [1•,6]. In cachectic patients, a loss of 25% of body weight represents an approximately 75% reduction in skeletal muscle protein [7]. The excessive weight loss of cachexia is an ominous sign, with roughly 20% of cancer deaths attributed to cachexia [8]. Thus, early identification of the factors predisposing an individual to cachexia is important for designing potential therapies to reverse and/or prevent the catabolic process.

Possible causal relationships between inflammation and cancer cachexia

The idea that cancer and inflammation are linked has been around since the hypothesis of Virchow in the 19th Century [9]. Apart from a role in cancer development and progression, cancer-associated inflammation may contribute to the development of cachexia. As inflammation is implicated in the elevated rates of muscle protein breakdown, reduced rates of muscle protein synthesis, and reduced intake of amino acids due to cancer-induced anorexia (Fig. 1 Fig. 1), it has been suggested to play a dominant mechanistic role in the development of cachexia-induced loss of skeletal muscle [3,9,10••].

Anorexia

Inflammatory cytokines released as part of the cancer-induced inflammatory response act upon the hypothalamus to limit food intake and thus the supply of amino acids to the muscle [2,11••]. This effect is thought to occur as a result of increased stimulation of melanocortin receptors in the hypothalamus [11••]. Reduced release of the orexigenic molecule neuropeptide Y may also contribute to this response [2]. Interestingly, circulating levels of the orexigenic hormone ghrelin are paradoxically elevated in cancer patients [12–14], suggesting possible inflammation-induced resistance to its actions.

Impaired muscle protein synthesis

Inflammatory-mediated signaling may limit muscle protein synthesis by several mechanisms. Inflammatory cytokines such as TNF-α and IL-6 are likely important in this regard. TNF-α can activate the transcription factor NF-κB, which inhibits the synthesis of the muscle-specific transcription factor MyoD, thereby inhibiting differentiation [10••]. As discussed below, TNF-α also influences the anabolic mTOR signaling pathway. The potential role of IL-6 in human cachexia has not received much attention; however, a recent study found that skeletal muscle protein synthesis was dramatically reduced by relatively low-dose IL-6 infusion in humans [15••].

Myostatin is a negative regulator of muscle mass, inhibiting myogenic proliferation and differentiation [10••,16••]. Animals and humans that lack myostatin exhibit markedly increased muscle mass [16••]. The study of the role of myostatin in cancer cachexia is still in its infancy; however, preliminary reports have described marked elevations in myostatin in cachectic cancer patients [10••]. Animal models suggest that the inflammatory cytokine TNF-α is at least partially responsible for this increase [17•].

As touched on above, inflammation initiates central anorexic pathways that limit dietary consumption of nutrients. As amino acids, and perhaps leucine in particular, are required for muscle protein synthesis [18•,19•,20••], the reduced availability of amino acids represents a major contributor to the inflammation-induced loss of skeletal muscle mass in cachectic patients. In addition to the reduced supply of amino acids, the anorexic response also reduces the exposure to insulin, a potent stimulator of muscle protein synthesis [21].

The mTOR signaling pathway is a major mediator of anabolic responses in skeletal muscle. Specifically, mTOR activation by insulin or amino acids activates the downstream targets eukaryotic initiation factor binding protein 4E and ribosomal S6 kinase 1, which promote translation initiation, and eukaryotic elongation factor, which stimulates elongation [18•]. Although more research is needed, limited human [22] and animal [20••] studies suggest that mTOR signaling is inhibited in cancer cachexia. Multiple mechanisms may contribute, including anorexia-induced reductions in amino acid intake as well as inflammatory mediators such as TNF-α, which potentially oppose mTOR signaling by several means [19•].

Recent work has identified dsRNA-dependent protein kinase (PKR), which is activated by the tumor-secreted proteolysis-inducing factor (PIF), as a potential inhibitor of skeletal muscle protein synthesis in cachexia [23••]. This effect is apparently because of phosphorylation of eukaryotic initiation factor (eIF) 2, which in turn interferes with the activity of eIF2B [23••] to promote translation initiation.

Stimulated muscle protein breakdown

Inflammatory stimulation activates pathways associated with muscle protein breakdown [10••]. In cancer cachexia, the ubiquitin proteasome pathway is greatly influenced [10••]. Many of these effects are thought to occur through activation of NF-κB by upstream factors such as TNF-α [10••] and PIF (acting through its stimulatory effect on PKR) [20••,23••]. NF-κB stimulates transcription of the ubiquitin E3 ligase muscle ring finger (MuRF)-1, which is known to positively regulate activity of the ubiquitin proteasome pathway [10••]. Members of the Foxo family of transcription factors may also stimulate expression of MuRF-1 and atrogin-1 [10••,24•,25]. Myostatin has recently been shown to stimulate expression of ubiquitin proteasome pathway elements in an NF-κB-independent manner that may involve regulation of Foxo [16••].

Although IL-6 has been considered as a procachectic inflammatory cytokine, it may reduce skeletal muscle protein breakdown [15••]. However, as its effect to reduce protein synthesis (see above) is greater than its effect on breakdown, the net response to IL-6 appears to be a loss of muscle protein [15••]. Interestingly, IL-6 infusion increases whole body protein turnover and reduces circulating amino acid concentrations, suggesting that profound effects on nonmuscle tissues may influence the response in skeletal muscle [15••].

Notwithstanding evidence for upregulation of elements of the ubiquitin proteasome pathway in cancer cachexia, we are not aware of studies in humans in which elevated rates of muscle protein breakdown have been reported. On the contrary, some studies suggest that muscle protein breakdown is unaltered by cancer in humans [26••,27]. In the study by Dillon *et al.*

[26••], this was demonstrated despite increased skeletal muscle IL-6 and NF-κB and systemic elevations of hs-CRP. Indirect measures of muscle protein breakdown in animal models suggest activation of skeletal muscle protein breakdown during cachexia [10••], although exceptions exist [28]. One possibility is that in animal models, in which the relative tumor mass is greater than in humans, the tumor represents a large enough 'sink' for amino acids that it effectively competes with skeletal muscle [29] and stimulates breakdown. Another possibility is that humans with cancer spend longer periods throughout the day in negative protein balance during the postabsorptive and postprandial periods than their healthy counterparts. Whether this effect is more pronounced as a result of a diminished synthetic response to a meal or enhanced protein breakdown due to the upregulation of elements of the ubiquitin proteasome pathway is not known. Clearly, this is an area in which further studies are warranted.

Therapeutic approaches

The inflammatory burden of cancer, with potential influences on appetite, muscle protein synthesis, and muscle protein breakdown, presents a challenge to the development of anabolic therapies. Cachectic patients often exhibit reduced appetite and early satiety, hampering their ability to ingest amino acid-dense foods such as meats to stimulate muscle protein synthesis. Further, cancer-induced inflammation appears to reduce the sensitivity of skeletal muscle protein synthesis to amino acid supplementation [26••] and may increase muscle protein breakdown [10••]. This tug-of-war kinetic scenario suggests that normal intake of food containing amino acids, as well as supplemental amino acids for preventing or reversing muscle loss could preferentially stimulate tumor growth [29] by stealing key nutrients away from muscle tissue. Accordingly, there exist several options for therapeutic intervention, namely anti-inflammatory treatments, appetite stimulation, anabolic agents to stimulate synthesis, and various approaches to reduce proteolysis. These approaches could in theory work in a synergistic manner to significantly ameliorate loss of skeletal muscle.

Anti-inflammatory treatments

If inflammatory signaling pathways are responsible for cachexia, then anti-inflammatory agents should ameliorate the condition. Accordingly, a number of anti-inflammatory agents have been tested for their potential to reduce the symptoms of cachexia. Eicosapentaenoic acid (EPA), a naturally occurring fatty acid in fish oils, has been shown to inhibit inflammatory responses. Animal studies using EPA have been promising, suggesting significant benefit on maintenance of body weight and lean body mass [10••]. Consistent with these findings, human studies have found beneficial effects of EPA on body weight, lean body mass, appetite, and quality of life [30••,31]. However, other studies have found marginal or no benefit [32]. Although a consensus on the use of EPA still does not exist, the weight of current evidence suggests marginal benefit [32,33].

Pharmacological inhibition of the inflammatory response has been moderately successful. Cyclooxygenase inhibition in cancer patients has been associated with improved survival and preservation of adipose tissue [34,35]; however, loss of lean body mass was not attenuated. Given the overlapping nature of inflammatory signaling, it seems likely that combination treatments may be necessary to see positive effects on skeletal muscle mass.

Appetite stimulation

The inflammation-induced anorexia promotes a catabolic state by limiting the supply of amino acids, limiting insulin exposure, and promoting an energetic state that does not favor stimulation of mTOR signaling. Although human trials are lacking, promising results have been obtained in animal models of cachexia through the use of melanocortin receptor

antagonists [11••]. In these models, melanocortin inhibition has been shown to reduce both the anorexia and hypermetabolism induced by implanted tumors, while preserving lean body mass [11••]. Ghrelin, the only known circulating orexigenic factor, stimulates orexigenic signaling by the melanocortin system [11••]. In an animal model of cancer cachexia, ghrelin has shown promising effects on lean body mass and appetite, apparently through both orexigenic and anti-inflammatory effects [36•].

Stimulation of muscle protein synthesis

Essential amino acids and leucine in particular are potent stimulators of muscle protein synthesis in healthy individuals [36•]. Until recently, however, it was not known whether this response is also present in cachectic skeletal muscle, in which inflammatory mediators and impaired energetic status may limit the response to amino acids. Fortunately, recent studies suggest that this response is also present in cachexia.

Dillon *et al.* [26••] tested the effectiveness of a 40 g balanced amino acid supplement in patients with ovarian cancer. Notably, these patients exhibited evidence of marked inflammation, with significantly increased levels of circulating C-reactive protein as well as elevations in skeletal muscle TNF-α and IL-6. Despite this state of inflammation, as well as ongoing treatment, the amino acid supplement improved skeletal muscle protein net balance. This effect was achieved through stimulation of muscle protein synthesis, with no effect on muscle protein breakdown. Notably, however, the anabolic response in these patients was tempered relative to an age-matched control group.

These findings are complemented by a recent study in cachectic mice that also demonstrated improved preservation of skeletal muscle mass in response to supplementation with branched chain amino acids [20••]. This effect was apparently due to improved muscle protein synthesis and a possible reduction in muscle protein breakdown [20••]. mTOR signaling was enhanced, which should favor increased translation initiation. In addition, phosphorylation of eukaryotic elongation factor 2 was reduced, consistent with a stimulation of translation elongation. This study also suggests that PKR activity is modulated by branched chain amino acids though induction of increased expression of protein phosphatase 1.

Biolo *et al.* [37] investigated the acute effects of BCAA on muscle protein metabolism in the setting of the combined stresses of cancer and recovery from surgery and radiation therapy. In this study, provision of a balanced mixture of amino acids had no effect on muscle protein synthesis and breakdown. However, when an isonitrogenous supplement that was enriched in essential amino acids was given, muscle protein synthesis was stimulated [37].

As insulin is anabolic to skeletal muscle and inhibits lipolysis, it is an attractive candidate for treatment of cachexia. Accordingly, Lundholm *et al.* [38••] studied the response to chronic insulin treatment (0.11 U/kg per day) in a large group of patients with assorted malignancies. Notably, both the control group and the insulin-treated group of patients in this study received anti-inflammatory treatment with indomethacin [38••]. Despite the concomitant indomethacin treatment, insulin did not affect lean body mass, although it did significantly increase body fat stores and survival [38••].

Biolo *et al.* [39••] also investigated the response to insulin. This study differed from the Lundholm *et al.* study in that it examined the acute response to insulin given to maintain euglycemia on the day after abdominal surgery in female cancer patients. In addition, the circulating insulin concentrations of both the control (hyperglycemic) and insulin (euglycemic) groups were higher than in the cancer patients studied by Lundholm *et al.* [38••]. Insulin significantly stimulated muscle protein synthesis and did not affect muscle

protein breakdown; thus, the net balance between synthesis and breakdown was improved by insulin under these conditions.

Finally, testosterone is anabolic to muscle protein through stimulation of the IGF-1 pathway [40]. Recent evidence suggests that testosterone also has anti-inflammatory properties, making this hormone a therapeutic candidate for use in cachectic patients [41–43].

Inhibition of muscle protein breakdown

As noted above, there may be a discrepancy between indicators of ubiquitin proteasome pathway activation and actual rates of muscle protein breakdown. Nevertheless, whether muscle protein breakdown is actually stimulated by cancer-induced inflammation or not, inhibition of breakdown represents a viable strategy for improving the net balance between muscle protein synthesis and breakdown.

One agent that may reduce muscle protein breakdown is insulin [44••]. However, in the study by Biolo *et al.* [39••] cited above, skeletal muscle protein breakdown was not reduced by insulin treatment. In the Lundholm *et al*. study [38••], muscle protein breakdown in response to insulin therapy was not measured; however, the lack of effect on lean body mass suggests that insulin did not affect muscle protein breakdown [38••].

Testosterone is a hormone with well known anabolic effects. It apparently increases muscle mass by reducing the loss of skeletal muscle amino acids, either by stimulating the reutilization of amino acids released from proteolysis for protein synthesis or by reducing the rate of muscle protein breakdown [45]. Thus, testosterone is an attractive candidate for reducing loss of muscle mass in cachectic patients. However, to date, testosterone treatment of cancer patients has not been reported.

Conclusion

Although the inflammatory burden of cancer exerts profound effects on skeletal muscle protein metabolism, recent studies suggest that appropriate interventions may ameliorate these responses.

Acknowledgments

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

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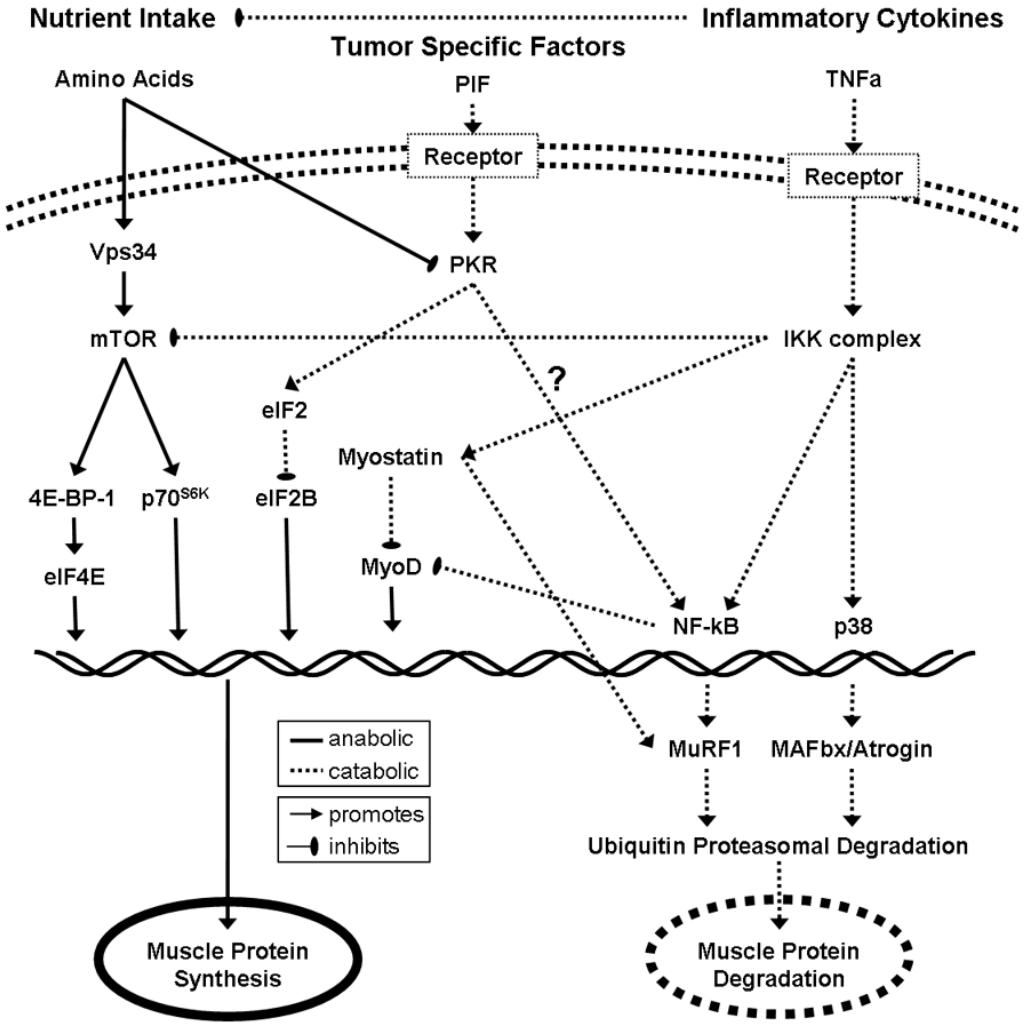

Figure 1.

Key signaling pathways between amino acids, inflammatory cytokines, and tumor-specific factors gr1

Amino acids stimulate muscle protein synthesis through the mTOR pathway. Inflammatory cytokines and tumor specific factors inhibit muscle protein synthesis and promote muscle protein degradation.