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Review Article

Understanding cachexia and its impact on lung cancer and beyond

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ABSTRACT

Cancer cachexia is a multifactorial syndrome characterized by loss of body weight secondary to skeletal muscle atrophy and adipose tissue wasting. It not only has a significant impact on patients' quality of life but also reduces the effectiveness and tolerability of anticancer therapy, leading to poor clinical outcomes. Lung cancer is a prominent global health concern, and the prevalence of cachexia is high among patients with lung cancer. In this review, we integrate findings from studies of lung cancer and other types of cancer to provide an overview of recent advances in cancer cachexia. Our focus includes topics such as the clinical criteria for diagnosis and staging, the function and mechanism of selected mediators, and potential therapeutic strategies for clinical application. A comprehensive summary of current studies will improve our understanding of the mechanisms underlying cachexia and contribute to the identification of high-risk patients, the development of effective treatment strategies, and the design of appropriate therapeutic regimens for patients at different disease stages.

Introduction

Lung cancer is one of the most frequently diagnosed cancer types and the leading cause of cancer-related death worldwide, with an estimated 2.2 million new cases and 1.8 million deaths in 2020.[1,2] Lung cancer is a highly heterogeneous disease characterized by a wide spectrum of clinicopathological features. It can be broadly categorized into two main types: non-small cell lung cancer (NSCLC), which accounts for approximately 85% of all diagnoses, and small cell lung cancer, constituting the remaining 15% of cases.[3,4] Lung cancer is characterized by aggressive progression and a relatively low 5-year survival rate, underscoring its status as a significant global public health challenge.[5] Patients diagnosed with lung cancer often have a high risk of developing cachexia, a condition that adversely affects the patient's prognosis.[6] Cachexia is characterized by fatigue, anorexia, involuntary weight loss, and progressive physical impairment, and it is frequently observed in patients with advanced stages of cancer.[7,8] An international consensus established in 2011 defined cancer cachexia as a multifactorial syndrome characterized by ongoing loss of skeletal muscle mass, with or without loss of fat mass, which cannot be fully reversed by conventional nutritional support.[9]

Cachexia was previously regarded as an unfortunate consequence of cancer. Therefore, its treatment has historically been neglected in clinical practice. However, cancer cachexia not only has a dramatic impact on patients' quality of life but also increases the risk of treatment-related toxicity.[10] Patients with cachexia are less able to tolerate cancer treatments, such as chemotherapy, radiation, and surgery, leading to treatment delays, dose reductions, and even treatment interruptions. Cancer cachexia may also lead to other complications, such as an increased risk of infection and impaired wound healing. Statistically, cancer cachexia is associated with reduced survival and a poor response to chemotherapy.[11–19] Cachexia occurs in most patients with terminal cancer and is responsible for an estimated 20% of all cancer-related deaths.[20]

Adipose tissue and muscle mass are two key characteristics of cachexia that reportedly serve as powerful prognostic factors in predicting the survival of patients with cancer, underscoring the importance of cachexia in clinical guidance.[21,22] Nevertheless, cachexia is a complex syndrome that involves more than just the loss of muscle and fat tissue. It is an insidious condition that causes extensive damage to patients' immune, nervous, and metabolic systems.[23] Although the mechanisms underlying cachexia are not fully understood, it is generally believed to involve multiple organs and various factors (Fig. 1). Treatment of cachexia in the clinical setting continues to be challenging. Therefore, a comprehensive and in-depth study of cancer cachexia is of great importance for gaining an understanding of its underlying mecha-

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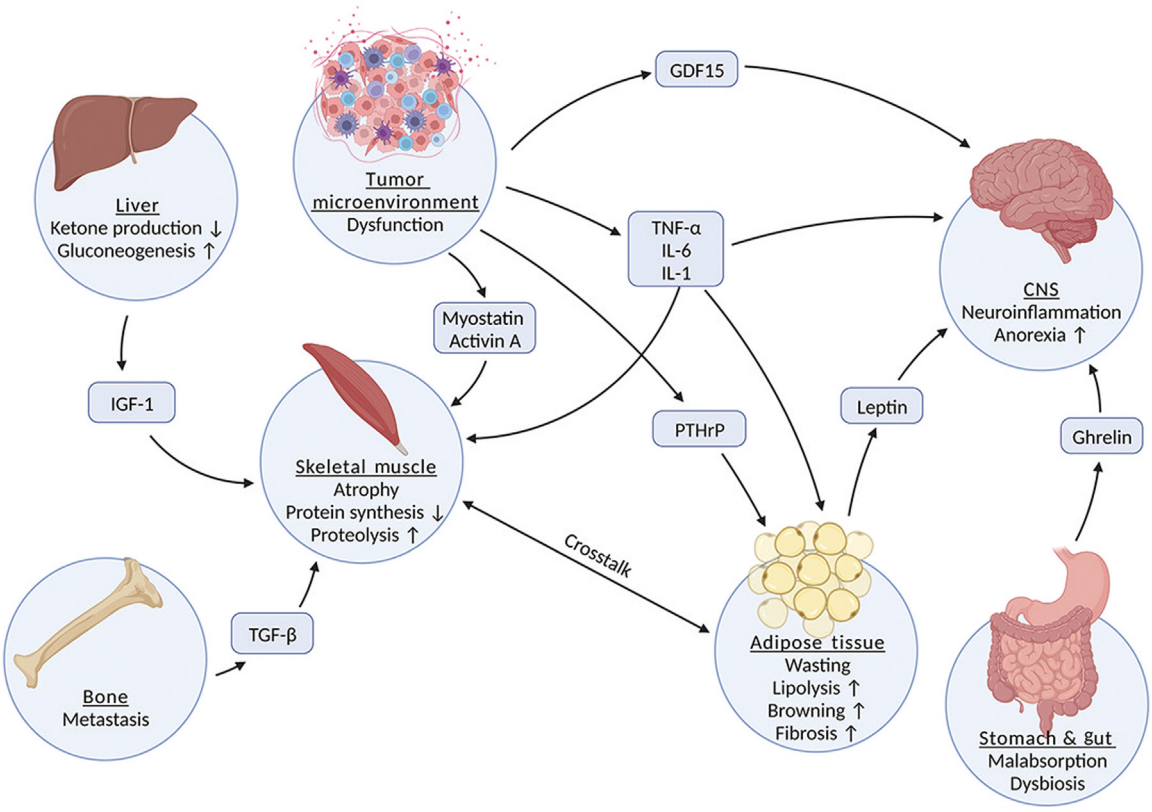

Fig. 1. Schematic illustration of multiorgan interactions in cachexia. This simplified diagram illustrates the major organs commonly affected during the progression of cachexia and the mediators involved in its development. Tumor microenvironment-derived proinflammatory cytokines and catabolic factors can directly act on skeletal muscle, adipose tissue, and the CNS, resulting in cachexia-associated muscle atrophy, adipose wasting, and neuroinflammation and anorexia, respectively. In addition, liver-derived IGF-1 and bone-derived TGF-β can contribute to the development of this wasting syndrome by acting on skeletal muscle. Adipose tissue-derived leptin and gastric enteroendocrine cell-derived ghrelin also act on the CNS to regulate appetite. Meanwhile, cross talk occurs between skeletal muscle and adipose tissue. Multiorgan and multifactorial interactions collectively contribute to the progression of cancer cachexia. Representative symptoms of each organ affected by cachexia are also indicated in the diagram. CNS: Central nervous system; GDF15: Growth differentiation factor 15; IGF-1: Insulin-like growth factor-1; IL-1: Interleukin-1; IL-6: Interleukin-6; PTHrP: Parathyroid hormone-related protein; TGF-β: Transforming growth factor-beta; TNF-α: Tumor necrosis factor-alpha.

nisms, developing effective treatment strategies, and improving clinical outcomes.

Diagnosis and staging of cancer cachexia

Considering the high incidence and adverse effects of cachexia in patients with cancer, it is important to establish a series of diagnostic and staging criteria for cachexia so that appropriate and physically tolerable treatment strategies can be implemented for patients who develop various symptoms during clinical management.

According to its severity, cancer cachexia can be divided into three stages: precachexia, cachexia, and refractory cachexia.[9] Notably, not every patient with cancer cachexia will develop all the three stages. During precachexia, patients mainly present with altered metabolism, such as anorexia or impaired glucose tolerance, accompanied by involuntary weight loss of ≤5%. Weight loss of >5% in the previous 6 months is described as cachexia that tends to be responsive to treatment. Patients with refractory cachexia present with a low performance status and have a life expectancy of <3 months. When cachexia has progressed to a clinically evident refractory stage, it is generally considered irreversible. During this phase, the goal of treatment is to alleviate the patient's symptoms and distress. Therefore, identification and intervention at an early stage of cachexia are important. However, this staging system lacks clear criteria and precise cutoffs for each stage, making clinical diagnosis and guidance challenging. Attempts have been made to stage cachexia according to clinical phenotypes. However, because of the complexity of the disease, the proposed staging systems differ in the number of cachexia stages and the criteria used for classification (Table 1).

In 2011, Argilés et al[24] developed the cachexia score (CASCO), a quantitative framework for staging cachexia as mild, moderate, severe, or terminal. The main components of the CASCO are as follows: body weight loss and composition, inflammation/metabolic disturbances/immunosuppression, physical performance, anorexia, and quality of life. However, owing to the extensive number of measurements and questionnaires involved, the CASCO is not suitable for rapid screening in the clinical setting, which limits its routine implementation. Therefore, researchers have proposed the miniCASCO (MCASCO), a simpler version of the CASCO that performs as well as its predecessor.[25] Nevertheless, both the CASCO and MCASCO require various indicators that are not routinely tested in clinical practice, making these scores difficult to apply on a large scale. Although current clinical data demonstrate the effectiveness of the CASCO and MCASCO to a certain extent, their sensitivity and specificity must be further validated in larger samples.[25]

Vigano et al[26] proposed four cancer cachexia stages (non-cachexia, pre-cachexia, cachexia, and refractory cachexia) and seven criteria (abnormal biochemistry, anorexia or decreased appetite, weight loss with/without muscle wasting, reduction in strength, and decreased function). Compared with the CASCO, this system is simpler to use; however, it still requires diagnostic tools that are not routinely available, such as dual-energy X-ray absorptiometry. Therefore, clinically applicable staging-assessment criteria with a briefer questionnaire were subsequently designed to make the classification system more practical

Table 1
Summary of cancer cachexia staging systems.

Study	Stage	Factors	References
Argilés JM et al (CASCO)	Mild cachexia Moderate cachexia Severe cachexia Terminal cachexia	Body weight loss and composition Inflammation/metabolic disturbances/immunosuppression Physical performance Anorexia Quality of life	24
Argilés JM et al (MCASCO)	Without cachexia Mild cachexia Moderate cachexia Severe cachexia	*Reduced number of items according to CASCO* Body weight loss and composition Blood measurements (albumin, anemia, CRP, and absolute lymphocyte number) A questionnaire containing 2 questions related with physical performance, 2 related with anorexia and 11 related with quality of life	25
Vigano AAL et al (CCS)	Non-cachexia Pre-cachexia Cachexia Refractory cachexia	Abnormal biochemistry Anorexia or decreased appetite Weight loss with and without muscle wasting Reduction in strength Decreased function	26
Vigano AAL et al	Non-cachexia Pre-cachexia Cachexia Refractory cachexia	*A subset of CCS* Biochemistry indicators Food intake Weight loss Performance status	27
Zhou T et al (CSS)	Non-cachexia Pre-cachexia Cachexia Refractory cachexia	Weight loss A simple questionnaire of sarcopenia Performance status Appetite loss Abnormal biochemistry	28
Blum D et al	No cachexia Pre-cachexia Cachexia Refractory cachexia	Weight loss and BMI	29
Martin L et al and Vagnildhaug OM et al	Grade 0–4	Percent weight loss and BMI	30, 31

BMI: Body mass index; CASCO: Cachexia score; CCS: Cancer cachexia stages; CRP: C-reactive protein; CSS: Cachexia staging score; MCASCO: MiniCASCO.

for clinicians.[27] This system contains only a subset of diagnostic indicators selected from the original seven classification criteria, including biochemistry indicators, food intake, weight loss, and performance status. Nevertheless, both methods failed to distinguish patients with pre-cachexia and those with cachexia.

Zhou et al[28] recently developed a clinically applicable cachexia-staging score that includes the following five components: weight loss, a simple questionnaire of sarcopenia, the Eastern Cooperative Oncology Group performance status, appetite loss, and a clinically available abnormal biochemistry criterion. This scoring system showed good discrimination for classifying cachexia in a single-center study with a small sample size. However, this system still contains some subjective evaluation elements, which makes it challenging to expand the system on a large scale.

The extensive number of indicators in the above diagnostic criteria restricts their application in terms of clinical diagnosis and large-scale analyses. Therefore, some studies use weight loss, the main symptom of cachexia, as the major indicator for classification. Specifically, the severity of body mass index-adjusted weight loss could serve as a valid diagnostic criterion when staging cancer cachexia.[29–31] However, it is generally accepted that the diagnostic criteria for cancer cachexia will inevitably include information beyond the mere assessment of weight loss, such as the presence of skeletal muscle atrophy, anorexia, and inflammation. More studies are required to identify novel diagnostic criteria that combine simplicity and effectiveness.

Lung cancer-related cachexia

Cachexia affects approximately 50–80% of patients with cancer, and the incidence varies among different cancer types.[20] Patients with lung cancer are often affected by cachexia, which significantly impacts their prognosis.[32] In a study of 10,128 patients with lung cancer, the body mass index and weight loss were found to be significantly associated with overall survival (OS), with a more pronounced impact on patients with NSCLC than on those with small cell lung cancer. This finding suggests that incorporation of a body mass index–weight loss grading scale may offer valuable prognostic insights for future clinical trials of patients with advanced lung cancer.[33]

Muscle wasting is a prominent characteristic of lung cancer, even in patients with normal or higher body weights.[34] A meta-analysis confirmed that approximately half of the individuals with lung cancer developed skeletal muscle loss, which was correlated with reduced OS.[14] Furthermore, in patients with lung cancer, cachexia has been demonstrated to be associated with heightened treatment toxicity.[16] Another study indicates that low pretreatment skeletal muscle mass is associated with a significantly higher risk of severe hematological toxicities, while high skeletal muscle density is linked to a reduced risk of dose-limiting toxicities. These findings further highlight the importance of research into tailoring platinum dosing based on skeletal muscle measurements to potentially mitigate toxicity without compromising treatment effectiveness.[35] In a retrospective study of 55 patients with stage IV NSCLC treated with nivolumab, subcutaneous fat mass was found to be a significant prognostic factor for OS, highlighting its potential as a valuable anthropometric parameter in this context.[36]

Lung cancer, with a mere 23% 5-year survival rate, continues to top the charts for cancer-related deaths globally, underscoring the pressing necessity to enhance both its diagnosis and treatment methodologies.[37] Furthermore, it emphasizes the importance of prioritizing research and interventions related to cachexia, the management of which could significantly improve patients' prognosis. Therefore, a profound understanding of cancer cachexia is imperative. Integration of data across different cancer types is expected to provide a comprehensive understanding of the pathogenesis of cachexia, providing valuable insights for management and is expected to improve overall patient prognosis.

Mediators involved in cancer cachexia

Cancer cachexia is a complex syndrome caused by a multitude of factors, including inadequate nutritional intake secondary to anorexia and obstruction of the digestive tract, metabolic imbalance particularly enhanced by catabolism and increased energy expenditure, and systemic disorders directly or indirectly induced by a series of mediators.[38–40] These mediators can be produced by both tumors and host tissues and can activate various signaling pathways that contribute to the development and progression of cachexia. In this context, we provide a brief summary of typical mediators associated with cancer cachexia and describe the corresponding molecular mechanisms (Fig. 2).

Microenvironment-derived proinflammatory cytokines

Studies of the mechanisms of cachexia have mainly focused on the inflammatory response. As early as 1997, proinflammatory factors produced by tumor or host immune cells, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-1, were considered to play a central role in both the loss of skeletal muscle protein and the initiation of the acute-phase response to inflammation.[41] Systemic inflammation is considered to be the driving force of muscle wasting, which is the most important characteristic of cachexia.[42]

TNF-α, also known as cachectin, was first characterized as a multipotent protein that is secreted by activated macrophages and exhibits

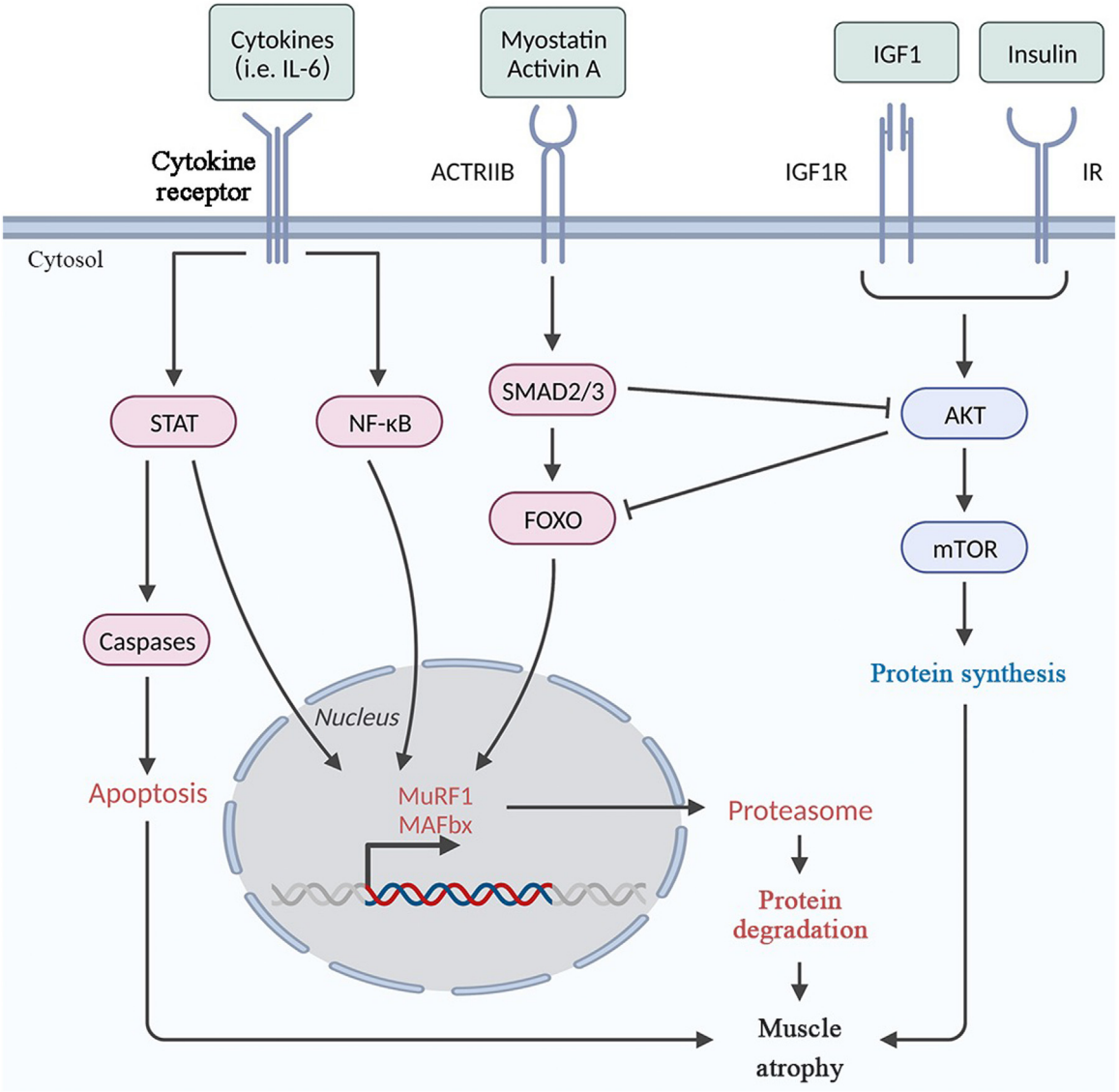

Fig. 2. Signaling pathways involved in muscle atrophy during cachexia. This schematic diagram illustrates the major signaling pathways involved in muscle atrophy. Cytokines, such as IL-6, activate the NF-κB and JAK/STAT signaling pathways, leading to increased protein degradation through transcription of genes encoding ubiquitin ligases, including MuRF1 and MAFbx. JAK/STAT signaling also induces apoptosis-associated caspase activation. Furthermore, binding of myostatin and activin A to ACTRIIB leads to the activation of SMAD 2/3 and downstream FOXO signaling. At the same time, SMAD 2/3 suppresses activation of the PI3K/AKT/mTOR signaling pathway, which is also involved in FOXO signaling. In addition, the binding of IGF-1 and insulin to their respective receptors, IGF-1R and IR, activates the PI3K/AKT/mTOR signaling pathway, which in turn stimulates protein synthesis. In this schematic diagram, the activated signaling pathways are indicated in red and the decreased signaling pathways are shown in blue. ACTRIIB: Activin type IIB receptor; AKT: Protein kinase B; FOXO: Forkhead box O; IGF-1: Insulin-like growth factor-1; IGF-1R: Insulin-like growth factor 1 receptor; IL: Interleukin; IR: Insulin receptor; JAK/STAT: Janus kinase/signal transducer and activator of transcription; MAFbx: Muscle atrophy F-box; mTOR: Mammalian target of rapamycin; MuRF1: Muscle RING-finger protein-1; NF-κB: Nuclear factor-kappaB; PI3K: Phosphatidylinositol 3-kinase; SMAD: Smad family member.

biological effects that induce wasting.[43,44] Animal experiments revealed that mice bearing TNF-α-secreting tumors developed severe cachexia and died more quickly.[45] TNF-α is considered to be a major factor in the induction of cachexia and is responsible for increased gluconeogenesis, loss of adipose tissue, and proteolysis, leading to reduced protein, lipid, and glycogen synthesis.[46] Mechanistic studies have revealed that TNF-α can lead directly to skeletal muscle decomposition by activating nuclear factor-kappaB (NF-κB).[47] When activated, NF-κB increases the expression of muscle RING-finger protein-1 (MuRF1) and muscle atrophy F-box (MAFbx), two muscle-specific E3 ubiquitin ligases that are transcriptionally increased during skeletal muscle atrophy.[48,49]

IL-6 is a well-studied cytokine that influences several biological functions, including the immune response, metabolism, hematopoiesis, and tumorigenesis. Patients with cachexia show significantly higher serum IL-6 levels than healthy control groups and patients without cachexia.[50–55] Animal experiments have further demonstrated that IL-6 is sufficient to induce cachexia.[56,57] Furthermore, in C26 tumor-implanted mice and an adenomatous polyposis coli (Apc)$^{Min/+}$ mouse model (genetically engineered to have a mutation in the *Apc* gene), attenuation of IL-6 signaling was effective in blocking the progression of cancer cachexia.[58,59] IL-6 acts mainly through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway. Activated STAT3 in muscle cells can upregulate myostatin, MuRF1, and MAFbx through CCAAT/enhancer-binding protein-δ (C/EBPδ), while also mediating the activation of caspase-3.[60,61] JAK/STAT signaling is also reported to be associated with satellite cell expansion. In aging and atrophic muscles, inhibition of the JAK/STAT signaling pathway effectively enhances tissue repair capacity.[62,63] In addition to muscle loss, IL-6 also induces fat loss by promoting lipolysis and browning of white adipose tissue,[64] and the occurrence of tissue cross talk *via* an IL-6 trans-signaling loop has been established.[65] IL-6 also reduces the hepatic ketogenic potential through suppression of peroxisome proliferator-activated receptor-alpha (PPARα), a key regulator of ketogenesis.[66] Restoration of ketone production with a PPARα agonist has been shown to prevent loss of skeletal muscle mass and body weight in mice with lung cancer.[67]

During peripheral tumor development, many cytokines act on the central nervous system (CNS) to elicit cachexia-associated phenomena such as anorexia and fatigue. IL-1 is among the most important of these cytokines.[68] Pro-opiomelanocortin neurons in the arcuate nucleus of the hypothalamus have been found to express IL-1 receptors.[69] Therefore, IL-1β can regulate central melanocortin signaling, a key neuronal circuit that regulates energy homeostasis. The response of brain endothelial cells to IL-1β is dependent on myeloid differentiation primary response protein (MyD88), and deletion of MyD88 greatly relieves the symptoms of cachexia.[70,71] CNS inflammation is sufficient to induce muscle atrophy, and alterations in peripheral protein metabolism are ameliorated when IL-1 receptors in the CNS are pharmacologically antagonized.[72,73]

Tumor-derived catabolic factors

The development and progression of cancer cachexia is a complex process that involves multidirectional interactions between the tumor and the host. In general, there is an overlap between tumor-secreted and host-secreted factors, and we herein summarize the functions of those factors that are primarily secreted by tumor cells.

Transforming growth factor-beta (TGF-β) signaling plays an important role in muscle development and is dysregulated in many diseases, including cancer.[74,75] Growth differentiation factor 15 (GDF15), also known as macrophage inhibitory cytokine-1, is a member of the TGF-β superfamily and has been implicated in regulation of food intake, energy expenditure, and regulation of body weight.[76] In both animal models and in patients with cancer, elevated levels of circulating GDF15 are associated with cachexia and reduced survival.[77,78] Studies in mice have further indicated that high circulating levels of GDF15 act as a potent inducer of cachexia and that blocking GDF15 signaling reverses the syndrome.[79,80] The function of GDF15 is mediated by its binding to its receptor, glial cell-derived neurotrophic factor family receptor α-like, in the CNS (specifically in the hindbrain region that regulates energy balance).[81–84]

Myostatin and activin A are two other important members of the TGF-β superfamily. Myostatin, also known as growth differentiation factor 8 (GDF8), was first identified as a negative regulator of skeletal muscle mass.[85] Activin A is a dimeric glycoprotein assembled from two beta subunits that can be combined with alpha subunits to form inhibins.[86] Myostatin and activin A exert their effects through the same surface receptors, namely activin type II receptors (ActRIIA/B), which in turn activate activin receptor-like kinase 4/5.[87] This signaling leads to activation of the Smad family member (SMAD) 2/3 and in turn stimulates forkhead box O (FOXO)-dependent transcription of MuRF1 and MAFbx.[88,89] Activated SMAD 2/3 also inhibits synthesis of muscle protein by suppressing phosphatidylinositol 3-kinase (PI3K)/AKT signaling.[90] The ActRIIB pathway plays an important role in limiting muscle growth. Inactivation of ActRIIB leads to muscle hypertrophy in transgenic mice, and ActRIIB antagonism has been found to effectively reverse muscle wasting in mouse models of cachexia.[91–93] Studies also suggest that myostatin can attenuate insulin-like growth factor-1 (IGF-1)-mediated myotube hypertrophy through AKT signaling.[94,95] In a clinical study, circulating activin A levels were positively correlated with weight loss. However, the myostatin level was significantly reduced in patients with cachexia, indicating that myostatin is neither a vital trigger for inducing cachexia nor a universal circulating marker of it.[96]

In addition to the above-mentioned factors secreted primarily by tumor cells, other members of the TGF-β superfamily are involved in cancer cachexia. For example, bone-derived TGF-β is known to contribute to muscle weakness by oxidation of ryanodine receptor-1, which leads to leakage of calcium ions and resultant decreased muscle force production.[97] TGF-β signaling is also associated with fibrosis of adipose tissue in cancer cachexia.[98]

Parathyroid hormone-related protein (PTHrP), the N-terminal of which is homologous to parathyroid hormone (PTH), was discovered as a tumor-derived hormone.[99] Tumor cells can directly activate adipose tissue browning through PTHrP secretion, which stimulates thermogenic gene expression in adipose tissue, and this phenotype can be reversed by PTHrP neutralization.[100,101] The serum PTHrP level was found to be independently associated with an increased risk of weight loss in a cohort of patients with cancer, indicating the diagnostic potential of PTHrP.[102]

Host-derived hormones

Cachexia is directly caused by alterations in the energy balance. Most hormones are involved in maintenance of the energy balance and play an important role in cancer cachexia. An imbalance of anabolic/catabolic hormones leads to increased energy expenditure, and changes in the appetite-regulating hormones affect dietary intake by altering the sensations of hunger and satiety.[103,104]

The first metabolic abnormality recognized in patients with cancer was glucose intolerance, which was described as early as 1919. Insulin plays an essential role in coordinating the oxidation and storage of glucose in the body.[105] In patients with cancer, elevated glycolysis in tumor tissues leads to lactate accumulation, which promotes gluconeogenesis in the liver, thereby increasing the production of glucose and energy expenditure. High glucose levels then result in overproduction of insulin, ultimately leading to insulin resistance.[106] Patients with cancer often develop insulin resistance, and reduced insulin sensitivity is associated with cachexia.[107] An animal study showed that insulin resistance was an early event in skeletal muscle atrophy and that treatment with the insulin sensitizer rosiglitazone alleviated early cachectic features, suggesting that insulin resistance contributes to cachexia.[108] Insulin is a potent anabolic hormone that regulates the synthesis and degradation of protein. Inactivation of the insulin pathway leads to inactivation of

the insulin receptor, which in turn leads to reduced AKT phosphorylation.[109] As a result, FOXO3 translocates to the nucleus and activates protein degradation. At the same time, reduced AKT phosphorylation leads to inactivation of the mammalian target of rapamycin, which prevents protein synthesis in both muscle and adipose tissue.[110]

IGF-1 is a polypeptide hormone with a structural basis similar to that of insulin, and it belongs to the family of growth factor hormones. It is a highly anabolic hormone affecting numerous areas of the human body and is reportedly associated with muscle atrophy.[111] Overexpression of IGF-1 in skeletal muscle leads to a hypertrophic phenotype that can resist atrophy.[112] In a mouse model of spinal and bulbar muscular atrophy, overexpression of IGF-1 reduced muscle pathology and reversed histopathological abnormalities.[113] IGF-1 acts through its receptor and activates a downstream signaling pathway similar to that activated by the insulin receptor. As mentioned above, AKT is involved in various intracellular metabolic activities, and the effects exerted by IGF-1 mainly result from dysregulation of the PI3K/AKT pathway.[114,115]

Appetite is mainly regulated by two endogenous hormones: ghrelin, which promotes appetite, and leptin, which suppresses it. Ghrelin, also known as the “hunger hormone,” is a circulating hormone that is secreted by gastric enteroendocrine cells and exerts its pro-appetitive effect by acting on the growth hormone secretagogue receptor in the CNS.[116] Administering ghrelin to patients has been shown to alleviate cachexia syndrome in individuals afflicted with cancer, chronic obstructive pulmonary disease (COPD), and chronic heart failure.[117–120] Specifically, ghrelin increases transcription of the orexigenic neuropeptides agouti-related protein and neuropeptide Y, leading to depolarization of the resting membrane potential.[121,122] In addition to its appetite-promoting effects, ghrelin also suppresses the production of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α[123–125] and directly protects against muscle wasting.[126,127] In clinical practice, elevated serum ghrelin has been reported in multiple types of cancer and is associated with cachexia.[128–131] Given its positive role in energy intake, ghrelin elevation is thought to be a compensatory effect for imbalanced energy metabolism.

By contrast, leptin is an adipocyte-derived hormone that suppresses appetite and increases energy expenditure by binding to leptin receptors in the hypothalamus and in certain peripheral organs such as adipose tissue.[132] In patients with advanced NSCLC, a significant correlation has been reported between leptin levels and the presence of cachexia.[133] Leptin has been found to antagonize the activity of ghrelin in the arcuate nucleus of the hypothalamus.[134] It also leads to reduced body weight by exerting a direct effect on brown and white adipose tissue.[135,136]

Therapeutic strategies for cancer cachexia

Cancer cachexia not only compromises the efficacy of many therapeutic interventions but is also exacerbated by cancer therapies.[137,138] Most patients with advanced cancer develop cachexia, for which no standard guidelines or treatments have been established. It is now becoming increasingly appreciated that cachexia is a systemic syndrome and cannot be reversed by a single agent. Therefore, a multimodal approach including anti-cachexia therapy, anti-cancer therapy, nutritional support, physical exercise, and psychosocial interventions would be a more promising direction in terms of clinical treatment.[10,139–141] A previous clinical trial demonstrated that early palliative care led to significant improvements in both quality of life and survival among patients with metastatic NSCLC.[142] The NEXTAC program, combining exercise and nutritional interventions, exhibited excellent compliance and safety in elderly patients with newly diagnosed NSCLC and pancreatic cancer undergoing chemotherapy.[143] A phase II study is currently underway to further assess functional prognosis.[144]

However, due to the complexity of cachectic patient manifestations, establishing standard prescriptions with non-pharmacological approaches is exceedingly challenging in clinical practice. Developing effective drugs targeting cachexia remains the most efficient way to benefit patients suffering from cachexia. It is encouraging that anamorelin, a ghrelin-like agonist, has been approved for treating NSCLC-related cachexia and is available in Japan. Ghrelin has an important role in appetite stimulation.[116] However, the clinical use of ghrelin is limited by its short half-life and the need for intravenous or subcutaneous injections.[145,146] Several ghrelin receptor agonists with oral activity and longer half-lives have thus been developed, including anamorelin, ibutamoren, relamorelin, and macimorelin.[147] Among these, anamorelin has demonstrated beneficial effects on lean body mass and anorexia in landmark clinical studies[148–151] and has been approved for the management of cachexia in patients with NSCLC, gastric cancer, pancreatic cancer, and colorectal cancer in Japan.[152] Currently, two phase III multicenter studies of anamorelin are still awaiting results for the treatment of malignancy-associated weight loss and anorexia in adult patients with advanced NSCLC (NCT03743051 and NCT03743064).[153] However, anamorelin was not licensed in Europe and the US due to lack of adequate data on patient benefits and safety. Even in Japan, anamorelin is not commonly used in routine practice, highlighting the necessity for more research on pharmacological approaches in cancer cachexia management. Current therapeutic approaches mainly focus on anti-inflammatory alterations to counteract wasting or the use of appetite stimulants like anamorelin to increase energy intake.[10,154,155] Here we briefly introduce selected pharmacological approaches with promising potential in cancer cachexia management (Table 2). Cannabinoids, the active components of cannabis, have a palliative effect in patients with cancer by preventing nausea, vomiting, and pain and stimulating appetite.[156] Cannabinoids exert their effects by interacting with two classical cannabinoid receptors: cannabinoid receptors type 1 and 2. Cannabinoid receptor 1 is the most abundant G protein-coupled receptor in the brain and forms part of the neural circuitry regulated by leptin, whereas cannabinoid receptor 2 is preferentially expressed on immunocytes.[157,158] Dronabinol, delta-9-tetrahydrocannabinol, and nabilone are the most frequently used cannabinoids, all of which have been reported to have a positive effect on anorexia.[159–162]

Megestrol acetate (MA), a synthetic progestogen, was approved by the U.S. Food and Drug Administration for the treatment of acquired immune deficiency syndrome (AIDS)-associated unintentional weight loss and anorexia in 1993.[163] Several studies have suggested that MA functions as an appetite stimulant by increasing regional hypothalamic neuropeptide Y concentrations and reducing the levels of proinflammatory cytokines.[164,165] Administration of MA to improve body weight has been demonstrated in various trials.[166] However, it has also been reported that MA does not lead to full recovery of the lost weight or improve quality of life to a significant extent.[167,168]

Non-steroidal anti-inflammatory drugs (NSAIDs) are approved by the U.S. Food and Drug Administration as antipyretic, anti-inflammatory, and analgesic agents. NSAIDs exert their effects mainly through the inhibition of cyclooxygenase-2 (COX-2) activity, which is associated with reactive oxygen species production and inflammatory signals.[169] NSAIDs may be nonselective (e.g., ibuprofen) or selective (e.g., celecoxib). Selective COX-2 inhibitors reduce adverse effects in the gastrointestinal tract by primarily targeting COX-2 while minimizing their impact on COX-1.[170] While some studies have revealed improved outcomes in terms of body weight and quality of life in patients with cancer who are treated with NSAIDs, there is insufficient evidence to support their clinical application in cancer cachexia treatment.[171–174]

Anticytokine therapy is a promising strategy for cancer cachexia, considering the importance of proinflammatory cytokines in its development. Thalidomide is a synthetic derivative of glutamic acid with anti-inflammatory and anti-angiogenic properties. It inhibits the production of proinflammatory cytokines, such as TNF-α and IL-6, by preventing binding of NF-κB to the promoters of its target genes.[175] However, the clinical outcome of treatment with thalidomide in patients with cachexia is not consistent, and there is insufficient evidence to support or oppose its use as a treatment for cancer cachexia.[176,177] OHR/AVR118 (Product R) is a peptide–nucleic acid immunomodulator with anti-inflammatory

Table 2
Summary of pharmacological strategies for patients with cancer cachexia and representative clinical studies.

Agent	Disease	Study	Results	Reference
Cannabinoids	Pan-cancer	Brisbois TD et al NCT00316563	Improved chemosensory perception Increased premeal appetite and increased proportion of calories consumed as protein Increased quality of sleep and relaxation	143
Megestrol acetate*	HCC	Chow PKH et al NCT00041275	Negatively associated with OS (not statistically significant) Worse global health status (not statistically significant) Reduced levels of appetite loss and nausea/vomiting	151
Anamorelin†	NSCLC	Temel JS et al NCT01387269 NCT01387282	Increased LBM, but not handgrip strength	156
NSAIDs	Pan-cancer	Mantovani G et al	Increased LBM and a significant decrease in TNF-α Improved grip strength, quality of life, and performance status	163
Thalidomide	Pan-cancer	Yennurajalingam S et al	Both the thalidomide and the placebo groups showed reduction in cytokines Improvements were not significantly different in two groups	168
OHR/AVR118 (Product R)	Pan-cancer	Chasen M et al	Weight stabilization or gain Improved appetite and depression	170
Infliximab	NSCLC	Jatoi A et al	Early evidence of the lack of efficacy prompted early trial closure	171
MABp1	Pan-cancer	Hong DS et al NCT01021072	Decreased plasma IL-6 concentrations Increased LBM	176
ALD518	NSCLC	Rigas JR et al	Improved lung symptom score, reversed fatigue, and reduced loss of LBM	173
Tocilizumab	LCC	Ando K et al	Rapidly lessened symptoms, improved appetite, and normalized CRP levels	175

*Approved by the FDA for the treatment of unintentional weight loss and anorexia in patients with AIDS. †Approved for the management of cachexia in patients with NSCLC, gastric cancer, pancreatic cancer, and colorectal cancer in Japan. AIDS: Acquired immunodeficiency syndrome; CRP: C-reactive protein; FDA: US Food and Drug Administration; HCC: Hepatocellular carcinoma; IL-6: Interleukin-6; LBM: Lean body mass; LCC: Large-cell carcinoma; NSAIDs: Non-steroidal anti-inflammatory drugs; NSCLC: Non-small cell lung cancer; OS: Overall survival; TNF-α: Tumor necrosis factor-alpha.

activity. It exerts this activity by inhibition of cellular proinflammatory cytokines and has been reported to be an effective treatment for AIDS- and cancer-associated cachexia.[178,179] Other cytokine inhibitors mainly target TNF-α (infliximab), IL-1α (MABp1), IL-6 (ALD518), or IL-6R (tocilizumab). However, in a clinical trial, infliximab not only failed to alleviate cancer-related weight loss but was also associated with an inferior quality of life, and the clinical trial was terminated.[180] MABp1, ALD518, and tocilizumab were found to be well tolerated in the clinical setting and have been reported to have a palliative effect in cancer-related cachexia.[181–186] However, more investigations are needed to confirm these findings.

Perspective

Cancer cachexia is a multifactorial paraneoplastic syndrome that involves dysfunction of the metabolic, neurological, and immune systems. In patients with lung cancer, screening for cachexia and implementing appropriate therapeutic approaches are imperative for improving the prognosis and enhancing overall quality of life. However, effective diagnostic, staging, and treatment strategies are still lacking. When cachexia has progressed to an irreversible stage, few treatments are effective. Research on the diagnosis and intervention of precachexia is therefore essential to prevent or delay the development of cachexia and improve clinical outcomes.

The pathogenesis of cachexia is complex and involves cross talk between many organs, making it challenging to identify the core signals and molecular mechanisms. Although many promising biomarkers of cancer cachexia have been identified, none have been approved for clinical use. It is now widely accepted that a single biomarker may be difficult to use as a reliable indicator of cancer cachexia, and the establishment of assessment criteria involving multiple potential biomarkers may be more appropriate for predicting and monitoring cachexia in a wide range of cancer populations. Full elucidation of the molecular mechanisms of this syndrome will help to establish diagnostic indicators and develop effective therapeutic strategies.

Current developments in sequencing and histological technologies will enable more systematic and comprehensive research into the relationship between the tumor microenvironment and dysregulation of multiorgan homeostasis, which could provide insight into whether specific mutated genes contribute to or specific types of patients are at higher risk of cachexia.[187] For example, live kinase B1, a key regulator of energy stress, acts as a critical barrier to pulmonary tumorigenesis and controls tumorigenesis, differentiation, and metastasis.[188,189] One study identified tumor live kinase B1 loss as a driver of cancer cachexia that serves as a genetic biomarker for this wasting syndrome in patients with lung cancer.[190] Furthermore, newly developed experimental models can be used to gain insight into the role of core signaling pathways and to develop combination therapies that target multiple pathways and molecules.[67,93,191] Once cancer cachexia can be suppressed, patients will be able to tolerate longer courses of cancer treatment. A better understanding of cancer cachexia is expected to improve treatment strategies that will ultimately benefit patients with cancer.

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Declaration of competing interest

The authors declare that there is no conflict of interests.

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