Cancer cachexia is a morbid wasting syndrome common among patients with head and neck cancer. While its clinical manifestations have been well characterized, its pathophysiology remains complex. A comprehensive literature search on cancer cachexia was performed using the National Library of Medicine’s PubMed. The Cochrane Library and Google search engine were also used. Recent evidence and new concepts on the pathophysiology of cancer cachexia are summarized. Targeted therapies are presented, and new concepts are highlighted. Cancer cachexia is characterized by complex, multilevel pathogenesis. It involves up-regulated tissue catabolism and impaired anabolism, release of tumor-derived catabolic factors and inflammatory cytokines, and neuroendocrine dysfunction. These culminate to create an energy-inefficient state characterized by wasting, chronic inflammation, neuroendocrine dysfunction, and anorexia. ©2007 Wiley Periodicals, Inc. Head Neck 29: 497–507, 2007

Keywords: cancer cachexia and anorexia; muscle wasting; weight loss

INTRODUCTION

Despite recent advances in treatment, clinical dilemmas persist for the surgeon treating patients with head and neck cancer with marked weight loss. At initial presentation, it is often difficult to accurately determine the cause of lost weight. The patient may be experiencing weight loss because
of cancer-induced odynophagia, aging, immobility, anorexia, chemoradiation therapy, cancer cachexia, starvation due to mechanical obstruction, or malnutrition due to alcoholism. Of these, cancer cachexia is the least understood cause of weight loss, and yet it is responsible for the greatest morbidity among patients with head and neck cancer.

The clinical manifestations of this syndrome have been characterized previously. They include skeletal muscle and adipose tissue wasting, exaggerated systemic inflammation, and anorexia. Recent findings have shed light on the pathologic basis for these manifestations. Skeletal muscle and adipose tissue wasting appear to be mediated by dysfunction in several overlapping pathways. First, dysregulation of muscle-specific cellular components such as the ubiquitin–proteasome system (UPS) and the dystrophin glycoprotein complex (DGC) facilitates muscle catabolism. Tumor-derived catabolic factors and circulating proinflammatory cytokines also augment muscle and adipose tissue catabolism. Finally, disruption of neuroendocrine pathways leads to anorexia.

The aim of this review is to clarify the mechanisms involved in the pathogenesis of cancer cachexia and to describe potential targets for anticachexia treatment.

**SKELETAL MUSCLE**

The most prominent clinical feature in cancer cachexia is progressive loss of skeletal muscle mass. This may approach 75% reduction in skeletal muscle protein mass, even with a total weight loss of only 30%. Loss of muscle protein plays a major role in the shortened survival time of cachectic cancer patients, who experience a final common pathway of progressive physical disability and impairment of respiratory function. Current data suggest that loss of muscle protein is mediated primarily by accelerated protein catabolism, but that impaired protein anabolism is also important. These appear to be 2 dynamic and interrelated processes that ultimately account for the progressive muscle wasting seen in cancer cachexia.

**ACCELERATED MUSCLE CATABOLISM**

Three important and recently identified factors play central roles in skeletal muscle wasting in patients with cancer cachexia. These are the ubiquitin–proteasome proteolytic system, the DGC, and proteolysis-inducing factor (PIF). The UPS is an important pathway for muscle protein degradation that appears to be up-regulated in animal models of cancer cachexia. The DGC is a cytoarchitectural framework in muscle cells whose dysfunction may help initiate muscle wasting. Finally, PIF is a tumor-derived catabolic factor that may initiate and augment muscle wasting in humans.

Current research on the pathogenesis of cancer cachexia posits that exuberant release of proinflammatory cytokines, such as interleukin (IL-) 1β, IL-6, tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ), causes skeletal muscle proteolysis through suppression of muscle genes and activation of ubiquitin–proteasome-mediated proteolysis. These circulating proinflammatory cytokines inhibit the expression of myosin heavy chain genes, leading to dissociation of myosin from its contractile apparatus in muscle cells. Free myosin is degraded by the UPS, whose components are activated by these same cytokines. Ubiquitin–proteasome-mediated muscle protein catabolism is also inducible by PIF, a purported tumor-derived catabolic factor. Current research also suggests that muscle breakdown in cachexia involves cellular dysregulation of the DGC, a membrane structure responsible for maintaining the functional integrity of muscle cells. Here we will describe 3 important components of skeletal muscle proteolysis in cancer cachexia: the UPS, PIF, and the DGC.

**Up-regulation of the Ubiquitin–Proteasome System.**

The UPS is a 750-kDa tube-like structure found within cells. This structure is hypothesized to be an important pathway underlying catabolic disease states such as starvation, sepsis, denervation atrophy, severe trauma, and cancer cachexia. It is the major catabolic pathway in cancer cachexia, and its overactivation has been reproduced by nearly all rodent models of cancer-associated muscle wasting tested thus far. Furthermore, research on human subjects with cancer has also demonstrated UPS overactivation.

Most intracellular proteins in skeletal muscle are degraded through the UPS proteolytic system. Muscle protein degradation involves enzymatic marking of proteins with multiple ubiquitin molecules in a multistep process that culminates in protein degradation within the proteasome. In the first step of this marking process, multiple ubiquitin molecules are covalently conjugated to contractile proteins by ubiquitin-activating (E1),
ubiquitin-conjugating (E2), and ubiquitin-ligating (E3) enzymes. In the second step, tagged proteins are recognized and degraded within the 26S proteasome complex, whose catalytic core is lined with proteolytic enzymes. The proteasome then releases oligopeptides that are rapidly degraded into amino acids by cytosolic peptidases. These amino acids are then transported to the liver, where they are converted to acute-phase proteins in an energy-wasting cycle that exacerbates inflammation and disrupts physiologic protein balance (Figure 1).

Proinflammatory cytokines such as IL-6, TNF-α, and IFN-γ have been shown to up-regulate muscle-specific expression of important components of the UPS. Recent data suggest that cytokine-mediated induction of 2 muscle-specific ubiquitin ligase genes, muscle ring-finger 1 (MuRF1) and muscle atrophy F box (MAFbx), may be major steps the induction of in skeletal muscle atrophy in cachexia. Importantly, TNF-α and IL-6 induce muscle-specific expression of IKK (inhibitor of NF-κB). This activates nuclear factor kappa B (NF-κB) and causes MuRF1 up-regulation, which results in severe muscle wasting in mice. Thus, the IKK/NF-κB/MuRF1 pathway is a cytokine-inducible signaling pathway that appears to mediate skeletal muscle wasting in cancer cachexia (Figure 2).

Induction of Muscle Breakdown by Proteolysis-Inducing Factor. PIF is a 24-kDa glycoprotein produced by tumor cells in both mice and humans that has been hypothesized to be responsible for cancer cachexia. PIF has been found in many human tumor types, including breast, ovarian, pancreatic, and colorectal tumors, and has been isolated from the urine of patients with cachectic cancer with weight loss. Furthermore, PIF appears to be present in patients with tumor-related cachexia, but absent in cancer patients not losing weight, or in weight-losing patients with benign disease. Longitudinal studies have shown that cancer patients expressing PIF in accelerated muscle catabolism in cancer cachexia thus appears to result from cytokine-mediated induction of the muscle-specific ubiquitin ligase genes MuRF1 and MAFbx and consequent activation of UPS proteolysis (Figure 3). The developing understanding of this system creates new targets for the treatment of cachexia. Gene knockout, MuRF1 and MAFbx suppression by IGF-1, and direct proteasomal inhibition might become targets for anticachexia treatment in the future.

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their urine lose weight over time, while patients not expressing this factor gain weight. PIF administration to mice and to cultured myocytes rapidly induces muscle catabolism, while PIF-induced weight loss in mice is reversed with anti-PIF monoclonal antibodies. PIF induces muscle wasting by several mechanisms. First, it induces the muscle-specific release of 15-hydroxyeicosatetraenoic acid, activating UPS-mediated proteolysis. PIF also stimulates the activation of NF-κB in tissue culture, which facilitates the release of proinflammatory cytokines and induces UPS-mediated proteolysis. Thus, by stimulating the release of proinflammatory cytokines and activating the UPS, PIF expression generates a series of events culminating in skeletal muscle wasting.

**Dysregulation of the Dystrophin Glycoprotein Complex.** New research shows that cancer cachexia may also involve the loss of an essential muscle protein complex. The DGC is a muscle-specific protein manifold that anchors sarcomere membranes in place and prevents them from being torn by shear forces produced during muscle contraction. Recent findings suggest that dysregulation of the DGC mediates the development of cancer-induced muscle wasting. Muscles from colon-26 adenocarcinoma-bearing mice exhibited membrane abnormalities associated with reduced levels of dystrophin and increased glycosylation of proteins within the DGC. The dysregulation of the DGC correlates positively with weight loss in patients with gastroesophageal adenocarcinoma. Also, mutant mice lacking the protein dystrophin show enhanced tumor-induced wasting, while transgenic animals expressing dystrophin—specifically in skeletal muscle—are spared from disease. These findings suggest that the loss of function of the DGC may cause muscle wasting in cancer cachexia.

Whether dysfunction of the DGC initiates, maintains, or promotes muscle breakdown in cancer cachexia is currently unclear. Overexpression of dystrophin appears to block the induction of MuRF1 and MAFbx but does not affect NF-κB activation in these muscles. This suggests that dysfunction within the DGC may mediate UPS-dependent muscle breakdown in a manner independent of NF-κB. However, the exact mechanism of this dysfunction remains to be elucidated (Figure 4).

**IMPAIRED MUSCLE ANABOLISM**

Although accelerated skeletal muscle wasting appears to be a primary mediator of cancer cachexia, another important feature is impaired skeletal muscle anabolism. One study found that the total body protein synthesis in healthy individuals was 53%, whereas in cachectic individuals it was only 8%. Several pathways appear to be involved in reduced skeletal muscle anabolism in cachexia. These include imbalance in the physiologic amino acid pool, reduced myosin expression, and up-regulation of the gene regulator myostatin.

**FIGURE 4.** The dystrophin glycoprotein complex. Simplistic view of proteins involved in the dystrophin–glycoprotein complex. This shows how disruption in the muscle membrane complex can disrupt the intramuscular cytoskeleton, leading to muscle breakdown.
Imbalance in the Amino Acid Ratio. Protein synthesis in patients with cancer cachexia is impaired by an imbalance in the physiologic amino acid ratio. As mentioned previously, free amino acids are released by the UPS following the breakdown of skeletal proteins. These are then taken up by the liver, where they are converted to acute-phase proteins in order to meet increased energy needs of chronic inflammation in cachexia. The large amount of amino acids consumed in skeletal muscle breakdown depletes the physiologic reserve of amino acids available for skeletal muscle synthesis. Without the proper ratio of free amino acids, general protein synthesis is inhibited. Thus, increased skeletal muscle breakdown appears to alter the free amino acid ratio, thereby inhibiting protein synthesis in skeletal muscle.

Reduced Expression of Myosin. Reduced myosin expression has also been implicated in impaired protein anabolism in cachexia. Cachectic tumor-bearing rats exhibit decreases in myosin expression that may be induced by circulating proinflammatory cytokines. Recent studies of cultured myocytes demonstrated that protein catabolism induced by TNF-α and IFN-γ suppresses the production of MyoD in an NF-κB-dependent manner (Figure 5). MyoD is a muscle-specific nuclear transcription factor that transcribes myosin heavy chain gene. Reduced MyoD expression is known to deplete the pool of myosin heavy chain, resulting in diminished muscle protein synthesis and cachexia. Thus, cytokine-mediated inhibition of MyoD production ultimately suppresses myosin heavy chain expression, preventing muscle formation and leading to atrophy.

Myostatin Up-regulation. Impaired skeletal muscle anabolism is also caused by overexpression of a muscle gene regulator known as myostatin. Myostatin is a muscle-specific negative regulator of skeletal muscle growth that can suppress muscle cell proliferation and differentiation in an NF-κB-independent manner. Muscles of tumor-bearing mice exhibit significantly higher levels of myostatin than muscles in non–tumor-bearing mice, and transgenic mice with overexpression of the myostatin gene develop a cachexia-like syndrome characterized by severe wasting. Although its role remains to be more accurately characterized, myostatin up-regulation appears to be an important factor in impaired muscle regeneration in cancer cachexia.

To summarize, skeletal muscle atrophy in patients with cancer cachexia is characterized by accelerated catabolism and impaired anabolism. Accelerated muscle catabolism is mediated by up-regulation of the UPS proteolytic pathway, tumor release of the muscle catabolic factor PIF, and dysregulation of the DGC. Impaired muscle anabolism is mediated by an imbalance in the amino acid pool, reduced myosin expression, and up-regulation of the muscle gene regulator myostatin.

ADIPOSE TISSUE

Cachexia also involves abnormalities in lipid metabolism, resulting in marked adipose tissue loss in the cachectic patient. Indeed, body composition analysis of lung cancer patients with loss of 30% or more of their premorbid weight showed an 85% fall in total body fat. Increased adipose tissue catabolism, rather than impaired anabolism, appears to be central to the etiology of fat loss in cachectic patients. This is characterized by increased lipolysis, hypertriglyceridemia, increased hepatic secretion of very low density lipoprotein, increased de novo fatty acid synthesis, and a futile cycle of fatty acids between the liver and adipose tissue. Adipose tissue catabolism appears to be stimulated by a tumor-derived factor called lipid-mobilizing factor and by circulating proinflammatory cytokines in the tumor-bearing host.
Lipid Mobilizing Factor. Lipid-mobilizing factor (LMF) is a 43-kDa lipolytic factor derived from both tumor and brown adipose tissue. It is homologous with human protein Zn-α2-glycoprotein, and has been isolated from the urine of both cachectic cancer patients and cachectic mice. It is known to cause a selective reduction in body fat, and is thought to be responsible for atrophy of adipose tissue in cachectic patients. One study found that cancer patients with weight loss had detectable concentrations of LMF in their urine, while cancer patients without weight loss did not.

LMF directly stimulates lipolysis by down-regulating lipoprotein lipase (LPL) and up-regulating hormone sensitive lipase. This results in elevated levels of glycerol and free fatty acids (FFAs). Although glycerol is cycled back to the liver to serve as a substrate for gluconeogenesis, FFAs are taken up by cells and are used as an alternate fuel source for oxidative phosphorylation and ATP production. circulating FFAs are oxidized in adipose tissue by mitochondrial uncoupling proteins, which are up-regulated by LMF. Therefore, LMF induces accelerated FFA oxidation in brown adipose tissue through up-regulation of uncoupling proteins, inducing fat catabolism. Importantly, this up-regulation of uncoupling proteins may represent the beginning of an important energy-wasting cycle. Uncoupling proteins normally decrease the coupling of respiration with the phosphorylation of ADP. Their action therefore generates heat instead of ATP and acts as an “energy sink,” since no ATP is produced when uncoupling proteins induce protons to cross the inner mitochondrial membrane. In a murine model of cachexia, murine adenocarcinoma 16 (MAC16) tumors caused overexpression of uncoupling protein-1 in brown adipose tissue, which resulted in increased thermogenesis, increased energy expenditure, and weight loss.

LMF therefore appears to be responsible for adipose tissue catabolism in cachexia, which it induces by directly stimulating lipolysis and by up-regulating expression of uncoupling proteins in brown adipose tissue, thereby increasing fatty acid oxidation.

Tumor Necrosis Factor-α. TNF-α promotes fat catabolism by inhibiting fat differentiation and increasing adipocyte apoptosis. The primary mechanism of TNF-α-induced fat loss in patients with cachectic cancer involves inhibition of LPL and stimulation of LMF. TNF-α inhibits LPL activity in human adipose tissue by down-regulating LPL protein expression. Increased LPL activity produces hyperlipidemia and prevents the storage of fat, while increased LMF release stimulates the release of FFAs from adipocytes and induces their oxidation by uncoupling proteins. Also, TNF-α and IL-1 have both been shown to inhibit glucose and FFA transport into adipose tissue. This ultimately decreases lipogenesis in adipose tissue. Additionally, TNF-α has been implicated in down-regulating several enzymes involved in lipogenesis, including acetyl-CoA carboxylase, fatty acid synthase, and acyl-CoA synthase.

To summarize, the total body fat loss in patients with cachectic cancer is mediated primarily by increased lipolysis rather than by decreased fat synthesis. Increased lipolysis is a result of the actions of both LMF and TNF-α. The mechanism of LMF-mediated lipolysis involves increased expression of oxidative uncoupling proteins in brown adipose tissue. TNF-α inhibits LPL and stimulates the release of lipid-mobilizing factor.

INFLAMMATION

In addition to skeletal muscle and adipose tissue catabolism, cancer cachexia is characterized by a profound chronic inflammatory state. Inflammation in cachexia has been established in a number of different animal models of cachexia. It is characterized by increased release of proinflammatory cytokines such as IL-1β, IL-6, TNF-α, and IFN-γ. These cytokines are thought to be the principal catabolic factors in skeletal muscle and adipose tissue wasting in cachexia. These cytokines produce many of biochemical and metabolic dysfunctions seen cachexia, including hypermetabolism, anorexia, decreased muscle protein synthesis, and increased UPS-mediated muscle proteolysis. IL-6, TNF-α, and IFN-γ have been shown to activate NF-κB, triggering UPS-mediated muscle breakdown and inhibiting muscle protein synthesis through reduction in MyoD expression. TNF-α, on the other hand, can directly induce lipolysis.

Proinflammatory cytokines appear to potentiate each other’s actions. This is seen in the activation of proteolysis (TNF-α + IFN-γ + IL-1β) and in the up-regulation of cytokine receptors (TNF-α + IFN-γ). Also, cytokines such as IFN-γ, IL-1β, and IL-6 are thought to be responsible for the induction of acute-phase protein production. Together, increased cytokine levels have been shown to reduce survival time in cachectic patients.
Following is a summary of the major proinflammatory cytokines involved in the pathogenesis of cancer cachexia.

**Interleukin-1β.** Derived from macrophages and lymphocytes, IL-1β concentrations increase in the cachectic state. IL-1β is thought to be partly responsible for muscle wasting in cachexia, and is known to cause effects similar to those seen by TNF-α, including stimulation of muscle catabolism. Also, IL-1β appears to be linked to the development of cachexia through the induction of the inflammatory response. In a murine model of head and neck cancer, mice with a double mutation in the Toll-like receptor-4 (TLR4) lack the ability to mount an appropriate inflammatory response. This model, wild-type cogenic mice receiving injections with equal numbers of a squamous cell carcinoma cell line, SCCF-VII, were found to be more cachectic and exhibited higher levels of IL-1β than mutant mice (personal communication, Marion Couch, MD, PhD). IL-1β is also thought to be responsible for the induction of anorexia in cachetic patients. It can induce anorexia when administered to animals, and it may increase the levels of corticotrophin releasing hormone, an anorexigenic neurotransmitter. IL-1β may also increase levels of tryptophan in the cerebrospinal fluid, increasing serotonic neurotransmission production in the hypothalamus and inducing anorexia.

**Interleukin-6.** IL-6 is a glycoprotein predominantly secreted by activated immune cells. It is involved in the amplification of inflammatory cascades in the immune response, and its concentrations are increased in patients with cancer cachexia and in patients with lung cancer in whom IL-6 acts to enhance the acute phase response. Elevated IL-6 concentrations are correlated with poor nutritional status, impaired performance and shorter survival, indicating that the inflammatory response induced in part by IL-6 may cause a substantial amount of the morbidity seen in cachexia. IL-6 has also been implicated as an important mediator of cachexia in murine models. In BALB-C nude mice bearing colon-26 adenocarcinoma tumors, IL-6 is markedly over-secreted. Robust production of IL-6 by tumor cells has been shown to induce cachexia in murine adenocarcinoma models, and serum IL-6 levels have been shown to be 35% higher in cachetic mice than in noncachectic mice.

**Tissue Necrosis Factor-α.** TNF-α is a 17.4-kDa protein produced by macrophages and natural killer cells that plays a complex and multifaceted role in cancer cachexia. It induces proteolysis, activates lipolysis, and suppresses expression of enzymes involved in lipogenesis. TNF-α has been implicated in muscle wasting in several animal models, including the Yoshida AH-130 hepatoma and Lewis lung carcinoma. Increased concentrations of TNF-α are seen in cancer cachexia in humans and have been shown to correlate with decreased food intake and body weight, increased body temperature, decreased glycogen, lipid, and protein synthesis, and increased gluconeogenesis, lipolysis, and proteolysis. As mentioned previously, TNF-α appears to suppress skeletal muscle differentiation by suppressing MyoD expression, and it can down-regulate myosin heavy chain in combination with IFN-γ. Both of these occur in an NF-kB-dependent manner. TNF-α also appears to be involved in adipocyte apoptosis, which it induces by activating cellular proteases known as caspases. Experimental treatment of cachexia with the synthetic anti–TNF-α antibody infliximab demonstrated weight stabilization in 1 of 4 patients with metastatic small cell lung cancer.

**Interferon γ.** IFN-γ is a pleiotropic cytokine involved in the regulation of nearly all phases of immune and inflammatory responses. Produced by T lymphocytes and natural killer cells, IFN-γ causes imbalance between orexigenic and anorexigenic signals in the body. As mentioned above, IFN-γ, when administered together with TNF-α, induces UPS-mediated proteolysis in mice. It has also been shown to produce progressive weight loss in mice inoculated with Lewis lung tumors. Finally, treatment with anti–IFN-γ antibodies counteracts this effect, indicating a potential future treatment for cachexia.

To summarize, the proinflammatory cytokine pathways involved in cancer cachexia are quite complex. At this time, relatively little is known about how these cytokines induce and maintain cachexia in humans. But as more is learned about the ability of each human tumor system to induce cachexia, the relative contribution of these cytokines to the pathogenesis of cachexia will be understood. A final common pathway may exist for all proinflammatory cytokines involved in cachexia. This might ultimately become an avenue for future treatment.
ANABOLIC HORMONE DYSREGULATION
In normal adults, bone growth and tissue maintenance rely on an intact growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis. There is mounting evidence that patients with cachexia may have alterations in this axis. Acquired GH resistance has been reported, but the role of the GH/IGF-1 axis in catabolic states such as cancer cachexia has not been adequately characterized. Administering GH as part of an acute therapy for ICU patients has been shown to cause increased mortality. Therefore, more research is needed before GH or IGF-1 can be considered as a possible therapy for wasting.

NEUROENDOCRINE DYSFUNCTION
Patients with cancer frequently suffer from anorexia. The prevalence of anorexia in cachectic patients may range between 15% and 40% at presentation. This may be an effect of the tumor itself or the consequence of treatments such as chemotherapy and radiation. It appears that anorexia is a consequence of weight loss, rather than its cause, since reduced food intake in cachectic patients is preceded by tissue wasting. The mechanisms of appetite dysregulation in cancer cachexia appear to involve disrupted communication between peripheral organs and homeostatic control centers in the hypothalamus. Neuroendocrine afferent signals originating from peripheral organs inform the brain about nutritional requirements and energy status. In the healthy patient, peripheral nutritional signals are integrated and processed within homeostatic control centers in the hypothalamus and an appropriate response is communicated via efferent pathways back to peripheral organs. In the cachectic patient, however, disruption within this signaling system results in anorexia and reduced food intake. Three neuropeptide mediators of this signaling pathway, leptin, ghrelin, and neuropeptide Y (NPY), are believed to be responsible for the disruption of this feedback loop in cachectic patients.

Leptin. A product of the ob gene, leptin is a neuroendocrine hormone secreted by adipose tissue. It has anorectic and lipolytic properties and is known to regulate weight by inhibiting feeding. In normal patients, weight loss lowers leptin levels, triggering the hypothalamus to stimulate feeding. In most experimental models of cachexia, however, leptin levels are elevated. This results in inhibition of orexigenic signals. Indeed, some of the proinflammatory cytokines implicated in cachexia can produce chronic leptin up-regulation, resulting in increased anorexia. Although elevated leptin has been found in patients with cachectic cancer, low levels of leptin have been found in cachectic mice. In MAC16-tumor-bearing mice, for example, circulating leptin levels were significantly reduced. This indicates that leptin may not consistently mediate cachexia, and that tumor products such as LMF and PIF are able to override the effects of low levels of leptin and independently cause appetite suppression and cachexia. From the above evidence, we conclude that the role of leptin has not been accurately characterized. It is unclear at this point whether leptin plays a leading role in the development of anorexia in cancer cachexia, or if it is overridden by tumor-derived factors (Figure 6).

Ghrelin. Ghrelin is a novel GH-releasing peptide that was first isolated from the stomach. Secreted from the stomach, it stimulates food intake and decreases energy expenditure, thereby increasing body weight. Ghrelin circulates in the bloodstream under fasting conditions and transmits a hunger signal from the periphery to the CNS, where it acts directly to increase feeding and decrease sympathetic nerve activity. Ghrelin appears to act as a counterpart to leptin, which decreases feeding and increases sympathetic nerve activities. Indeed, cancer cachexia involves inordinately increased levels of active ghrelin. This may be a compensatory response to marked weight loss in the cachectic patient.

Neuropeptide Y. NPY is an orexigenic neurotransmitter that is involved in regulation of circadian rhythms, sexual functioning, anxiety, peripheral vascular resistance and cardiac contractility. Although widely distributed throughout the brain, it is found abundantly in the arcuate nucleus of the hypothalamus. A potent feeding-stimulatory peptide, NPY has been shown to reverse
anorexia induced by the proinflammatory cytokines IL-1β and ciliary neurotrophic factor. However, it has also been found to be dysfunctional in anorectic tumor-bearing rodents, making it a possible mediator of cancer cachexia in humans (Figure 7).

NEW CONCEPTS

Cancer Cachexia and Aging. As natural consequences of aging, patients with head and neck cancer often experience sarcopenia, physical inactivity, and reduced protein regeneration. Their sarcopenia from aging may be due to down-regulation of the growth hormone axis and decline in testosterone concentrations, while their physical inactivity may be multifactorial and their impaired protein synthesis a result of resistance to muscle-specific anabolic signals. Patients with cachectic head and neck cancer suffer from systemic inflammation and reduced food intake in addition to these aging-related processes. Therefore, treatment of patients with cachectic cancer requires a multipronged, multidisciplinary approach. Treatment plans should incorporate physical therapy to improve mobilization, high protein intake to maximize muscle anabolism, and neu-traceutical or pharmacologic intervention to blunt inflammation and improve food intake.

Cancer Cachexia: An Autoimmune Disease? Finally, not all tumors are the same, and all hosts are physiologically different. Certain tumors may secrete more catabolic factors or induce a more exaggerated inflammatory response in their hosts than other tumors. However, given the same tumor type and burden, why do some patients with cancer develop cachexia while others do not? We propose that there may be single nucleotide polymorphisms in a variety of important immune receptors that may predispose certain patients to develop cachexia. The presence of such polymorphisms might explain the interindividual differences seen in the clinical manifestations of cachexia.

One set of candidates for this genetic variability is the family of Toll-like receptors (TLRs). These cell-surface receptors are involved in immune regulation and mediate both sterile and infectious inflammatory responses and the complex responses involved in autoimmunity. Their stimulation produces a robust cytokine response, which includes elaboration of IL-1β, IL-6, TNF-α, and IFN-γ. Ten TLR paralogs have been identified in humans, which together recognize exogenous mol-
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Further investigation into the distribution of single nucleotide polymorphisms in TLR genes may explain interindividual differences in the clinical manifestations of inflammation in cancer cachexia. This may ultimately enable us to prevent the development of muscle wasting, adipose tissue loss, and anorexia in patients with cancer.

CONCLUSION

Cachexia represents a complex metabolic state characterized by progressive weight loss, muscle and fat atrophy, and neuroendocrine dysfunction mediated mainly by tumor- and host-derived factors. Disruption of specific physiologic processes mediates the clinical manifestations of this disease. For example, cytokine-mediated up-regulation of the UPS, tumor secretion of PIF, and dysregulation of the DGC mediate accelerated muscle catabolism. Imbalance in the amino acid pool, reduced myosin expression, and myostatin up-regulation result in impaired skeletal muscle development, while LMF and TNF-α appear to control fat wasting. A host of proinflammatory cytokines, including IL-1β, IL-6, TNF-α, and IFN-γ, mediate systemic inflammation, although the exact mechanisms for their actions have not become clear. Additionally, neuroendocrine mediators like leptin, ghrelin, and NPY contribute to disruption of hypothalamic neuroendocrine pathways and thereby induce anorexia.

Areas for treatment of cachexia are emerging. Proteasome suppression, anticytokine treatment, and inhibition of NF-xB may develop as means for anticachexia therapy. Future therapies may also focus on correcting neuroendocrine deficits or promotion of muscle anabolism by targeting the proteolytic effects of inflammatory and catabolic factors. Adequate clinical studies remain to be performed to determine the most effective means of anticachexia therapy.

Finally, new concepts are evolving in this field. These include the role of aging in cancer cachexia and the role of TLR gene polymorphisms in altering responses to the cachectic state. We hope further research into these areas will answer remaining questions about the underlying mechanisms of cachexia.

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