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Advances in cancer cachexia: Intersection between affected organs, mediators, and pharmacological interventions

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Abstract

Advanced cancer patients exhibit cachexia, a condition characterized by a significant reduction in the body weight predominantly from loss of skeletal muscle and adipose tissue. Cachexia is one of the major causes of morbidity and mortality in cancer patients. Decreased food intake and multi-organ energy imbalance in cancer patients worsen the cachexia syndrome. Cachectic cancer patients have a low tolerance for chemo- and radiation therapies and also have a reduced quality of life. The presence of tumors and the current treatment options for cancer further exacerbate the cachexia condition, which remains an unmet medical need. The onset of cachexia involves crosstalk between different organs leading to muscle wasting. Recent advancements in understanding the molecular mechanisms of skeletal muscle atrophy/hypertrophy and adipose tissue wasting/browning provide a platform for the development of new targeted therapies. Therefore, a better understanding of this multifactorial disorder will help to improve the quality of life of cachectic patients. In this review, we summarize the metabolic mediators of cachexia, their molecular functions, affected organs especially with respect to muscle atrophy and adipose browning and then discuss advanced therapeutic approaches to cancer cachexia.

Keywords

Cachexia; Cancer; Skeletal muscle wasting; Adipose tissue browning; Mediators; Cytokines

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Declaration of competing interest

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1. Introduction

The majority of cancer patients with advanced metastatic disease exhibit cachexia, a condition characterized by the loss of body weight due to extensive loss of skeletal muscle and adipose tissue. Besides cancer, cachexia is prominent in other diseases such as chronic obstructive pulmonary disease, acquired immunodeficiency syndrome (AIDS), chronic renal failure, diabetes, chronic heart failure, and rheumatoid arthritis [1]. Cancer cachexia accounts for one-fourth of cancer-related deaths, and the degree of cachexia depends on both tumor type and stage. Although cachexia predominantly affects skeletal muscle, which comprises almost half of the body weight, it also damages other organs such as adipose tissue, liver, brain, gut, pancreas, bone, and heart. Several factors, such as negative energy balance due to metabolic dysregulation, increased catabolic processes in muscle and fats and neurohormonal dysregulation, worsen this multifactorial syndrome [2].

Anorexia or loss of appetite is commonly seen in cancer patients. Cachexia, in combination with anorexia, reduces the quality of life (QOL) and overall survival of patients [3]. While tumor and host-derived factors play an essential role in the advancement of cachexia, chemotherapy and radiotherapy exacerbate cachectic syndrome [4,5]. A decrease in skeletal muscle index or increase in muscle loss during chemotherapy or surgery is associated with poor survival in advanced-stage ovarian cancer [6]. Furthermore, cachexia-mediated muscle wasting significantly increases the toxicity of chemotherapy [7]. The clinical management of cachexia is challenging due to the complexity of this multifactorial metabolic disorder and lack of definitive therapies. Here in this article, we provide an overview of the underlying molecular mechanism and pathophysiology of muscle wasting and adipose browning in cancer cachexia and explore therapeutic strategies that could combat and offer more effective care for this devastating multifactorial syndrome.

2. Cancer cachexia prevalence and stages

Cancer cachexia is well-defined as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass and body weight, with or without loss of fat mass, which cannot be fully reversed by conventional supplementation of nutrition [8,9]. Another condition of involuntary loss of skeletal muscle mass and strength is known as sarcopenia, which is prevalent in the elderly population. Although wasting disorders such as cachexia (50%–80%) and sarcopenia (15%–50%) are both prevalent in cancer patients, the underlying mechanism of muscle loss in cachexia and sarcopenia differ [10]. Sarcopenia is an age-associated decrease in muscle mass due to reductions in muscle synthesis, while the rates of muscle protein degradation are unchanged. Besides reduced muscle mass, sarcopenia is often associated with an increase in fat mass that accompanies advanced age in older adults [11]. In contrast, cachexia results from increases in muscle protein degradation, total energy expenditure, basal metabolic rates, and either unaltered or a decreased adipose mass. While an estimated 50–80% of cancer patients exhibit cachexia, it is more prevalent in patients with advanced lethal cancers, like pancreatic, gastrointestinal, and non-small cell lung cancers (NSCLC) [12]. Cachectic syndrome causes significant morbidity and mortality in both localized and metastatic cancer patients, and by itself contributes to almost 20% of deaths in cancer patients [13]. The reported deaths associated with cachexia represent cancer

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patients with observed weight loss of more than 30–40%; however, due to lack of proper diagnostic techniques, cachexia-associated deaths of cancer patients remain underreported.

Weight loss is the first sign of cachexia and serves as an independent predictor of mortality in cancer patients [14]. Multiple factors such as systemic inflammation, cancer type and stage, low food intake, and treatment-associated toxicities can contribute to the progression of cachexia; concomitant anorexia contributes to lower caloric intake and further worsens the patient's condition. Cachexia may progress even in the absence of anorexia [15]. Recently, the cachectic syndrome was classified into three stages: pre-cachexia, cachexia, and refractory cachexia, based on the degree of reduction of energy stores and body protein or body mass index, along with the extent of ongoing weight loss [9]. Less than 5% weight loss, along with anorexia and glucose tolerance is referred to as a pre-cachectic stage. Clinically, cachectic patients are characterized by an involuntary weight loss of > 5% within six months that cannot be entirely reversed by conventional nutritional support. Finally, in refractory cachexia, due to the higher level of active catabolism, weight loss management is no longer possible and patients are unlikely to benefit from any treatment. At this stage, patients usually have less than three months of survival. The stages of cachexia and the amount of weight loss are directly correlated to survival in cancer patients [16]. At the stage of refractory cachexia, the only goal of therapy is palliative to reduce distress in patients (Fig. 1).

3. Energy imbalance in cancer cachexia

It is important to understand the role of energy balance in the development of cancer cachexia. Cancer cachexia is often associated with a negative energy balance driven by anorexia along with increased energy expenditure or abnormal metabolism. Almost half of cancer patients exhibit a high metabolism or high resting energy expenditure (REE), which indicates development of cachexia. The degree of REE is highly dependent on the type of cancer, pathological stage, and duration of disease [17]. Elevated REE has been reported in the majority of patients with gastric, esophageal, pancreatic, and lung cancers (NSCLC) and typically exacerbates the disease [17]. Cachexia results from the concurrent hyperactivation of numerous metabolic pathways that subsequently leads to energy dissipation in the form of heat, and systemic inflammation, which contribute to shorter survival in patients with metastatic cancer [18]. Tumors have an abnormally high glucose requirement compared to normal tissue, and upregulated glycolysis is a hallmark of cancer cells [19]. This high demand for glucose even in the presence of sufficient oxygen, known as the Warburg effect, results in elevated production of lactic acid by the tumor cells to compensate for their inefficient energy production [20,21]. Warburg estimated that highly glycolytic tumors generate as much as 50% of their energy from glycolysis [22]. The amount of energy produced by tumors is based on the degree of utilization of the glycolytic pathway (an anaerobic process) versus oxidative phosphorylation (an aerobic process). The Cori cycle, which is responsible for energy dissipation in the form of heat lipolysis in adipose tissue, and protein catabolism in the muscle tissue both contribute to increased liver gluconeogenesis in cancer patients. Further, increased expression of mitochondrial uncoupling proteins (UCPs) can generate heat as an alternative of ATP and speed up the hypermetabolic processes in cancer cachexia. Recently, it has been reported that ER stress

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and unfolded protein response are elevated in the skeletal muscle of cachectic patients [23–25]. Despite accelerated glycolysis and lactate production, numerous circulating factors, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interferon-gamma (IFN-γ), myostatin, and parathyroid hormone-related peptide (PTHrP) are believed to be responsible for the hypermetabolic state in cachectic patients. Altogether, these metabolic factors could help to identify the pre-cachexia stage, which would be highly beneficial for high-risk patients.

4. Muscle wasting in cancer cachexia

Skeletal muscle comprises a significant proportion of body weight in the human body and is necessary for numerous biological activities such as movement, support to soft tissue, and respiration. Skeletal muscle is one of the most metabolically active tissues in the body and serves as a storehouse of protein and free amino acids. During normal physiological conditions, adult muscle mass remains constant due to a balance in protein synthesis and degradation. A well-coordinated network of various hypertrophic (anabolic) and atrophic (catabolic) signals within the skeletal muscle is required to ensure a balance between synthesis and wasting of the muscle, a function that is commonly disrupted during the tumor progression. Indeed, extensive loss of skeletal muscle represents a key manifestation of cancer-associated cachexia. Cachexia primarily results from an acceleration of protein degradation, often combined with reduced protein synthesis in skeletal muscle. Muscle progenitor cells with disrupted metabolism contribute to the impaired muscle generation in cachexia [26]. Several factors such as fasting, exercise, aging, and disease, affect the homeostatic balance of muscle by decreasing muscle protein synthesis or increasing the degradation of muscle, which worsens the cachexic condition [27]. Overall, muscle wasting due to the cachexic condition reduces QOL and contributes to mortality (Fig. 2).

4.1. Increased protein degradation or muscle atrophy in cachexia

In patients with cancer cachexia, activation of the ATP-dependent ubiquitin-proteasome proteolytic pathway (UPP) causes the breakdown of myofibrillar proteins and plays a crucial role in muscle wasting [28,29]. This pathway involves the hyperactivation of muscle-specific E3 ubiquitin ligases (muscle atrophy F box protein, MAFbx/atrogin-1) and muscle RING finger-containing protein 1 (MuRF1), which are responsible for the selective polyubiquitination of proteins targeted for degradation [30,31]. The upregulation of MAFbx/atrogin-1 has been reported in the majority of cancer cachexia cases and is considered as a marker of acute muscle atrophy [32]. Genetic deletion of muscle-specific E3 ligases *MAFbx/atrogin-1* or *Murf1* protected skeletal muscle from atrophy, suggesting their role in skeletal muscle breakdown [33]. Protein degradation via activation of the UPP was observed in a pre-clinical tumor-bearing mouse model of cancer cachexia [34]. Ubiquitin ligases of the N-end rule pathway (UBRs) control the ubiquitination of muscle protein and have a role in muscle wasting in cachectic mice [35]. Recently, loss of UBR4 was shown to induce hypertrophy via decreased ubiquitination of target proteins, especially the histone-binding complex (HAT1/RBBP4/RBBP7), which suggests a role for UBR4 in myofiber hypertrophy [36]. A recent report suggested that the autophagic lysosomal system along with the UPP coordinate cachexia-induced muscle loss in gastric patients [37]. Hsp70 and Hsp90 may also

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drive cancer cachexia, as they were highly secreted by Lewis lung carcinoma (LLC) cells and induced muscle catabolism via activation of Toll-like receptor (TLR4) [38]. Further, cachectic muscle showed mitochondrial dysfunction, which may alter amino acid metabolism via decreasing cationic amino acid transporter (CAT1) expression as well as degrading mitochondrial proteins [39].

TGF-β family members, such as myostatin and activin A, have also been shown to promote muscle loss through the myostatin/activin receptor type IIB (ActRIIB), and overaction of the ActRIIB pathway has been observed in many cancers [40–42]. Myostatin, commonly known as growth/differentiation factor 8 (GDF8), inhibits myoblast differentiation and facilitates Forkhead box O (FoxO) activation and the expression of ubiquitin ligases in response to inflammatory signals [43]. Transgenic overexpression of FoxO3 in the skeletal muscle caused skeletal muscle wasting, and inhibition of FoxO prevented skeletal muscle atrophy in a mouse model of cancer cachexia [44]. However, deletion of myostatin in mice showed an increase in muscle mass, suggesting myostatin is a negative regulator of muscle growth [45]. Similarly, inhibition of bone morphogenetic protein signaling abolished the hypertrophic phenotype observed in myostatin-deficient mice and caused muscle atrophy via the upregulation of muscle ubiquitin ligase of the SCF complex in atrophy-1 [46]. However, overexpression of the myostatin gene in adult mice showed profound muscle loss and fat wasting similar to human cachexia, suggesting that myostatin is a potential pharmacologic target for managing cachexia [47]. Another report suggested that myostatin can inhibit the activation of satellite cells (muscle stem cells) [45].

Interestingly, transgenic mice with dominant-negative *ActRIIB* exhibited hypertrophy of skeletal muscle, and blockade of ActRIIB improved cachexia in tumor-bearing mice [48,49]. In addition to the prevention of muscle wasting, blockade of ActRIIB also reversed prior loss of skeletal muscle and cancer-induced cardiac atrophy via inhibition of the atrophy-specific ubiquitin ligases and stimulation of muscle stem cell growth in muscle. ActRIIB blockade significantly prolonged survival, even in the absence of a beneficial effect on tumor growth [48]. In addition, activin A induced the secretion of IL-6 from ovarian cancer cells in an autocrine manner, and blocking ActRIIB with antibody reduced serum levels of IL-6 and reversed cachexia in cachectic tumor-bearing mice, suggesting the therapeutic potential of targeting activin A and IL-6 signaling pathways [50].

Metabolic changes in the adipose tissue can also regulate the muscle wasting. PGC-1α, a transcriptional coactivator of PPARγ in brown adipose tissue, regulates the expression of genes involved in oxidative metabolism during exercise. High expression of PGC-1α4 (an isoform of PGC1α) prevents skeletal muscle atrophy by activating the expression of IGF1 and repressing myostatin activity. Transgenic mice that overexpress PGC-1α4 and bear LLC tumors showed a dramatic resistance to muscle wasting, suggesting PGC-1α4 protects against muscle atrophy [51].

4.2. Muscle wasting through pro-inflammatory cytokines and NF-kB signaling/pathway

Treatment of mice with TNF-α and IL-1 can cause skeletal muscle atrophy similar to that observed in cachectic cancer patients [52]. TNF-α activates the NF-κB pathway and subsequently inhibits the differentiation of muscle cells via downregulation of MyoD,

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suggesting NF-κB is activated in skeletal muscle wasting [53]. NF-κB signaling not only augments the expression of UPP proteins that target specific muscle proteins for degradation, but also interferes with myogenic differentiation during muscle atrophy [54]. UPP-mediated proteolytic processing of NF-κB and IκB family proteins is a prerequisite for NF-κB activation [55,56]. Transgenic mice with constitutively active IKKβ exhibited profound muscle wasting similar to cachectic patients. Muscle atrophy was reduced, however, in IKKβ-expressing mice crossed with MuRF1-knockout mice, suggesting that IKKβ-induced muscle wasting is facilitated by the upregulation of the MuRF1 gene [57].

NF-κB signaling can also promote muscle wasting by increasing the expression of inflammation-related molecules, including cytokines, chemokines, and matrix metalloproteinases (MMPs) [58]. Several of these pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 activate NF-κB in a positive feedback loop, causing over-stimulation of the NF-κB pathway and enhanced muscle wasting [58]. Overall, therapeutic approaches to inhibit the NF-κB pathway can augment muscle performance in cachectic cancer patients. The pro-inflammatory cytokines induced by NF-κB contribute to muscle wasting and cachexia through additional mechanisms such as activation of JAK/STAT signaling [59]. Indeed, in an experimental model of cancer cachexia, STAT3 activation was both necessary and sufficient for muscle wasting. Inhibition of JAK/STAT signaling attenuated cancer cachexia in colorectal and lung cancer [60,61]. However, the outcome of a randomized, double-blind phase II clinical trial of ruxolitinib, a JAK1/JAK2 inhibitor, in combination with capecitabine, did not improve the survival of patients with metastatic pancreatic cancer [62].

4.3. Decrease in anabolic signals (insulin-like growth factor 1)

Although most of the studies involving cachexia research focused on the factors responsible for skeletal muscle wasting, studies examining relevant muscle hypertrophy factors have provided detailed insights into the mechanisms underlying cachexia-induced muscle wasting. Insulinopenic rats exhibit skeletal muscle atrophy, suggesting that insulin is the key anabolic factor opposing the catabolic effects of glucocorticoids [63]. Insulin-like growth factor 1 (IGF1) is the most studied anabolic factor, and the transgenic mice overexpressing IGF1 exhibit skeletal muscle hypertrophy [64]. IGF1 promotes anabolic signaling in muscle via binding with its tyrosine kinase receptor, IGF1 receptor (IGF1R) [65]. The binding of ligands to IGF1R induces transphosphorylation of the dimeric receptor and facilitates the recruitment of insulin receptor substrate 1 (IRS1) [66]. IRS1 phosphorylation is crucial for the downstream signaling of IGF1 and leads to the activation of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, as well as other downstream signals. Prolonged insulin stimulation can cause ubiquitin-mediated degradation of IRS1 through the PI3K pathway and inactivate IGF1 signaling [67–69]. The IGF1-PI3K-AKT pathway induces muscle growth primarily by stimulating protein synthesis through mTOR kinase [67]. The activation of PI3K is required for IRS1 degradation independent of mTOR signaling [69]. Studies from transgenic mice suggest that acute activation of Akt in the skeletal muscle is sufficient to induce rapid and significant muscle hypertrophy by activation of the downstream Akt/p70S6 kinase protein synthesis pathway [70]. The IGF-I/PI3K/Akt pathway can suppress transcription of atrophy-related E3 atrogin-1 and reduce the degradation of muscle protein

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[71]. IRS1 is rapidly degraded after IGF1 stimulation by several E3 ubiquitin ligases, and this limits the downstream hyperactivation of the IRS1/PI3K/Akt pathway. It has been shown that SOCS1 or SOCS3 targets IRS1 and IRS2 for ubiquitin-mediated degradation, respectively [72]. Another ubiquitin ligase, Cbl-b, facilitates the degradation of IRS-1 and acts as a dual mediator of both increased protein degradation and reduced protein synthesis in unloading-induced muscle atrophy [73]. Muscle-specific mitsugumin 53 (MG53), also known as TRIM72, mediates the degradation of IRS1 and insulin receptors and also inhibits myogenesis [74,75]. F-box-containing protein Fbxo40 is another physiologic regulator of IGF1 signaling, and Fbxo40 null mice have enhanced muscle size. Overall, a decrease in circulating IGF-1 levels and insulin resistance has been reported in cancer cachectic patients, and mouse models of cachexia suggest that an IGF-1-mediated decrease in anabolic signal contributes to muscle wasting [27,64,76].

5. Mediators of muscle atrophy in cancer cachexia

Tumors secrete a diverse array of potential mediators, which can cause cachexia, and their production and secretion vary from one type of tumor to another. Increased expression of these mediators has been reported in different cancer cell lines and tumor tissue, suggesting that tumors are the potential source of these mediators. Although the mechanisms of action of these mediators have not been elucidated completely, pro-inflammatory cytokines are thought to be critical in inducing muscle and adipose wasting [77].

5.1. Glucocorticoids

Glucocorticoids (GC) are released either endogenously in response to stress and disease, or are administered exogenously as drugs to treat inflammation. GC alter protein and glucose metabolism in skeletal muscles [78]. GC increase the rate of skeletal protein catabolism and decrease the rate of protein synthesis, eventually leading to skeletal muscle atrophy via increases in FoxO-dependent transcription of E3 ubiquitin ligases [79,80]. Elevated levels of GC have also been observed in cancer patients [81]. Further, intact GC signaling in skeletal muscle is required for cancer-induced cachexia [82]. However, in rodent models of cancer cachexia, treatment with GC antagonist RU38486 failed to prevent the loss of skeletal muscle, thereby raising doubts about the direct role of GC in cancer cachexia [83].

5.2. Tumor necrosis factor-alpha

Tumor or immune cell-derived tumor necrosis factor-alpha (TNF-α) is one of the most prominent pro-inflammatory cytokines and mediators of tumor-induced adipose and skeletal muscle wasting [84–86]. TNF-α activates the ubiquitin E3 ligase pathway to promote muscle protein breakdown [87–89]. TNF-α was reported to stimulate the degradation of muscle proteins, including adult myosin heavy chain (MHC) in muscle rather than altering the rate of protein synthesis [84]. Along with myofibrillar breakdown, TNF-α was found to inhibit skeletal myocyte differentiation [53]. Acute treatment with recombinant TNF-α in rats resulted in increased degradation and decreased synthesis of muscle protein, suggesting that TNF-α causes muscle wasting via activating the ubiquitin E3 ligase pathway as well as diminishing the formation of new muscle protein [90]. In addition to adipose and muscle wasting, TNF-α exerts pleiotropic effects to alter carbohydrate, protein, and lipid

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metabolism, induce insulin resistance and mediate systemic inflammation in cancer-cachexia. Enhanced TNF-α expression in skeletal muscle is associated with insulin resistance in cancer patients in part by stimulation of stress-related protein kinases (JNK) and inhibitor kappa beta kinase beta (IKKβ)/NF-κB [91,92]. In cachexia, increased TNF-α and high energy-wasting conditions enhance the content of mitochondrial cardiolipin, which leads to reduction in mitochondrial oxidative phosphorylation [93].

5.3. Interleukin-6

Interleukin-6 (IL-6) is a well-studied cytokine that impacts several biological functions such as immune response, metabolism, hematopoiesis, and tumorigenesis. IL-6 exhibits both pro and anti-inflammatory functions, depending on context and tissue type. The role of IL-6 is well established in both rodent and human muscle wasting, and elevated levels of serum IL-6 are associated with cancer cachexia [94]. Transgenic mice overexpressing IL-6 showed an increase in ubiquitin-related proteins, suggesting the role of IL-6 in accelerating proteolysis [95]. However, only supra-physiological doses of IL-6 induced muscle atrophy in tumor-free animals [96]. Over-expression of IL-6 accelerated muscle and fat wasting, while deletion of the IL-6 gene prevented the development of cachexia in an ApcMin/+ mouse model of colorectal cancer [97]. Similarly, IL-6 administration reduced skeletal muscle protein synthesis, a condition similar to what is observed in patients with cachexia [98]. Furthermore, IL-6 levels corresponded to the magnitude of muscle wasting in APCMin/+ mice [99]. In this model, suppression of protein synthesis is one of the early events in progression of cachexia, while elevated ATP-independent protein degradation occurs in the later stages [100]. Treatment with IL-6 receptor antibody prevented the progression of cancer cachexia via suppression of muscle protein degradation [100]. Further, IL-6 can stimulate pro-inflammatory cytokines (e.g., IL-1) to enhance muscle atrophy. IL-6 has also been shown to regulate food intake and metabolism via signaling through neural gp130 receptors, suggesting that IL-6 could play a role in anorexia [101,102]. In a clinical study, treatment of NSCLC cachectic patients with anti-IL-6 antibody (ALD518) improved anorexia, but failed to reverse the loss of lean body mass [96]. The mechanisms by which IL-6 directly induces muscle atrophy are not well known. However, activated macrophages secrete IL-6 to initiate the acute phase response, which may eventually mediate cancer cachexia. Altogether, IL-6 is a potent mediator for muscle wasting in cancer, while its direct role in normal muscle is uncertain. Another interleukin, IL-8 released from cancer and tumor-associated stromal cells, has been reported to induce muscle atrophy in pancreatic cancer [103].

5.4. Growth differentiation factor 15

Growth differentiation factor 15 (GDF15), also recognized as macrophage inhibitory cytokine-1 (MIC-1), is a member of the TGF-β superfamily, which is expressed broadly in several tissues. The circulatory levels of GDF15 rise in several pathological conditions such as inflammation, injury, cardiovascular and kidney disease, and many malignancies where it often correlates with poor prognosis [104]. Elevated GDF15 levels were observed in patients with anorexia-related loss of appetite and weight [105]. In patients with cancer cachexia, circulating levels of GDF15 were elevated in early onset of cachexia and remained elevated in the advanced stages of cachexia [106]. Further, tumor-derived GDF15 was sufficient to

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trigger the cachexia phenotype in an animal model, and treatment with anti-GDF15 antibody reversed the bodyweight loss and restored muscle and fat tissue mass in cachectic mice [106]. GDF15 caused its anorectic effect by directly acting on the feeding center of the brainstem [107]. Recently, several studies have shown that mice treated with recombinant GDF15 exhibit a decrease in food intake and body weight, and these effects are mediated by the receptor GFRAL (glial-cell-line-derived neurotrophic, a GDNF family receptor-a like) [108–112]. Overexpression of GDF15 in skeletal muscle initiates muscle atrophy, although the mechanism for the direct effect of GDF15 on muscle cells remains poorly understood. In vitro, GDF15 increased the expression of atrogin-1 and MuRF-1 in myotubes [113,114]. Altogether, these reports suggest that along with its strong anorectic effects, GDF15 might directly induce skeletal muscle wasting in cancer cachexia, and the level of circulating GDF15 could be a biomarker of cancer cachexia.

5.5. Growth differentiation factor 11

Growth differentiation factor 11 (GDF11) is another member of the TGF-β superfamily and is homologous to myostatin (Mstn). Mstn is a known negative regulator of skeletal muscle growth [115]. Both GDF11 and myostatin bind to ActRIIB and activate the SMAD2/3 pathway. However, circulating GDF11 levels are associated with skeletal and cardiac muscle wasting, a function that is distinct from Mstn. Further, deletion of GDF11 in mice caused skeletal abnormalities, suggesting its role in skeletal development. Supraphysiological levels of GDF11 can cause skeletal and cardiac muscle wasting [116], and high doses of GDF11 cause severe cachexia and death in mice [117]. Due to its low serum concentration and structural similarity with Mstn, existing techniques to measure GDF11 need to be validated.

5.6. Parathyroid hormone-related peptide

Parathyroid hormone (PTH) and parathyroid hormone-related protein (PTHrP) cause hypercalcemia by stimulating renal calcium reabsorption and bone resorption [118]. Cancer patients with high PTHrP levels exhibit humoral hypercalcemia of malignancy (HHM), a condition characterized by increased osteoclastic bone resorption. Although primary myotubes treated with PTHrP did not show signs of atrophy, PTHrP treatment in tumor-bearing mice increased expression of muscle-atrophy-associated genes [119]. Anti-PTHrP antibody treatment decreased circulating PTHrP levels in a mouse model of cancer cachexia and somewhat reversed skeletal muscle wasting. However, the main beneficial effect was seen in preventing adipose tissue loss and energy expenditure. Since PTHrP does not have direct effects on primary muscle cells, it probably promotes skeletal muscle wasting in collaboration with other factors or by facilitating crosstalk between adipose and skeletal muscle tissues [119,120]. Further, patients with high circulating PTHrP exhibited higher REE and a lower lean mass [121]. In cancer patients, PTHrP predicts body weight loss, suggesting that circulating PTHrP could be used as a biomarker of cancer cachexia [119].

6. Adipose browning in cancer cachexia

Loss of skeletal muscle and adipose tissue (AT) are both symptoms of cachexia [122]. While much is known about muscle wasting, information about the mediators and mechanism of AT loss in cancer patients with cachexia is scarce. As shown in Fig. 3, the tumor secretes

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several mediators such as TNF-α, IL-6, IFN-γ and LIF during cachexia. TNF-α, also known as cachectin [123], is also released from the AT and may mediate cancer cachexia by reducing the expression of glucose transporter 4 (GLUT4), which in turn inhibits glucose transport and lipogenesis [124]. In cancer cachexia, TNF-α activates expression of monocyte chemoattractant protein 1, which attracts monocytes to the AT that subsequently promote inflammation in AT [123]. AT-infiltrating macrophages are responsible for the activation of other cytokines (IL-6 and IL-1β), which results in further recruitment of macrophages [125]. Activated macrophages (a major source of TNF-α) in the AT facilitate the mobilization of lipids and dysregulation of metabolic pathways, both of which contribute to body weight loss in patients [14]. Interferon-gamma (IFN-γ) is a pleiotropic cytokine that plays a vital role in deregulated fat metabolism in cancer cachexia. In rodent tumor models, elevated IFN-γ correlated with anorexia and weight loss during tumor development [126]. Additionally, in cachexia patients, IFN-γ mediates insulin resistance via reduction of glucose uptake; this leads to enhanced lipid breakdown in white adipose tissue (WAT) [127]. Another cytokine that cooperates with TNF-α to promote cancer cachexia is IL-6. During cachexia, IL-6 levels were further upregulated by pro-inflammatory cytokine IL-1, resulting in weight loss and reduced survival in cancer patients [128,129]. Chronic inflammation mediated by IL-6 promotes early cancer cachexia by regulating WAT lipolysis and late cachexia by WAT browning [130]. Scant evidence is available regarding the mechanisms by which IL-6 facilitates lipid mobilization in both mice and humans [14].

In addition to TNF-α, activated macrophages also secrete IL-6 during cancer cachexia, which activates the acute-phase response from the liver. The first step in this pathway is binding of IL-6 to the membrane-bound receptor gp130, which activates the downstream JAK/STAT pathway with translocation of STAT into the nucleus, thereby inducing transcription of acute-phase proteins [131]. In a recent study, tumor humoral factor (i.e., leukemia inhibitory factor [LIF], a member of the IL-6 cytokine family from cancer cells), was found to induce AT lipolysis [132] by binding receptor LIFR-α and co-receptor gp130, which activates JAK/STAT signaling. Activated JAK/STAT resulted in the upregulation of adipose triglyceride lipase (ATGL) for fat degradation. In addition, in vivo administration of rLIF into Balb/c mice resulted in a decrease in body weight and AT loss, but little change in overall food intake. Similarly, in genetically hyperphagic mouse models [leptin deficient (*ob/ob*) and its signal deficient (*db/db*)], administration of rLIF decreased food intake and promoted AT loss along with > 10% reduction in animal body weight [132]. Overall, these studies suggest that inflammatory cytokines TNF-α and IL-6 are involved in the depletion of AT in cancer cachexia. Moreover, the function of cytokines in cancer cachexia depends on the type of tumor and the complex network mediators within it rather than a single cytokine alone [133].

In humans, AT is classified as either WAT, which stores triglycerides in the form of lipid droplets, or brown adipose tissue (BAT), which is the primary site of non-shivering thermogenesis [134]. Although WAT dysfunction is not directly implicated in cachexia, the switching of WAT to a more BAT-like phenotype is associated with cancer cachexia [135]. This phenomenon called WAT “browning” occurs when WAT acquire brown fat characteristics, including high mitochondrial content [136,137]. The transformation of WAT into “beige” or “brite” cells requires a sophisticated transcriptional machinery, including the

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transcriptional coregulator PR domain-containing 16 (PRDM16). Mice deficient for fat-specific PRDM16 exhibit reductions in browning, thermogenesis, and WAT atrophy [119]. Beige cells are phenotypically distinct from both WAT and BAT, and can emerge in response to extensive cold exposure [138], adrenergic stimulation [139], and prostaglandin synthesis enzyme (cyclooxygenase2) [140]; these cells can significantly contribute to total energy expenditure and promote fat reduction [141]. WAT browning in mice with cancer cachexia resulted in increased energy expenditure in interscapular BAT. Tumors directly activate thermogenesis in beige cells via secretion of PTHrP, which induces UCP1 [119]. UCP1 stimulates thermogenesis at the cost of ATP synthesis, leading to increased lipid mobilization and energy expenditure in cachectic mice. Moreover, cancer cachexia patients have higher expression of UCP1 in AT compared with cancer patients without cachexia, a change that presumably results in atrophy and subsequently leads to more thermogenesis [142]. Targeting upstream PTHrP with neutralizing antibodies reduced the intensity of cancer cachexia and atrophy [119]. WAT browning can also be inhibited by β3-andrenergic receptor antagonists or non-steroidal anti-inflammatory drugs, which improved wasting in mice. Therefore, targeting WAT browning is a promising approach for cancer cachexia patients.

7. Cachexia as a multi-organ metabolic syndrome

Cachexia is a multi-organ syndrome. Although the skeletal muscle and AT are the primary targets of cachexia, other tissues such as brain, liver, heart, bone, pancreas, cardiac muscle, and gut are directly involved in the cachectic process. Alterations in other organs also influence the degree of muscle wasting in cachectic patients (Fig. 4).

7.1. Brain and food intake (anorexia)

The hypothalamus controls energy expenditure and food intake by coordinating the neuropeptide Y (NPY)/agouti-related peptide (AgRP) and pro-opiomelanocortin (POMC)/cocaineamphetamine-regulated transcript (CART) neurons that stimulate energy production and inhibit food intake, respectively. These functions in the CNS are regulated by release of the protein leptin by adipose tissue. Leptin is part of a regulatory feedback loop that stimulates and inhibits several hypothalamic neuropeptides, including NPY and corticotropin-releasing factor (CRF). Administration of inflammatory cytokines, such as TNF-α and IL-1, in cancer patients and a mouse model of inflammation increased the expression of leptin in adipocytes and caused an increase in plasma levels of leptin despite starvation, suggesting a mechanism by which leptin levels contribute to cancer anorexia [143,144]. Tumor-induced cytokines impair hypothalamus functions by persistent stimulation of anorexigenic pathways and inhibition of orexigenic pathways [145]. Several pro-inflammatory cytokines, such as IL-1, hyperactivated the POMC/CART pathway in cancer cachexia [146,147]. Further, hypothalamic inflammation influenced anorexia-cachexia syndrome via the hypothalamic-pituitary-adrenal axis and serotonin pathway activation. It has been reported that serotonin is associated with the development of cancer anorexia by activating the melanocortin system, and blocking of melanocortin receptors ultimately reversed cancer-mediated anorexia in rats [148]. In addition, IL-1 may also increase the secretion of hypothalamic serotonin, which activates POMC/CART neurons,

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resulting in decreased appetite and anorexia [149]. These findings suggest the significance of the hypothalamic serotonin-melanocortin axis in cancer cachexia pathogenesis and its relevance as a potential therapeutic target for cancer cachexia.

7.2. Liver

The liver is a highly metabolic organ that contributes to energy wasting in cancer cachexia though futile metabolic cycles. In cancer patients, tumors were capable of renewing glucose from lactate via hepatic gluconeogenesis, which leads to high amounts of energy loss [150]. Further, in the case of cachexia, free amino acids resultant from muscle protein degradation can drive the liver acute phase response (APR) and energy wasting [151]. An increase in macrophage infiltration due to hepatic APR has reported in cachectic pancreatic cancer patients compared to non-cachectic patients, suggesting a significant role of liver macrophages in cancer cachexia [152]. Activated macrophages secrete IL-6, which in turn stimulates the synthesis of hepatic acute-phase proteins [153]. Further, hyperlipidemia was reported in a rodent model of cachexia due to increased liver lipogenesis with tumor burden [151]. Hepatic steatosis, commonly seen in nonalcoholic fatty liver disease, has also been documented in patients with cancer cachexia and is associated with muscle loss, further suggesting crosstalk between the liver and muscle under energy-wasting conditions [154]. The mechanism may involve enhanced expression of transcription factor TGFβ1-stimulated clone 22 D4 (TSC22D4) and nuclear receptor cofactor receptor-interacting protein 140 (RIP140), which could lead to hepatic steatosis by preventing the mobilization of hepatic triglyceride stores [155,156]. Additional hepatic alterations were reported during progression of cachexia including increased deposition of collagen and fibrosis in the Lewis lung carcinoma mouse model of cachexia [157]. Finally, the changes in the liver directly or indirectly contribute to energy wasting and cachexia in cancer patients.

7.3. Pancreas

Metabolic deregulation, such as impaired glucose tolerance and decreased insulin sensitivity, is the hallmark of the majority of cancer patients [2]. Insulin resistance is a risk factor for cancer development and seen in the majority of cancer patients during the onset of cachexia [127]. Further, mice bearing colon-26 tumors can develop insulin resistance before the onset of cachexia, suggesting the role of insulin resistance in cachexia pathogenesis [158]. Islets of Langerhans isolated from the pancreas of Walker 256 tumor-bearing rats showed resistance to glucose stimulation [159]. Furthermore, this decrease in insulin sensitivity was not associated with structural changes in pancreatic islets, but instead with changes in insulin signaling [160]. Rosiglitazone (insulin sensitizers) treatment in mice bearing colon-26 tumors improved insulin sensitivity and diminished the early markers of cachexia [158]. In the clinical setting, daily insulin treatment for weight-losing cancer patients diminished the progression of cancer cachexia, suggesting a role for insulin in palliative care for cachectic cancer patients [161].

7.4. Gut

Several alterations in gut composition and function have a role in cancer cachexia including gut barrier dysfunction, altered ghrelin production, and microbiota dysbiosis [162]. Cancer patients receiving radiotherapy and/or chemotherapy often develop gut barrier dysfunction,

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mainly leakage of the gut epithelial barrier. The barrier becomes more permeable due to decreased expression of tight junction proteins (ZO1 and occludin) and macrophage infiltration. The leaky barrier facilitates entry of either bacterial cell wall components (endotoxin or lipopolysaccharide) or intact bacteria into the circulation and causes inflammation. Apc(Min/+) mice with colorectal cancer exhibited compromised intestinal gut barrier integrity, elevated plasma endotoxin concentration, and cachexia symptoms [163]. Interestingly, anti-IL-6 antibody treatment restored gut integrity in a C26 cachexia model, which suggested inflammation may contribute to gut dysfunction in cancer [164]. Further, cancer-associated gut barrier dysfunction can cause malabsorption of nutrients, diarrhea, and other complications that contribute to the negative energy balance in patients with cancer.

The gut-derived hormone ghrelin, also known as the hunger hormone, is elevated in multiple cancers [165]. In the case of cachexia, even increased levels of ghrelin fail to induce the appetite, known as ghrelin resistance. The ghrelin receptor, growth hormone secretagogue receptor 1α, is expressed in the hypothalamic and pituitary regions and mediates growth hormone release and enhances appetite; however, the mechanism of action remains elusive [166,167]. Besides controlling hormonal release, energy homeostasis, and appetite, ghrelin suppresses inflammation via the release of IL-10, an anti-inflammatory cytokine. Ghrelin-mediated induction of IL-10 reduced levels of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α [168]. Furthermore, ghrelin reduced muscle catabolism via suppression of the NFκB-mediated ubiquitin-proteasome pathway [169]. Ghrelin administration in mice reduced atrogin-1, MuRF-1 and dexamethasone-induced skeletal muscle atrophy [170].

Gut microbiota play an important role in the context of cancer cachexia during chemotherapy/radiotherapy regimen. Gut microbiota influences the host's immunity and metabolism, and decreased levels of bacteria were found in an experimental model of cachexia [164]. Another study provided evidence that administration of exogenous bacteria restores intestinal homeostasis and prolongs survival in leukemic mice [171]. The amino acid bioavailability and metabolites generated by the gut microbiota can influence energy expenditure in the muscle cells, highlighting the role of the gut microbiota - skeletal muscle axis in cancer cachexia. Gut microbiota release lipopolysaccharide and peptidoglycan, which can stimulate the Toll-like receptors and subsequently activate muscle-specific NF-κB to facilitate muscle wasting [172]. In addition to muscle wasting, gut microbiota influence the accumulation of triacylglycerol into the adipose tissues [173].

7.5. Bone

The skeletal muscle and bone are well connected, and functions of both organs are tightly coupled during growth and development [174,175]. Recent evidence suggests that several cytokines secreted from muscle cells (myokines), such as insulin-like growth factor 1 (IGF-1), fibroblast growth factor 2 (FGF-2), myostatin/GDF8, and IL-6, not only regulate skeletal muscle development and maintenance, but also have a role in bone cell function [176]. For example, IGF-1 and FGF-2 both stimulate bone formation [177,178]. Myostatin negatively regulates muscle growth and development, and is upregulated in atrophic conditions. When administered to mice, myostatin induces cachexia, likely by activating the ubiquitin proteolytic system in the muscle through a FoxO1-dependent mechanism

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[179,180]. Several growth factors embedded in the bone matrix, primarily involved in normal bone physiology, can also modulate the functions of the skeletal muscle. Cancer cells disrupt the normal bone remodeling cycle during bone metastasis and facilitate the release of growth factors. One of the bone-derived factors Indian hedgehog (Ihh) promotes myoblast survival and myogenesis in mice [174]. Preclinical mouse models of breast cancer bone metastases and multiple myeloma both showed osteolytic bone destruction, reduced forelimb grip strength, and systemic muscle dysfunction, further suggesting the impact of bone-derived factors on muscle wasting [181]. A recent observation showed that osteoclast-mediated release of latent TGF-β from the bone matrix could affect intracellular calcium signaling and skeletal muscle functions in mice with bone metastases [182]. Further, inhibition of sclerostin, a soluble Wnt inhibitor that represses osteoblast differentiation and bone formation, has been shown to alleviate bone metastasis burden, muscle weakness, and overall survival in a mouse model of breast cancer [183]. Altogether, this evidence suggests that bone microenvironment can modulate muscle wasting, and identification and characterization of factors involved in this bone-muscle crosstalk will provide new possibilities for therapeutic intervention in cancer cachexia-associated muscle wasting.

7.6. Cardiac muscle

In addition to losing skeletal muscle mass and function, many cachectic patients have shown heart muscle wasting and dysfunction. Preclinical studies showed that potential signaling pathways contributing to cardiac atrophy and muscle wasting overlap, such as activation of NF-kB. The ApcMin/+ mouse model of colorectal cancer showed a decline in cardiac mass during cachexia progression by affecting AMPK, Akt, and mTOR signaling in the heart. Other mechanisms for loss of cardiac mass in this model include Akt-independent suppression of anabolic signaling and increased levels of Beclin1 or autophagy [184]. The cancer itself and its treatment can further worsen underlying heart disease in cancer cachexia. Most of the anticancer drugs, such as docetaxel, anthracycline, and fluorouracil, are associated with cardiotoxicity in cancer patients [185]. Further, chemo and/or radiotherapy increase the occurrence of cachexia in cancer patients. Cardiac muscle wasting is exceptionally lethal, and thus screening for it and managing it may improve the response to anticancer treatments, QOL, and chances of survival. Taken altogether, early detection of cardiac atrophy, personalized therapies, and mechanistic studies are needed, so that cardiac muscle wasting can be better managed in cancer cachexia patients.

7.7. Neural invasion

Tumor cells can invade in, around, and through nerves in a process known as perineural invasion, which most commonly occurs in pancreatic cancer patients. Recent studies suggest that perineuronal invasion is associated with cachexia and can include nerve damage, as well as astrocyte activation and microglia stimulation in the spinal cord [186]. However, the mechanisms by which perineuronal invasion could contribute to cachexia are not well known. One possibility is that damaged peripheral nerves activate astrocytes in the spinal cord which may induce muscle atrophy as well as lipolysis, perhaps via stimulating the sympathetic nervous system [186]. However, despite significant muscle loss, neuromuscular junctions remain structurally intact in cancer cachexia patients, suggesting that denervation of skeletal muscle is not a major driver of cachexia [187].

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8. Current and emerging pharmacological management of cancer cachexia

The present existing treatment options for cachexia are limited, and most of the available therapies are palliative in nature. Because cancer cachexia is a multi-organ syndrome, multimodal treatment approaches, including exercise, appetite stimulation, nutrient supplementation, and pharmacological intervention may prove beneficial [1]. Most cancer patients show symptoms of anorexia, which is strongly associated with development of cachexia. Therefore, calorie supplementation and appetite stimulants are primarily used as treatment for this disease. In addition, control of appetite and food intake requires precise balance between prophagic and anorexigenic signals to the hypothalamus.

8.1. Nutritional interventions and appetite stimulants to combat cachexia

A large-scale meta-analysis discovered that nutritional interventions are beneficial in increasing energy intake, body weight, and improving QOL in malnourished patients with cancer [188]. Some beneficial effects of anti-inflammatory nutrient supplementations, such as eicosapentaenoic acid (EPA) or fish oil, on muscle loss have been reported [1]. In mice bearing MAC-16 tumors, EPA prevented the development of cancer cachexia [189]. In pancreatic cancer cachectic patients, EPA can downregulate the production of pro-inflammatory cytokines (mainly suppression of IL-6 production) and the acute phase protein response [190]. Further, EPA has shown some beneficial effects on muscle mass and weight in patients with NSCLC receiving chemotherapy [191]. Overall nutritional interventions to combat the cancer cachexia have been listed in Table 1.

Megestrol acetate (Megace), a synthetic progestin, is widely used as an appetite stimulant and is approved for the treatment of weight loss and severe malnutrition in patients with AIDS [192]. Megace improves appetite and is associated with slight weight gain in cancer and AIDS patients with anorexia-cachexia syndrome [193,194]. A high dose of Megace resulted in a significant improvement in appetite and body weight in some patients with cancer cachexia [195–197]. However, the increase in body weight was primarily due to an increase in fat mass rather than an increase in lean body mass [198,199]. Recent in vivo studies showed that Megace improved survival and reduced skeletal and heart muscle wasting through the downregulation of autophagy, leading to a significant improvement of cardiac function; thus, this therapy may have a role in cancer cachexia-induced cardiomyopathy [200]. Although Megace is well tolerated, the use of Megace as an appetite stimulant has a red box warning as it has been associated with an increased risk of thromboembolic events and inadequate response to chemotherapy [201,202]. Dronabinol (marijuana) is a synthetic oral derivative of cannabinol and has limited FDA approval for anorexia-associated weight loss in AIDS patients. In cachectic cancer patients, dronabinol is known to stimulate appetite and weight gain but is not able to restore weight loss. Although dronabinol has a beneficial effect on cancer-related anorexia/cachexia syndrome, dronabinol is less effective than Megace against anorexia in clinical trials for advanced cancer [203,204].

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Other appetite stimulants include corticosteroids such as dexamethasone and prednisolone, which are among the earliest drugs evaluated for cancer cachexia. In a randomized clinical trial, dexamethasone increased appetite but did not affect body weight due to its catabolic effects on muscle and bone [205]. One preliminary study showed dexamethasone treatment significantly improved patient-reported cluster scores for fatigue/anorexia-cachexia/depression (FAD) symptoms after two weeks in advanced cancer patients [206]. Another novel immunomodulatory, OHR118, affects the synthesis of chemokines and cytokines, including TNF-α. In a phase 2 study, OHR118 significantly improved appetite, dyspepsia, and depression in cancer patients [207].

Ghrelin, a neuropeptide released from the stomach, is known to stimulate energy intake in cachectic cancer patients [208]. In a pre-clinical study, ghrelin was shown to increase food intake and body weight due to an increase in body fat composition. In a clinical trial, RC-1291, a ghrelin mimetic, increased muscle strength and lean body mass but did not affect body weight and QOL [170,209,210]. In a multicenter clinical trial, ghrelin receptor agonist anamorelin (ONO-7643) improved appetite, lean body mass, and body weight in advanced unresectable gastrointestinal cancer cachectic patients [211].

Advanced stages of malignancy, which account for many cachectic patients, eventually acquire resistance to cancer therapy and are hard to cure. Nutritional status is a key consideration for the initiation of cancer therapy, and patients with poor nutritional status should be carefully monitored throughout the treatment regimen [212]. In obese cancer patients, chronic inflammation may influence the relationship between cancer and host immunity; therefore, the patient's inflammatory status, metabolism, and weight, should be taken into consideration before starting cancer immunotherapy [213]. Although nutritional supplements and appetite stimulants are currently being used extensively for the management of cachexia, these interventions are often inadequate. The benefits of nutritional supplementation may be limited because they have minimal impact on the underlying catabolic processes responsible for skeletal muscle wasting. Data from at least 40 prospective randomized clinical trials in cancer patients showed that nutritional interventions had minimal clinical efficacy, particularly in improving muscle mass, QOL, and long-term survival [214].

8.2. Direct targeting of the mediators of cachexia

Although appetite stimulants have proven beneficial in improving QOL, they do not improve functional outcomes. Recent pre-clinical and clinical studies have explored targeted therapies in cancer-induced muscle wasting and have shown encouraging results. In a preclinical study, a monoclonal antibody against fibroblast growth factor-inducible 14 (Fn14), which targets the receptor for the TWEAK cytokine (TNF receptor superfamily), prevented cachexia and prolonged survival in a C26 tumor-bearing mouse model of cachexia [215]. However, adding infliximab, a recombinant anti-TNF-α antibody, to gemcitabine therapy had no effect on efficacy or safety in pancreatic cancer patients with cachexia [216]. In a clinical trial, ALD518, a humanized monoclonal antibody against human IL-6, significantly improved handgrip strength, fatigue, and cancer-related cachexia in advanced NSCLC patients [217,218]. Another humanized monoclonal antibody, MABp1, targeting

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cytokine IL-1a, prolonged median overall survival compared to Megace in advanced colorectal cancer (CRC) patients with cachexia [219,220]. Treatment with anti-inflammatory drugs like cyclooxygenase (COX) inhibitors (indomethacin, ibuprofen) had beneficial metabolic effects and prolonged survival in weight-losing cancer patients by attenuation of resting metabolism; it also improved appetite due to decreased systemic inflammation [221]. Further, the novel histone deacetylase (HDAC) inhibitor AR-42 suppressed the production of multiple inflammatory cytokines and proteins related to cancer cachexia (IL-6, IL-6Rα, leukemia inhibitory factor, Foxo1, Atrogin-1, MuRF1, adipose triglyceride lipase, uncoupling protein 3, and myocyte enhancer factor 2c) and ultimately showed therapeutic potential against loss of muscle and AT in C-26 colon adenocarcinoma and LLC murine models of cancer cachexia [222]. Non-steroidal selective androgen receptor modulator GTx-024 (enobosarm) showed a promising effect on lean body mass improvement and muscle function in a pre-clinical study [223]. Furthermore, the combination of GTx-024 with AR-42 showed a synergistic effect on cachexia improvement in the C-26 murine model of cachexia [224].

Since diabetes and cancer cachexia share certain metabolic features, an oral type 2 diabetes mellitus drug, metformin, was evaluated in tumor-bearing rats and found to minimize tumor-induced muscle wasting in rats [225]. Similarly, glucose intolerance in cachexia patients prompted evaluation of insulin treatment, which significantly increased food intake, increased whole-body fat, and improved survival; however, it did not affect the lean body mass of weight-losing cancer patients [161]. Further, a combination of metformin and insulin treatment attenuated the progression of cancer cachexia and improved the metabolism of weight-losing cancer patients via increasing their total body fat.

Cachectic patients showed a better response to adjuvant therapy with early intervention rather than at late-stage or refractory cachexia. In some cancer patients, effective treatment of the primary tumor may compromise one’s appetite, weight loss, and muscle wasting [226]. Thus, a major obstacle in evaluating anti-cachexia therapy is how to address the confounding effect of systemic chemotherapy on muscle wasting. Comprehensive metabolic profiling suggests that cachexia induced by cancer is associated with different metabolic derangements than cachexia induced by chemotherapy; thus, effective therapeutic interventions should take into account different drivers of cachexia [227]. Integrative strategies to target multiple cachexia mechanisms have been tested in preclinical and clinical investigations in recent years with limited success. In an early phase II study, combined treatment with polyphenol-enriched diet, antioxidants, medroxyprogesterone acetate, and anti-cyclooxygenase-2 inhibitor (celecoxib), was shown to be effective and safe for cancer cachexia [228]. Bimagrumab (BYM338), a human dual-specific anti-ActRIIA/ActRIIB antibody, showed better efficacy in improving muscle mass compared to blockade of a single receptor [229]. Recently, a HASPIN kinase (a nuclear Ser/Thr kinase) inhibitor (CHR-6494) reduced cancer cachexia in APCmin/+ mice [230]. In a preclinical study, the steroidal lactone, Withaferin-A ameliorated ovarian cancer-induced cachexia via reduced production of NF-kB-mediated pro-inflammatory cytokines [231]. Toll-like receptor (TLR7/8) agonist R848 improved cachexia in the PDAC mouse model of cachexia [232].

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Taken together, although several promising agents are in development that target tumor-induced inflammation, muscle wasting, and adipose browning associated with cancer cachexia, to date, most of the therapeutic strategies to manage cachexia are palliative (Table 2).

9. Summary and future directions

Cachexia is a multifactorial syndrome best characterized by a severe loss of body weight and increased protein catabolism. Pathologically, negative energy and protein imbalance due to systemic inflammation, muscle wasting, and impaired metabolism contribute to cachexia. The prevalence of cancer cachexia is high in advanced cancer. Cachexia research has made a significant advancement in the understanding of this multifactorial disorder. However, the available therapeutic options are limited, and the mechanisms underlying cachexia development are not well defined. Most cachexia research has focused on the involvement of pro-inflammatory cytokines in inadequate food intake or anorexia, improper energy expenditure, altered hepatic function, skeletal muscle wasting, and lipolysis/browning in adipocytes. Several pre-clinical studies have revealed potential mediators, signaling pathways, and novel therapeutic targets, but cancer cachexia is still the leading cause of morbidity and mortality in cancer patients. Several tumor- and host-derived pro-inflammatory cytokines (i.e., TNFα, IL-6 and IL-1, and PTHrP) are the key mediators of cancer cachexia. These molecules play an essential role in cancer growth, inhibition of apoptosis, tumor angiogenesis, and metastasis, along with other factors. Given the complex multifactorial nature of the cachexia secretome, targeting any single dominant circulating factor is unlikely to reverse cachexia. In the array of tumor- and host-derived chemokines and cytokines, which mediators are most responsible for driving cachexia requires further investigation.

The use of appropriate diagnostic criteria among different stages of cachexia may be beneficial to halt the advancement of this disorder. Generally, cancer cachexia is diagnosed at the terminal stage of cancer patients, but it can arise in any phase of cancer progression. Therefore, continuous weight loss should be taken into account for early assessment of cachexia symptoms; this would enable timely treatment decisions. In obese patients, the assessment of lean muscle mass versus bodyweight loss is essential for proper diagnosis of cachexia. Further, the accurate diagnosis of cachexia is challenging due to the growing prevalence of obesity. Weight loss in obese cancer patients may get overlooked because patients appear normally nourished; however, unnoticed severe muscle wasting may exist, and muscle degradation is one of the most critical consequences of cancer cachexia. Screening and monitoring for muscle degradation currently requires muscle biopsies, which are intrusive. Therefore, the identification of more sensitive and specific mediators of muscle atrophy may support development of promising biomarkers for early detection of disease, before the evident signs of active muscle wasting or loss of body weight.

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Abbreviations:

ActRIIB	Activin type-2 receptor
CART	Cocaine-amphetamine-regulated transcript
COX	Cyclooxygenase
IGF-1	Insulin-like growth factor
IL	Interleukin
IFN-γ	Interferon-gamma
IRS1	Insulin Receptor Substrate 1
LCC	Lewis lung carcinoma
MAFbx	Muscle atrophy F box protein
MIC-1/GDF15	Macrophage inhibitory cytokine/growth differentiation factor-15
MuRF-1	Muscle RING finger protein
PTHrP	Parathyroid hormone-related peptide
NF-κB	Nuclear factor κB
NSCLC	Non-small cell lung cancer
POMC	Pro-opiomelanocortin
QOL	Quality of life
REE	Resting energy expenditure
TGF-β	Transforming growth factor-beta
STAT	Signal transducers and activators of transcription
TNFR	TNF-receptor
TNF-α	tumor necrosis factor-alpha
TWEAK	TNF receptor superfamily
UCP	Uncoupling protein
UPP	Ubiquitin-dependent proteasome pathway

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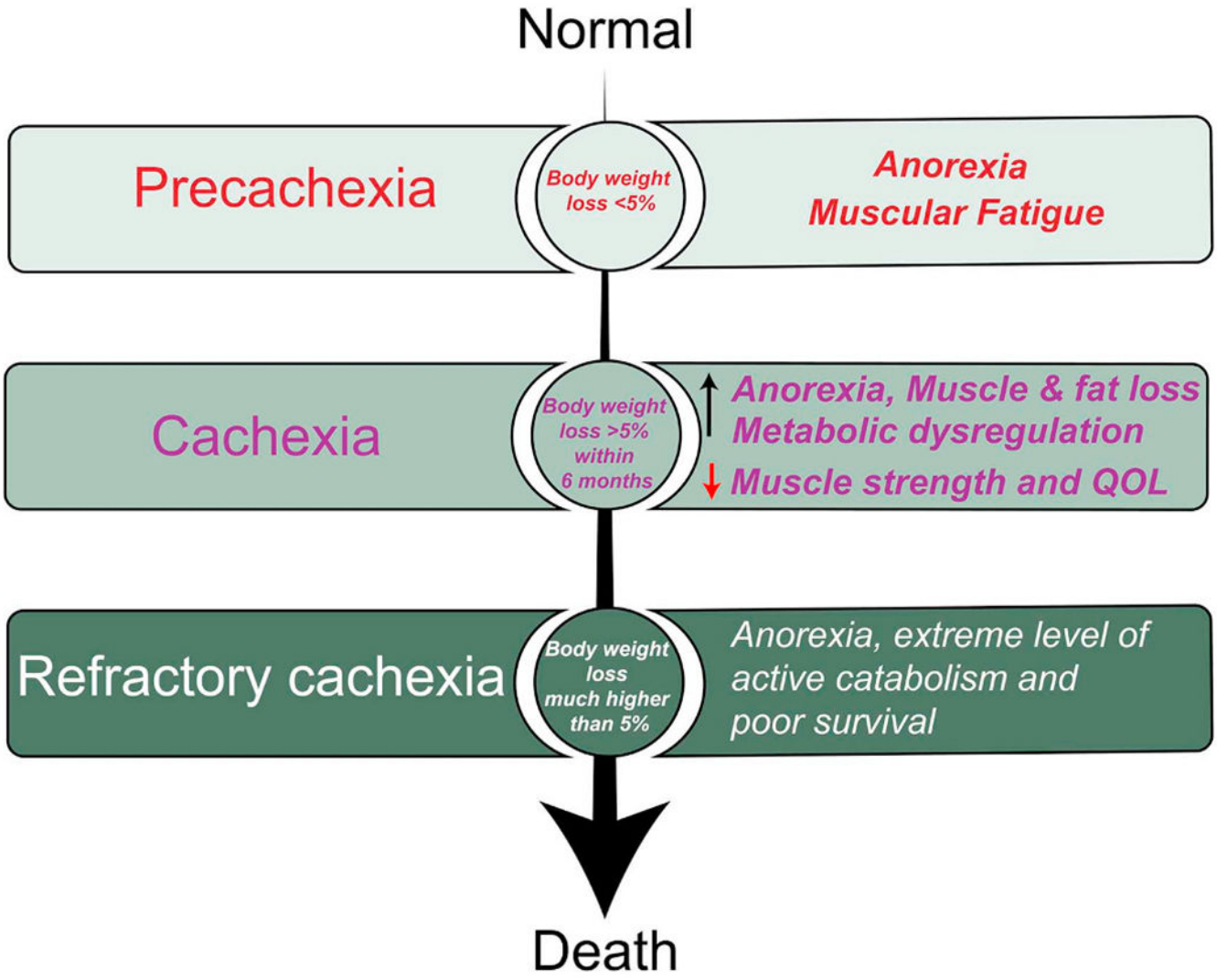

Fig. 1.

Different stages of cancer cachexia. Based on the severity of disease and degree of loss of body weight, cachexia syndrome is classified as pre-cachexia, cachexia, and refractory cachexia. Pre-cachexia: Pre-cachexia is a condition with less than 5% of weight loss accompanied by anorexia and muscular fatigue. Cachexia: Patients with an involuntary weight loss of > 5% within six months that cannot be entirely reversed by conventional nutritional support and leads to progressive functional impairment. An increase in anorexia, weight loss (due to loss of muscle and fat), inflammation, metabolic dysregulation, and a decrease in muscle strength, mobility, and quality of life are the clinical symptoms of cachexia. Refractory cachexia: Weight loss is variable. Due to the higher level of active catabolism and increased expression of ubiquitin ligases, weight loss management is no longer possible, and patients are unlikely to benefit from any treatment, with very poor chances of survival. A severe reduction in skeletal and respiratory muscle strength leads to impaired mobility and inadequate respiration.

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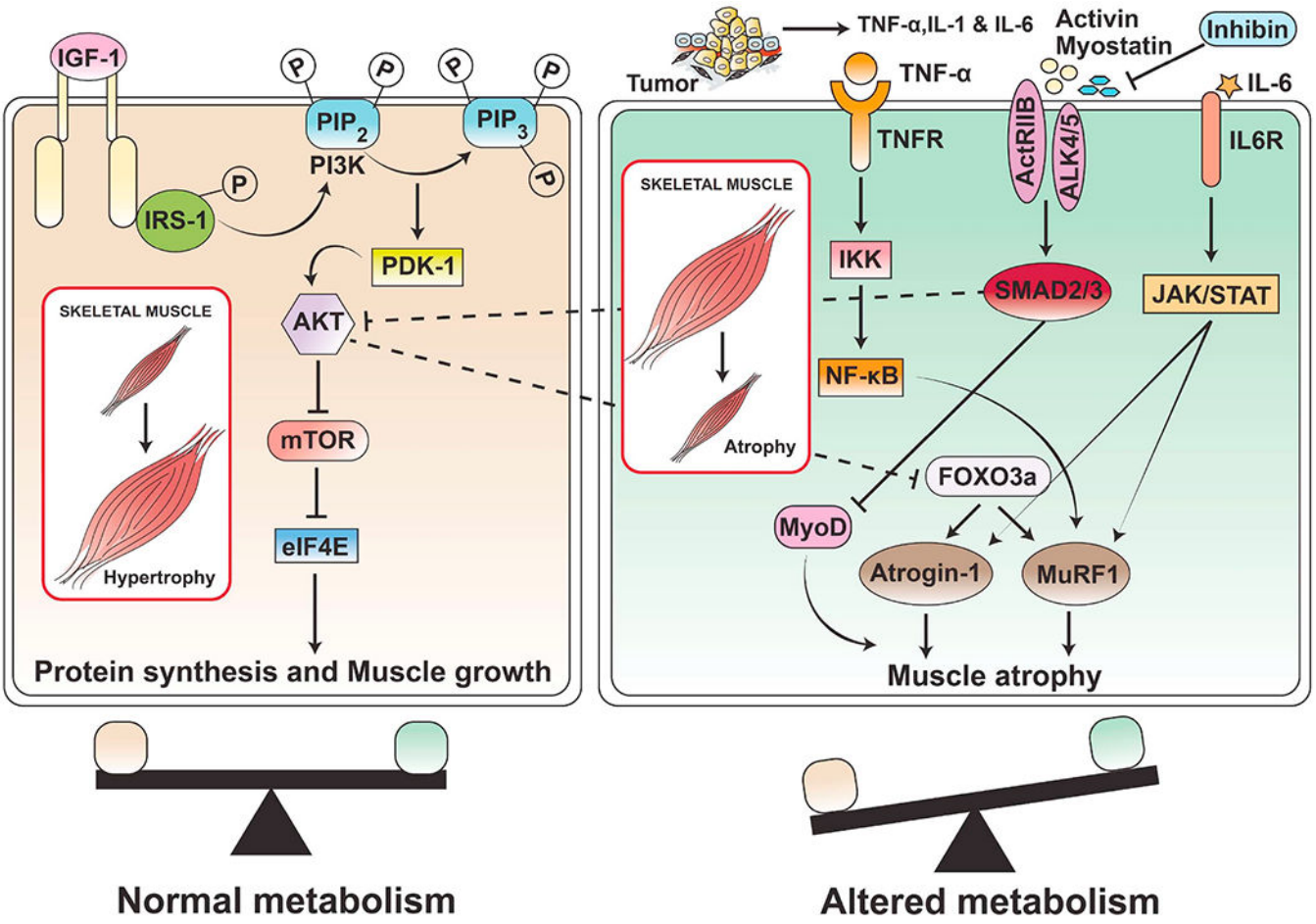

Fig. 2.

Muscle anabolic and catabolic signaling and regulation of muscle wasting in cancer cachexia. Reduced muscle anabolic signaling: IGF-1 acts as an anabolic growth factor that stimulates muscle protein synthesis as well as proliferation and differentiation of muscle stem cells (satellite cells). IGF-1 binds with its receptor IGF1R, resulting in phosphorylation of insulin receptor substrate (IRS) and activation of PI3K/AKT signaling. Activation of PI3K/AKT signaling leads to the activation of downstream targets required for protein synthesis. Cancer cachexia causes impaired IGF-1 signaling, which leads to muscle atrophy. In addition to protein synthesis, AKT signaling also phosphorylates and inactivates the FoxO transcription factor, which is a negative regulator of myogenesis, and finally inhibits the expression of the muscle-specific ubiquitin ligases atrogin-1 and MuRF1. Increased muscle catabolism signaling: Tumor and immune cells induce inflammatory cytokines IL-1 and TNF-α, which activate transcription factor NF-κB via IKK. NF-κB signaling causes muscle wasting in cachexia through increased activity of Murf-1 and atrogin-1. Myostatin and activin bind to activin type II receptor (ActRIIB) and ALK4/5 and subsequently phosphorylate Smad2/3. Phosphorylated Smad2/3 makes a complex with Smad4 that translocates to the nucleus and induces muscle wasting. In addition, myostatin/activin signaling inhibits FoxO phosphorylation via reducing AKT activity, which increases the expression of ubiquitin ligases (Murf-1 and atrogin-1) as well as activates autophagy,

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subsequently increasing muscle protein breakdown. Another cytokine IL-6 binds to its receptors IL-6R and activates JAK/STAT3 signaling, which is implicated in muscle protein wasting.

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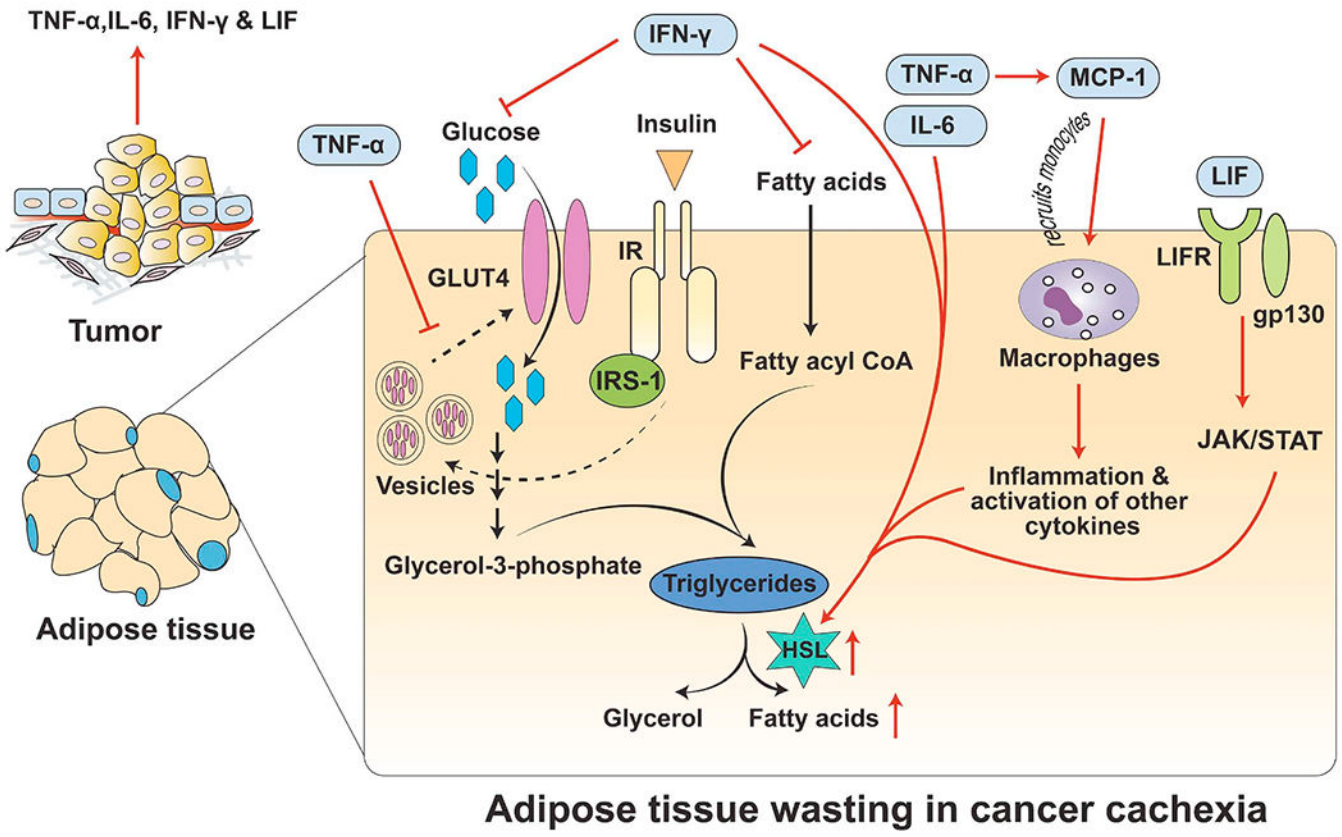

Fig. 3.

Regulation of adipose wasting in cancer cachexia. During cancer cachexia, the tumor secretes several inflammatory cytokines such as TNF-α, IL-6, IFN-γ, and LIF. After secretion from the tumor, TNF-α inhibits the recycling of GLUT4 from the cytoplasm to the plasma membrane. In addition, it also activates monocyte chemotactic protein (MCP-1), which recruits monocytes followed by activated macrophages in the adipose tissue (AT), leading to inflammation. Inside the AT, macrophages also secrete TNF-α and IL-6, which induce lipolysis by activating hormone-sensitive lipase (HSL). Similarly, IFN-γ prevents uptake of glucose as well as free fatty acids, which results in insulin resistance along with lipid breakdown in the AT. Finally, LIF binds to its receptor LIFR and co-receptor gp130 and activates the JAK/STAT pathway. Activation of the JAK/STAT pathway further upregulates HSL activity. Overall, cytokines released from the tumor during cachexia lead to AT wasting, which may contribute to body weight loss in cachectic patients.

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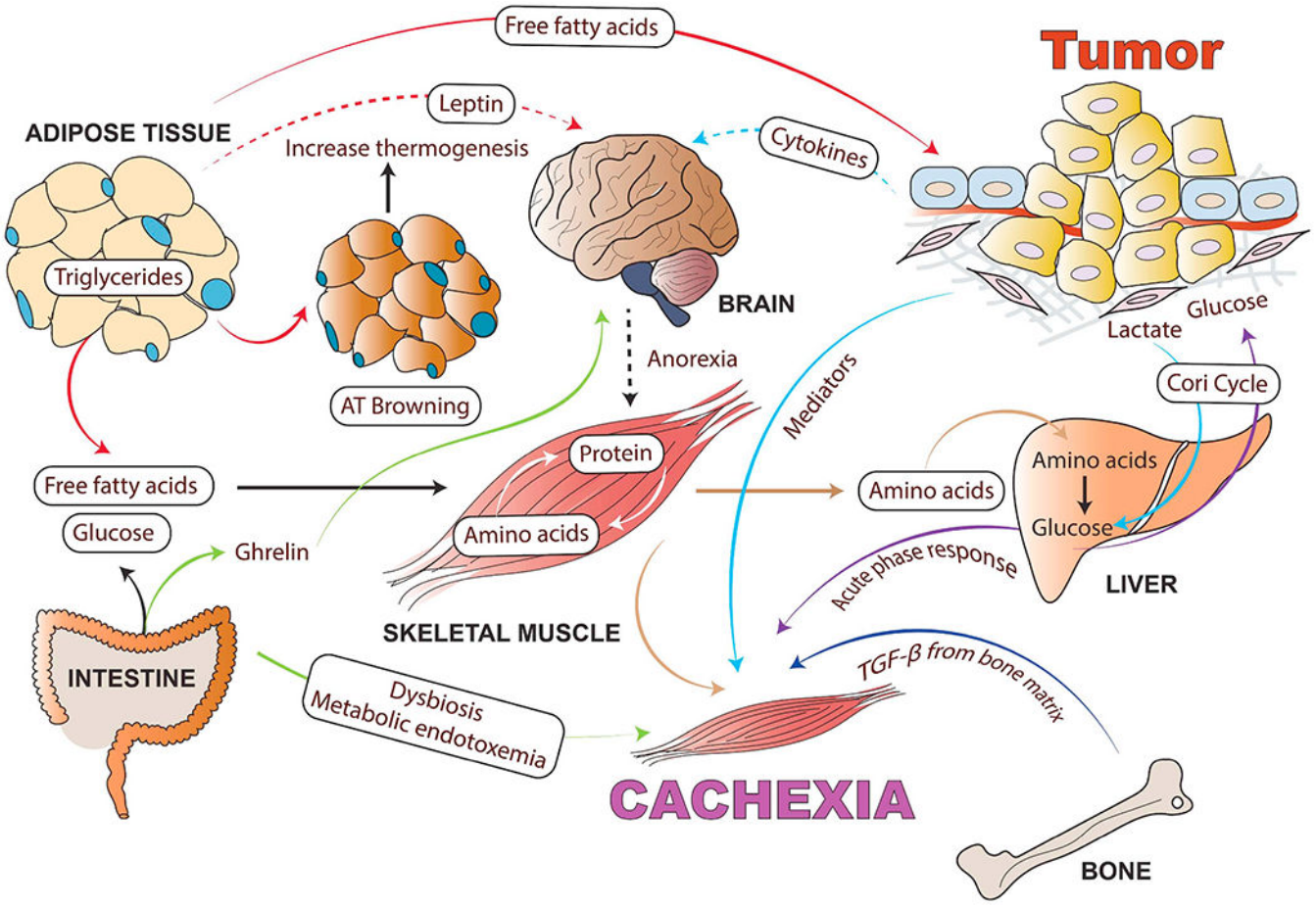

Fig. 4.

Cancer cachexia as a multi-organ metabolic syndrome: Although muscle and adipose tissue wasting are the main characteristics of cancer cachexia, tumor and host-derived factors and systemic inflammation also influence many other organs such as brain, liver, heart, bone, pancreas, cardiac muscle, and gut, which are involved in the cachectic process. Tumor-derived cytokines cause systemic inflammation in the hypothalamus and stimulate neuropeptides involved in the regulation of food intake. Anorexia exacerbates body wasting in cancer cachexia. In addition to tumor-derived mediators, adipokines, muscle-derived cytokines (myokines) and brain-derived anorexia factors also influence the wasting of skeletal muscle and AT as well as increase inflammation in the tumor microenvironment. This inter-tissue communication directly or indirectly influences tissue metabolism and the severity of the cachexia syndrome. Inflammatory cytokines can increase lipolysis in white adipose tissue (WAT), which releases free fatty acids that further fuel the tumor and facilitate muscle wasting. Cachexia can cause adipose tissue browning (WAT switches to brown adipose tissue) and increased thermogenesis. In turn, the myokines activate pathogenic mechanisms in the skeletal muscle and adipose tissue. Muscle wasting releases free amino acids resulting from active protein degradation during cancer cachexia, which drives the acute phase response in the liver. Cancer-associated gut microbiota dysfunction alters mitochondrial energy metabolism in skeletal muscle, contributing to the negative energy

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balance in cachectic cancer patients. In the case of cancer-mediated bone metastasis, increased activity of the osteoclasts results in the activation of TGF-β from the bone matrix, which can facilitate muscle wasting and reduce muscle strength. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Table 1

Appetite enhancing agents investigated for combating cancer cachexia

Therapy/Class	Effects	Possible mode of action	Reference
Eicosapentaenoic acid or fish oil	Improves muscle mass and appetite	Downregulates the production of pro-inflammatory cytokines (Mainly IL-6)	[189,190]
		Acute-phase protein response	
Megestrol acetate or Megace (Synthetic progestin)	Improves appetite, Increases body weight due to the increase in fat mass and water retention	Unknown, Probably by antagonizing the effects of catabolic cytokines, Neuropeptide Y release, Reduction of serum levels of IL-1, IL-2, IL-6, and TNF-a	[191–193, 195, 196, 198, 199
Dronabinol (Marijuana) A derivative of cannabinol	Stimulates the appetite and weight gain, fails to restore the weight loss	Activates the cannabinoid receptors (CB1 and CB2) in CNS	[203,204]
Metformin (Oral type 2 diabetes mellitus drug)	Improves the appetite	Minimized the tumor-induced muscle wasting	[225]
OHR118 (Immunomodulator)	Improves the appetite, dyspepsia, and depression	Modulates the synthesis of chemokines and cytokines including TNF-α	[207]
Anamorelin or Ghrelin, (Stomach released neuropeptide)	Increases food intake and body weight due to an increase in body fat composition and reduces the muscle catabolism	Binds with growth hormone secretagogue receptor 1α (GHSR-1α) expressed in the hypothalamus and pituitary and mediates growth hormone release	[208–211]

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Table 2

Direct targeting the mediators of cancer cachexia

Therapy/Class	Effects	Possible mode of action	Reference
Fibroblast growth factor-inducible 14 (Fn14, monoclonal antibody)	Inhibits cachexia and prolonged survival in C26 tumor-bearing mice	Via targeting the receptor for the TWEAK cytokine (TNF receptor superfamily)	[215]
ALD518 (Humanized monoclonal antibody)	Improves muscle strength and fatigue	A humanized monoclonal antibody against human IL-6	[217,218]
MABp1 (Humanized monoclonal antibody)	Stabilize the symptom of cachexia via anti-inflammatory activity	Targeting cytokine IL-1α	[219,220]
COX inhibitors (indomethacin, ibuprofen)	Attenuation of resting metabolism, improved appetite and prolonged survival	Decreased systemic inflammation	[221]
AR-42 (Histone Deacetylase inhibitor)	Protects loss of muscle and adipose tissue	Suppressed the production of inflammatory cytokine and protein (IL-6, IL-6Rα, leukemia inhibitory factor)	[222]
GTx-024 (Enobosarm)	Increases lean body mass	Androgen receptor modulator	[223]
Bimagrumab (BYM338),(Dual anti-ActRIIA/IIB antibody)	Inhibits muscle wasting	Activin type-2 receptor (ActRIIA/ActRIIB)	[229]
CHR-6494 (HASPIN kinase inhibitor)	Inhibits the loss of body weight	HASPIN kinase (a nuclear Ser/Thr kinase) inhibitors	[230]
Withaferin-A (Steroidal lactone)	Rescue the loss of muscle strength	Reduces NF-kB-mediated pro-inflammatory cytokines production	[231]
R848 (Toll-like receptors (TLR7/8) agonist)	Decreases cardiac and lean mass catabolism	Reduces the Hypothalamic inflammatory gene expression	[232]

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