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VIEWPOINT

# The role of interleukin-6 family cytokines in cancer cachexia

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**Keywords**
adipose tissue wasting; cancer cachexia; interleukin-6; leukemia inhibitory factor; muscle atrophy; oncostatin M

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(Received 30 November 2023, revised 5 June 2024, accepted 26 June 2024)

doi:10.1111/febs.17224

Cachexia is a wasting syndrome that manifests in more than half of all cancer patients. Cancer-associated cachexia negatively influences the survival of patients and their quality of life. It is characterized by a rapid loss of adipose and skeletal muscle tissues, which is partly mediated by inflammatory cytokines. Here, we explored the crucial roles of interleukin-6 (IL-6) family cytokines, including IL-6, leukemia inhibitory factor, and oncostatin M, in the development of cancer cachexia. These cytokines have been shown to exacerbate cachexia by promoting the wasting of adipose and muscle tissues, activating mechanisms that enhance lipolysis and proteolysis. Overlapping effects of the IL-6 family cytokines depend on janus kinase/signal transducer and activator of transcription 3 signaling. We argue that the blockade of these cytokine pathways individually may fail due to redundancy and future therapeutic approaches should target common downstream elements to yield effective clinical outcomes.

## Introduction

Cachexia is a wasting syndrome characterized by dramatic weight loss due to the atrophy of adipose and skeletal muscle tissues. The term "cachexia" originated from the Greek words *kakos* and *hexis* and can be translated as "bad condition". Cachexia impacts the lives of over half of all cancer patients and is linked to about 20% of cancer-related deaths [1]. In patients with pancreatic and gastric cancer, weight loss occurs at a very high rate (60–80%) compared to those with lung, colorectal, prostate, or head and neck cancer, where the rate of weight loss exceeds 50% [2]. Cachexia negatively influences the quality of life and worsens the prognosis of cancer patients [3]. Clinical diagnostic criteria for cancer cachexia are centered around body weight changes over time. Cachexia is typically defined as more than 5% body weight loss within 6 months or loss exceeding 2% in individuals already exhibiting a noticeable reduction in body weight or skeletal muscle mass [3]. The complex nature of cachexia involves inflammation, hormonal factors, and alterations in energy metabolism that result in a rapid breakdown of lipid and protein resources [4]. Apart from skeletal muscle and fat tissue, cachexia also impacts the cardiovascular, gastrointestinal, hematopoietic, and central nervous systems, leading to symptoms such as heart failure, nutrient malabsorption, systemic inflammation, appetite loss, and metabolic disturbances [5].

**Abbreviations**
CLC, cardiotrophin-like cytokine; CNTF, ciliary neurotrophic factor; CT-1, cardiotrophin-1; ERK, extracellular signal-regulated kinase; gp130, glycoprotein 130; IL-11, interleukin-11; IL-27, interleukin-27; IL-31, interleukin-31; IL-6, interleukin-6; JAK, janus kinase; LIF, leukemia inhibitory factor; mTOR, mammalian target of rapamycin; MuRF1, muscle RING-finger protein-1; OSM, oncostatin M; PI3K, phosphoinositide 3-kinase; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription.


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Muscle wasting is one of the hallmarks of cachexia stemming from an imbalance between protein anabolism and catabolism in favor of the latter. Enhanced proteasomal degradation mediated by E3 ubiquitin ligases, Atrogin1 and MuRF1, and the activation of the autophagy-lysosome pathway drive the breakdown of myofibrillar proteins leading to loss of muscle mass and performance [6]. Activation of these pathways is generally regulated by pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interferon-gamma (IFN-γ), which are elevated under cachectic conditions [6,7]. Increased levels of inflammatory mediators also disrupt adipose tissue homeostasis causing the depletion of fat stores. This process involves the enhanced breakdown of lipids, or lipolysis, reduced lipid uptake mediated via lipoprotein lipase, diminished rates of lipogenesis, and transformation of white adipose into metabolically active brown fat through a process referred to as browning [5,8,9]. Browning of white adipose tissue triggers metabolic inefficiency stemming from enhanced mitochondrial uncoupled respiration [9–12]. The net result of these effects is a significant reduction in adipose tissue mass due to increased mobilization of fat stores and elevated energy expenditure [13].

Clinical cancer cachexia is usually associated with anorexia, a prevalent eating disorder occurring in about 50% of the cases, especially in gastrointestinal cancers, and leading to malnutrition and weight loss [4,14]. Anorexia in cancer patients has multifactorial causes, including tumor-related factors, side effects of therapy and changes in taste and smell, all contributing to reduced caloric intake [15]. The hypothalamus, which regulates appetite, may not function properly in cancer patients, leading to insufficient energy intake [15]. This condition is also linked to systemic inflammation that affects the hypothalamus by altering the activity of orexigenic (appetite stimulant) and anorexigenic pathways [16,17]. Despite the significant impact of cachexia on mortality, therapeutic options are still limited. Available treatments provide little benefit to the patients and nutritional supplementation alone is ineffective [4,14]. There is a need for a multi-targeted approach that addresses the underlying molecular and metabolic pathways contributing to wasting [18]. IL-6 signaling has long been implicated in mediating cancer cachexia, including the wasting of both adipose and muscle tissues and the stimulation of anorexia. Cytokines related to IL-6, such as leukemia inhibitory factor (LIF) and oncostatin M (OSM) have also been associated with wasting. This article reviews the literature on the roles of IL-6 family cytokines in cancer cachexia and discusses potential drug targets for future therapies.

## Interleukin-6 family cytokines and their receptors

IL-6 family, also known as the glycoprotein 130 (gp130) cytokine family, includes IL-6 itself, IL-11, OSM, LIF, IL-31, ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1) and cardiotrophin-like cytokine (CLC). These cytokines share two common features: gp130 transmembrane subunit in their receptor complex and a 4-helical bundle structure with specific motifs for receptor binding [19,20]. They all use a signal-transducing receptor β-subunit, gp130 (also known as IL-6Rβ), except for IL-31, which uniquely employs a gp130-like subunit [21]. Their receptor complex also contains either a ligand-binding non-signaling receptor α-subunit or a signaling receptor β-subunit that is similar to gp130 [22]. Only IL-6 and IL-11 utilize a gp130 homodimer to signal. While IL-6 interacts with IL-6 receptor alpha (IL-6Rα), IL-11 binds to IL-11 receptor alpha (IL-11Rα) [23,24]. All other cytokines use a single gp130 molecule in their receptor complex [22]. IL-27 interacts with IL-27 receptor alpha (IL-27Rα). Both LIF and CT-1 utilize LIF receptor β (LIFRβ) heterodimerized with gp130. Although OSM binds to OSM receptor beta (OSMRβ), it can also signal through the gp130/LIFRβ complex [25]. CNTF and CLC execute their signaling via a complex comprised of CNTFRα, LIFRβ and gp130. IL-31, which does not require gp130, utilizes a receptor complex containing OSMRβ and IL-31 receptor subunit-α (IL-31Rα) [22] (Table 1).

In the classical signaling mode, signal transduction is restricted to cells expressing the receptor complex. Alternative mechanisms such as trans-signaling and trans-presentation also exist. In contrast to classical signaling which depends on membrane-bound receptors, trans-signaling involves soluble receptors. For instance, in IL-6 trans-signaling, a soluble form of IL-6Rα enhances the bioavailability of circulating IL-6 and directly engages with membrane-bound gp130 to promote IL-6 signaling in cell types that do not normally express IL-6Rα [26]. Similar trans-signaling mechanisms have also been described for IL-11 [22]. However, only IL-6 has been shown to mediate trans-presentation in which a cell with membrane-bound IL-6Rα presents the IL-6/IL-6Rα complex to a nearby cell expressing gp130 [27].

IL-6 family cytokines induce intracellular signaling using the janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. The binding of



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**Table 1.** Roles of interleukin-6 family cytokines in cachexia-associated phenotypes: muscle atrophy, adipose tissue wasting, and anorexia.

| Cytokine | Receptor complex | Muscle | Adipose | Anorexia |
|---|---|---|---|---|
| IL-6 | IL-6Rα/gp130 or soluble IL-6Rα | Promotes muscle atrophy via activation of atrophy-related genes and inhibition of mTOR pathway [45–47] | Promotes lipolysis and thermogenic activity in adipocytes [13,60], induces browning of white fat [61] | Influences appetite suppression [65], inversely interacts with leptin [68] |
| LIF | LIFRβ/gp130 | Major contributor to muscle atrophy in cachexia models [83–85] | Promotes lipolysis [90], inhibits adipocyte differentiation [91], induces browning of white fat [92] | Elevated levels lead to significant weight loss [72,93], suggesting a role in anorexia pathophysiology [95,97] |
| OSM | OSMRβ/gp130 or LIFRβ/gp130 | Induces muscle atrophy by activating atrophy-related genes [101,107,111,112] | Inhibits adipocyte differentiation [108], induces lipolysis and suppresses insulin response [114,115] | No data |
| IL-11 | IL-11Rα/gp130 or soluble IL-11Rα | Inhibited myogenic differentiation and decreased myotube formation [121,122] | Induces lipid breakdown [122,124] | No data |
| CNTF | CNTFRα/LIFRβ/gp130 | Promotes muscle atrophy in certain contexts [126–128] | Influences energy metabolism [125] | No data |
| CT-1 | LIFRβ/gp130 | Not directly linked to muscle atrophy | Induces fatty acid oxidation, glucose uptake, enhances browning and lipolysis [130] | Reduced food intake [130] |
| CLC | CNTFRα/LIFRβ/gp130 | Not directly linked to muscle atrophy | No data | No data |
| IL-27 | IL-27Rα/gp130 | No data | No data | No data |
| IL-31 | OSMRβ/IL-31Rα | No data | No data | No data |

ligands to the receptor complex generally activates the JAK/STAT3, the phosphoinositide 3-kinase/protein kinase B/Akt (PI3K/Akt) and the mitogen-activated protein kinase (MAPK) pathways [28]. Non-signaling alpha receptors coordinate with signal-transducing β receptors, namely gp130, LIFRβ and OSMRβ, for the initiation of signal transmission [22]. Several mechanisms also exist for the negative regulation of IL-6 family cytokine signaling, such as internalization of receptors, inactivation of receptors and signaling molecules, breakdown of transcripts encoding the cytokines or receptors, and the stimulation of protein inhibitors of activated STAT (PIAS) and suppressor of cytokine signaling (SOCS) proteins [22]. Particularly, SOCS3 has a predominant role in suppressing JAK/STAT3 activation and targeting cytokine receptor complexes for proteasome degradation [29].

IL-6 family cytokines play vital roles in chronic inflammation, autoimmunity, infectious diseases, and cancer. Therefore, they are useful as indicators for diagnosis, prognosis, and therapy response [22]. Activation of JAK by these cytokines often leads to the phosphorylation and subsequent dimerization and nuclear translocation of transcription factor STAT3 (Fig. 1). Since STAT3 can function as an oncogene, it has a crucial role in linking inflammation and cancer [30]. STAT3 is also activated by several growth factor receptors such as epidermal growth factor receptor (EGFR) and hepatocyte growth factor (HGF) [31]. While IL-6 family members activate similar signaling pathways, their physiological roles are determined by factors like tissue specificity of ligand and receptor expression, the magnitude and kinetics of their induction, and their biological availability [32]. IL-6, LIF and OSM from this family have been implicated in taking part in cancer cachexia.

## Interleukin-6

### Introduction

IL-6 was first recognized for its roles in B-cell differentiation and acute phase immune response [33,34]. In fact, IL-6 has diverse physiological functions ranging from inflammation to metabolism, such as apoptosis, cell differentiation, bone homeostasis, and angiogenesis [35]. IL-6 signaling is essential for innate and adaptive immune responses and its deficiency reduces the effectiveness of the immune system [36]. The signaling mechanism of IL-6 involves classical activation, trans-signaling and trans-presentation signaling [37]. While IL-6 binding to membrane-bound IL-6Rα



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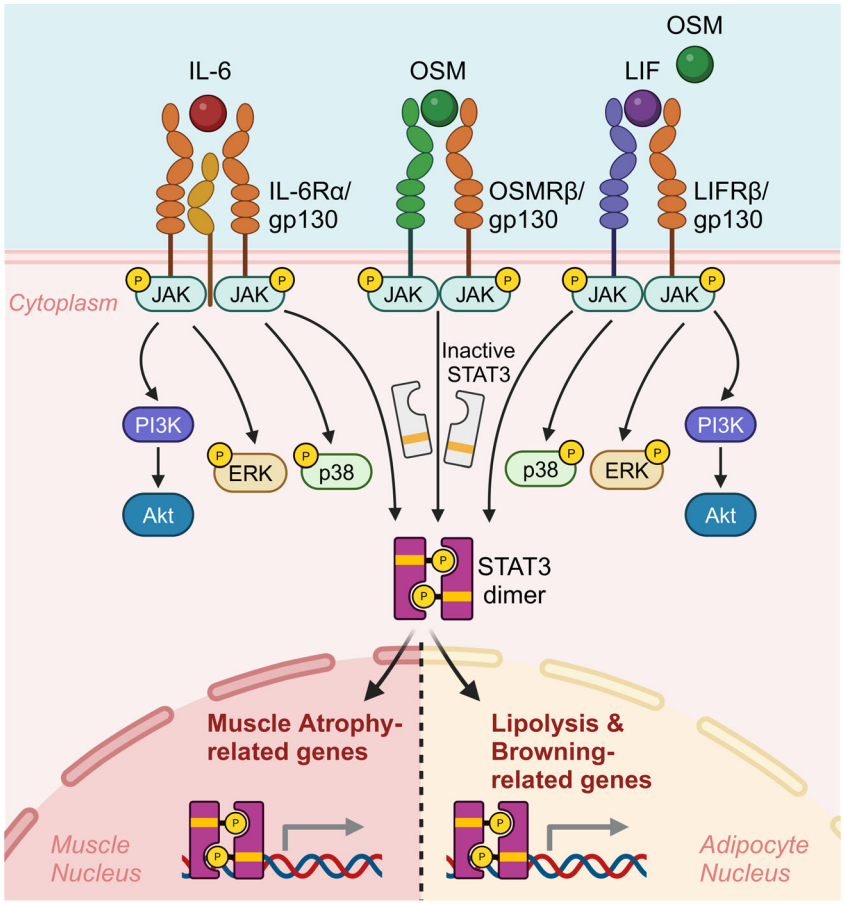



**Fig. 1.** Interleukin-6 (IL-6), leukemia inhibitory factor (LIF) and oncostatin M (OSM) signaling pathways in cancer cachexia. Intracellular signaling pathways activated by the IL-6 family cytokines, specifically IL-6, LIF, and OSM in the context of cancer cachexia are shown. Binding of these cytokines to their respective receptors (IL-6Rα/gp130 for IL-6, LIFRβ/gp130 for LIF and OSM, and OSMRβ/gp130 for OSM) activate the janus kinase (JAK) pathway leading to the phosphorylation (P) of Signal Transducer and Activator of Transcription 3 (STAT3). The activation of receptors triggers downstream signaling pathways including phosphoinositide 3-kinases/protein kinase B (PI3K/Akt), extracellular signal-regulated kinases (ERKs), and p38 mitogen-activated protein kinases. However, JAK/STAT3 pathway has been shown to play a more prominent role in cancer cachexia-associated adipose and muscle wasting. Activation of this pathway stimulates the expression of muscle atrophy-related genes in muscle cells and lipolysis and browning-related genes in adipocytes.

initiates classical signaling in the same cell or trans-presentation signaling in a neighboring cell, a soluble form of IL-6Rα produced by proteolysis or alternative splicing activates trans-signaling in gp130-expressing cells [26,27]. IL-6 signaling mechanisms lead to the activation of multiple intracellular pathways, including JAK/STAT, PI3K/Akt, p38-MAPK and extracellular signal-regulated kinase (ERK) (Fig. 1) [38–40]. While classical signaling is required for anti-inflammatory and regenerative effects of IL-6, trans-signaling is involved in pro-inflammatory responses [41]. Trans-presentation signaling is found in the priming of pathogenic T helper 17 cells [35]. Chronic activation of IL-6 signaling often leads to upregulation of suppressor of cytokine signaling 3 (SOCS3), which reduces the activity of the JAK/STAT3 pathway [42]. Overexpression of SOCS3 downregulates the IL-6-JAK/STAT3 pathway leading to inhibition of tumor growth and metastasis [42,43].

## Pathophysiological mechanisms

Although IL-6 signaling can induce muscle growth acutely, its sustained activation has been shown to promote muscle atrophy [44]. In cultured C2C12 myotube cells, recombinant IL-6 treatment induced atrophy by increasing the expression of atrophy-related genes, including *Atrogin1* and consequently decreasing the diameter of myotubes [45]. Recombinant IL-6 administration to mice also induced the loss of muscle mass [46]. IL-6 treatment inhibited the mammalian



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target of rapamycin (mTOR) pathway and subsequently reduced the phosphorylation of mTOR and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) [45]. Therefore, IL-6 diminishes protein synthesis and simultaneously activates the muscle atrophy mechanism. In fact, local IL-6 infusion into the tibialis anterior muscles of rats led to decreased mTOR-mediated phosphorylation of ribosomal S6 kinase (pS6K1), reduced total and myofibrillar protein content and resulted in muscle atrophy [47]. In addition, IL-6-overexpressing transgenic mice suffered from severe muscle wasting, which was blocked by the administration of an IL-6Rα antibody [48].

IL-6 signaling has been regarded as a critical mediator of cancer cachexia as it contributes to inflammation, directly stimulates muscle breakdown and disrupts oxidative capacity [49–51]. In fact, elevated serum IL-6 was also detected in cancer patients exhibiting weight loss [52]. IL-6 levels also correlated with the development of cachexia in mice bearing C26 colon carcinoma tumors [53]. Similarly, high systemic IL-6 levels were associated with increased STAT3 phosphorylation and *Atrogin1* expression in the muscles of $Apc^{Min/+}$ mice, which displayed cachexia [54]. The depletion of IL-6 in these mice ($Apc^{Min/+}$; $IL\text{-}6^{-/-}$ mice) rescued the cachexia phenotype and reduced muscle wasting [55]. In fact, the neutralization of IL-6 with a specific antibody in C26 tumor-bearing mice reduced muscle loss compared with controls [56]. IL-6 neutralization also prevented muscle wasting in other cachexia tumor models [48,56–59].

In addition, IL-6 plays a significant role in cachexia-induced adipose tissue wasting. IL-6 administration promoted lipolysis and thermogenic activity in adipocytes [13,60]. Elevated levels of IL-6 and a positive correlation between serum IL-6 and free fatty acids were observed in patients with cachexia at both early and late stages, suggesting an impact on adipose lipolysis [61]. Administration of an anti-IL-6Rα antibody to cachectic mice was shown to suppress lipolysis and prevent the loss of white adipose tissue [61]. Furthermore, increased IL-6 levels were linked to the stimulation of browning of white adipose tissue in cachectic mice whereas the use of an anti-IL-6Rα antibody blocked the browning of white fat in mice carrying tumors [61]. Similarly, tumor-induced adipose tissue browning was reverted by the neutralization of circulating IL-6 or its depletion in tumors, which ameliorated adipose wasting [9].

The JAK/STAT3 pathway has been shown to mediate the cachexia-inducing effects of IL-6. In the C26 model, STAT3 activation correlated with increased expression of muscle E3 ubiquitin ligases and loss of muscle mass, which was mitigated by the overexpression of a dominant-negative STAT3 [46]. The neutralizing of IL-6 in C26 tumor-bearing mice blocked STAT3 activation leading to reduced muscle loss [56]. STAT3 was found to influence muscle wasting through multiple mechanisms, such as increasing the expression of muscle atrophy genes (e.g., *Atrogin1*, *MuRF1*, *Myostatin*) by stimulating CCAAT/enhancer binding protein (C/EBPδ) [62] and promoting posttranslational modifications in JAK/STAT3 components, which enhanced STAT3 localization to the nucleus [46]. Additionally, cancer cell-derived IL-6 trans-signaling was shown to induce autophagy in myotubes [63]. IL-6 trans-signaling originating from muscle tissue also stimulated lipolysis in adipose tissue in pancreatic ductal adenocarcinoma xenograft models, which also contributed to muscle wasting indirectly [64]. Elevated expression of soluble IL-6Rα in atrophying muscles led to the accumulation of this receptor protein in plasma and subsequent stimulation of lipolysis in adipose tissue, indicating that crosstalk between the wasting of these tissues involves IL-6 signaling [64].

IL-6 also has additional roles in the regulation of body weight and fat mass. IL-6 overexpression studies in animals demonstrated reduced fat accumulation and weight gain [65,66]. Moreover, IL-6-deficient models exhibited mature-onset obesity [67]. Studies suggested that IL-6 elicits appetite-suppressing effects by interacting with leptin [68] and regulates food consumption by influencing hypothalamic neuropeptides [65]. In esophageal cancer patients, a reduction in circulating levels of leptin was detected, which also inversely correlated with plasma IL-6. A meta-analysis on the impact of inhibitors of IL-6 signaling on body weight revealed that these inhibitors are associated with weight gain and increased body mass index and indicated that high IL-6 levels well correlate with weight loss linked to cancer cachexia [69]. All of these findings suggest that the IL-6 pathway involving the JAK/STAT3 axis is a promising therapeutic target for preventing cancer cachexia [59] (Table 1 and Fig. 2).

## Leukemia inhibitory factor

### Introduction

The leukemia inhibitory factor (LIF) was identified as a secreted protein that inhibits the proliferation of mouse myeloid leukemia cells by inducing their differentiation [70]. However, LIF serves diverse functions across various physiological systems, including roles in inflammatory and immune responses, neural development, embryogenesis and bone metabolism [71]. LIF



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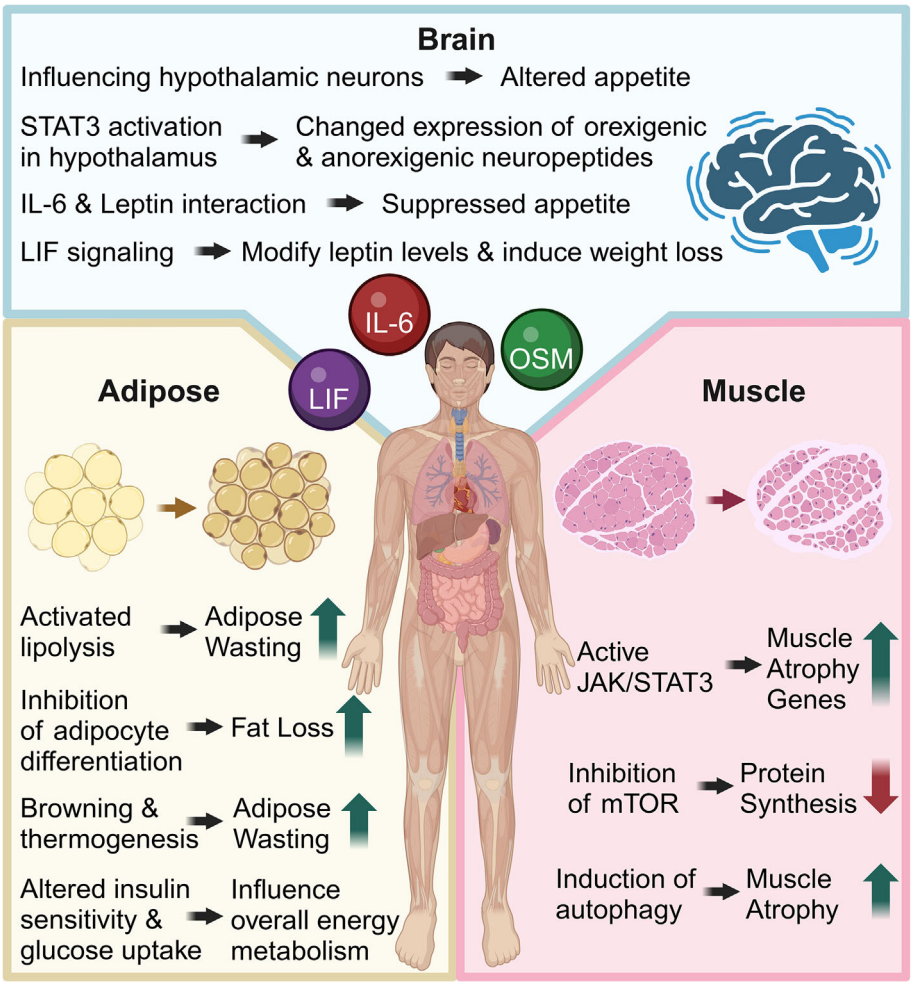



**Fig. 2.** Schematic representation of the systemic effects of IL-6 family cytokines on cancer cachexia. The figure illustrates the multifaceted role of cytokines, such as IL-6, LIF and OSM, in mediating catabolic processes in adipose and muscle tissues and their appetite-altering effects in the brain. IL-6, interleukin-6; JAK, janus kinase; LIF, leukemia inhibitory factor; mTOR, mammalian target of rapamycin; OSM, oncostatin M; STAT3, activator of transcription 3.

binding to its specific receptor (LIFRβ) and the gp130 co-receptor initiates signaling involving JAK/STAT, ERK, PI3K/Akt pathways (Fig. 1) [72]. LIFRβ is expressed particularly in muscle cells, adipocytes, breast epithelium, macrophages, and hepatocytes [73]. High levels of LIF expression were also detected in tumors of various cancer types, such as pancreatic, colorectal, esophageal, ovarian, gastric, and testicular cancers [74]. In fact, circulating LIF is usually associated with poor prognosis [71,75]. For instance, in pancreatic ductal adenocarcinoma (PDAC) cells, LIF expression in conjunction with Yes-associated protein 1 (YAP1) upregulation promoted tumorigenesis [76]. LIF-dependent STAT3 activation in breast and colorectal cancer cells induced endothelial to mesenchymal transition (EMT) [77]. Elevated levels of LIF in colorectal cancer patients suppressed the p53 protein and enhanced resistance against chemo- and radiotherapy, and promoted tumor recurrence [78,79].

## Pathophysiological mechanisms

Leukemia inhibitory factor was identified as a cachexia-inducing agent in studies where the inoculation of LIF overexpressing cell lines resulted in severe weight loss, including the loss of adipose mass [80,81]. In fact, LIF administration was found to promote lipolysis in adipocytes [82]. A direct link between LIF and muscle atrophy was also observed [83,84]. Particularly, LIF was described as the major contributing factor to muscle atrophy in the C26 colon carcinoma model [85]. Direct administration of recombinant LIF



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to C2C12 myotubes reduced cell diameter in a manner similar to the treatment of C26 cell-conditioned medium [85]. CRISPR-mediated knockout of LIF in the C26 model led to a marked reduction in weight loss, including the wasting of muscle and fat tissues, emphasizing LIF's role in the development of cachexia [86]. In fact, the neutralization of LIF and the inhibition of JAK1/2 and STAT3 in C2C12 myotubes prevented the atrophic effects of the medium conditioned with C26 cells [85]. These results suggest that the JAK/STAT3 pathway downstream of LIF signaling drives muscle atrophy. Tumor-induced LIF expression in muscle tissue was also linked to the atrophy process while the overexpression of a microRNA targeting LIF (miR-29c) mitigated the cachectic phenotypes observed in the Lewis lung carcinoma (LLC) tumor model [87]. Interestingly, LIF was also described as a myokine associated with exercise. LIF expression in muscle tissue was upregulated upon exercise without changing the circulating levels [88]. LIF-induced satellite cell proliferation could contribute to muscle adaptation to exercise [88,89]. Therefore, the exact role of LIF in muscle physiology appears to be context-dependent.

Leukemia inhibitory factor elicits various effects on adipocyte function and thereby contributes to adipose wasting linked to cachexia. These include promoting lipolysis, inhibiting adipocyte differentiation, inducing browning of white adipose tissue, and the dedifferentiation of mature adipocytes [72]. Recombinant LIF stimulated lipolysis in cultured adipocytes [90]. Peripheral administration of LIF in mice resulted in substantial decreases in adipose tissue mass (over 50%) and body weight (over 10%), accompanied by a brief reduction in food consumption attributed to decreased leptin levels [90]. By enhancing lipolysis through the upregulation of adipose triglyceride lipase (ATGL) and activating the JAK/STAT signaling pathway, LIF drives the mobilization of lipid stores, contributing significantly to the cachectic phenotype [90]. Simultaneously, LIF prevents the transformation of pre-adipocytes into mature fat cells by suppressing essential markers of adipocyte differentiation, effectively inhibiting the process of adipogenesis [91]. Additionally, LIF also triggers the conversion of white adipose tissue into brown fat [92].

Elevated LIF expression, as demonstrated in various animal models, not only diminished food intake but also led to significant weight loss, arguing for its potential as a key player in anorexia [72,93]. Anorexia emerges as a common and debilitating symptom in cancer patients, exacerbated during tumor progression and treatment phases [94]. In gastric cancer, activation of Toll-like receptor 5 (TLR5) signaling pathway through interleukin-1 receptor-associated kinase-1/4 (IRAK-1/4) resulted in increased LIF expression, subsequently causing anorexia [95]. LIF induced the secretion of alpha-melanocyte stimulating hormone (α-MSH) from arcuate nucleus proopiomelanocortin neurons in the hypothalamus [96], a process associated with increased STAT3 phosphorylation. Additionally, elevated levels of LIF correlated with an increase in orexigenic neuropeptides and a decrease in anorexigenic neuropeptides in the hypothalamus [97]. In the early stages of cachexia, elevated leptin levels likely contribute to the promotion of anorexia. However, in later stages, decreasing circulating leptin helps to inhibit anorexia [72]. In fact, recombinant LIF administration in mice also led to acute anorexia, which was counterbalanced by reduced leptin signaling [90]. Similarly, in colon adenocarcinoma, anorexia was induced with activation of the JAK/STAT signaling pathway in the hypothalamus by LIF [98]. With its elevated circulating levels in numerous cancers, LIF is likely a key contributor to wasting and anorexia in cachectic patients (Table 1 and Fig. 2). Clinical studies testing LIF levels in the circulation and atrophying tissues are needed to establish the link between LIF and the progression of cancer cachexia.

## Oncostatin M

### Introduction

Oncostatin M (OSM) was originally recognized for suppressing the growth of certain tumor cell lines but not normal fibroblast cells [99]. Since its first identification, OSM activity has been linked to various physiological functions, including hematopoiesis, liver regeneration, inflammation, wound healing, fibrosis, and metabolic processes [22,100]. In mouse cells, the signal transduction of OSM initiates with its binding to gp130 which then recruits the OSM receptor (OSMRβ). However, in humans, the OSM-gp130 complex can recruit either LIFRβ or OSMRβ as the receptors [101]. The OSM-receptor complex activates JAK1/2 kinases and stimulates STAT3-dependent gene regulation, including the *Osmr* transcript (Fig. 1) [102–104].

### Pathophysiological mechanisms

Elevated levels of OSM have been detected in cancer and inflammatory diseases [100,105–107]. OSM secreted by immune cells, such as macrophages, can inhibit the differentiation of adipocytes and myoblast



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cells [108,109]. Although OSM was identified as a potent inducer of muscle stem cell quiescence and satellite cell OSMR was essential for injury-induced muscle regeneration [110], recent studies have associated OSM with cancer cachexia and inflammatory responses in skeletal muscle [111]. Administration of a recombinant OSM protein in myotube cultures promoted cellular atrophy by inducing the expression of a variety of muscle atrophy-related genes, including *Atrogin1* [107,111,112]. The atrophy-inducing effects of OSM in myotubes depended on JAK/STAT3 signaling [111,112]. OSM-dependent activation of STAT3 signaling via OSMRβ or LIFRβ was negatively regulated by SOCS3 [113]. Interestingly, relative to IL-6 and LIF, OSM induced a more substantial atrophic effect in myotubes, accompanied by a larger impact on the transcriptional profiles of these cells [111]. The potency of OSM likely reflects the high expression level of its receptor in muscle cells.

Furthermore, OSM overexpression in muscle tissues of mice also induced the JAK/STAT3 pathway and the expression of atrophy-related genes, thereby stimulating localized muscle wasting [101,111]. *Osmr* and other OSM target genes were upregulated in the muscles of mice upon tumor inoculation [111]. In fact, the depletion of OSMR in the skeletal muscles of tumor-bearing mice preserved muscle mass and strength [107]. OSMR deficiency suppressed tumor-induced expression of *Atrogin1*, *MuRF1* and *Eda2r* [107]. EDA2R-NIK signaling has recently been implicated in muscle wasting and OSM was shown to upregulate muscle EDA2R [107]. In fact, OSM and EDA2R ligand, EDA-A2, treatment additively induced atrophy-related genes and cellular atrophy in myotubes, indicating that these two pathways may function in parallel to drive muscle wasting [107]. In addition, OSM also has a broad influence on adipose tissue metabolism including adipogenesis, lipolysis, insulin sensitivity, and food intake during cancer cachexia [114]. The differentiation of adipocytes was inhibited by OSM, which is likely released by macrophages residing in adipose tissue [108]. OSM was also shown to induce lipolysis in adipocytes and suppress the insulin response, suggesting a role in the dysregulation of lipid metabolism in adipose tissue [115] (Table 1 and Fig. 2).

Elevated levels of OSM were detected in the plasma of tumor-bearing mice [106,107]. Upon administration of an OSM-neutralizing antibody, tumor-induced expression of atrophy-related genes and loss of muscle mass were attenuated [111]. In addition, tumor-bearing mice exhibited a trend for improved physical activity in response to OSM neutralization [111]. Therefore, OSM is a promising candidate target to prevent muscle wasting linked to cancer cachexia. In fact, muscle biopsies of cachectic patients with PDAC displayed elevated OSMR levels compared with PDAC patients without cachexia and non-cancer healthy controls. An OSM-targeted gene set in muscle cells were also enriched in muscle biopsies of cachectic patents. Furthermore, increased levels of OSMR and other OSM target genes were also detected in muscle biopsies of patients with muscular dystrophies, including Duchenne muscular dystrophy (DMD) and Facioscapulohumeral muscular dystrophy (FSHD). Inflammatory responses have been implicated in the progression of these diseases, in which OSM may also play a role [116,117]. Additional studies are needed to determine how circulating OSM levels change in muscular dystrophy and cancer cachexia patients.

## Other IL-6 family members

Other members of the IL-6 family have also been implicated in cachexia although relatively fewer numbers of studies addressed their roles. Interleukin-11 (IL-11) was characterized as a key regulator of hematopoiesis, platelet production, and macrophage differentiation with pleiotropic effects in the bone, intestines and the immune system [118]. IL-11 downstream signaling involves JAK/STAT, MAPK/ERK, and PI3K/Akt pathways and it has been associated with tumorigenesis, cell cycle progression, and angiogenesis in cancer [22,25]. High IL-11 levels were linked to poor prognosis in clear-cell renal carcinoma and the inhibition of IL-11 signaling in gastrointestinal and endometrial cancer cells retarded tumorigenesis and metastasis [119,120]. IL-11 inhibited myogenic differentiation of C2C12 cells and decreased myotube formation and myosin heavy chain expression arguing for a potential role in muscle atrophy [121]. In fact, exogenous administration of IL-11 facilitated cachexia in LLC tumor-bearing mice [122]. However, an independent study indicated that recombinant IL-11 administration did not promote tumor growth or weight loss in the LLC cachexia model [123]. In nude mice, inoculation with IL-11-expressing MMG-1 human tumors caused weight loss, which was linked to decreased activity of lipoprotein lipase and increased fat breakdown [124]. IL-11 was also shown to induce cachexia and lipid breakdown even in the absence of a tumor [122]. Further studies are needed to uncover the exact role of IL-11 in cancer cachexia (Table 1).

Ciliary neurotrophic factor acts as a neurotrophin that promotes neurogenesis, survival of neural cells and their regeneration [125]. However, it shares



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structural and functional characteristics with the IL-6 family cytokines. In addition to its protective effects on neurons, CNTF also regulates energy metabolism by promoting fatty acid oxidation and suppressing insulin resistance [125]. The administration of a recombinant CNTF protein or its overexpression in glioma tumors caused weight loss due to reduced food intake and enhanced muscle atrophy [126–128]. However, a link between CTNF and cancer cachexia remains to be elucidated (Table 1).

Cardiotrophin-1, initially recognized for its role in cardiomyocyte hypertrophy, has also been shown to function in the liver and nervous system [25]. Utilizing LIFRβ and gp130, CT-1 activates JAK/STAT, MAPK, and PI3K/Akt pathways and participates in cancer cell proliferation and invasiveness [25,129]. Administration of a recombinant CT-1 protein was shown to induce fatty acid oxidation and glucose uptake in skeletal muscle and adipose tissues along with reduced food intake and enhanced browning and lipolysis in fat tissue [130]. Despite these diverse metabolic effects, there is currently no direct evidence suggesting the involvement of CT-1 in cancer cachexia (Table 1).

Cardiotrophin-like cytokine has roles in immune regulation, B-cell activation and survival of neurons [131]. Mutations in this gene cause suckling defects in infants due to reduced numbers of facial motor neurons and subsequent atrophy of facial muscles [132]. CLC is also involved in tumor progression [133]. However, no studies have linked this cytokine to cancer cachexia.

Interleukin-27 (IL-27) is a pleiotropic cytokine with pro- and anti-inflammatory roles in immune regulation and diverse effects in T-cell differentiation, innate immune responses, and tumor growth [134]. IL-27 has also been associated with antitumor immunity [135,136]. However, any involvement in cancer cachexia has not been reported. IL-31 is another cytokine without reported roles in cancer cachexia. IL-31 has been shown to inhibit tumor growth and promote antitumor immunity by increasing cytotoxic T-cell infiltration and down-regulating immunosuppressive cell populations [35].

## Conclusion

Interleukin-6 has long been implicated as an important mediator of cancer cachexia. Elevated circulating IL-6 was detected in tumor-bearing cachectic mice and cancer patients exhibiting weight loss [46,52,55]. In fact, the use of antibodies neutralizing IL-6 ameliorated muscle wasting in different models of cancer cachexia [48,56–59]. However, a clinical trial utilizing a humanized IL-6 monoclonal antibody (ALD518) failed to yield a clear improvement in lean body mass of non-small cell lung cancer (NSCLC) patients [137]. LIF and OSM have also been associated with cancer cachexia and high levels of these cytokines were measured in tumor-bearing mice [106,107]. Compared with IL-6, these cytokines were found to elicit more pronounced effects in cultured myotubes, including greater changes in JAK/STAT3 phosphorylation, atrophy-related gene expression and cellular atrophy [85,111]. In fact, increased transcript levels of OSM target genes were detected in muscle biopsies of PDAC patients and the neutralization of OSM preserved muscle mass in a mouse model of cancer cachexia. Therefore, therapies targeting OSM and LIF may benefit cachectic cancer patients. Humanized monoclonal antibodies against OSM and LIF have been generated and tested for their safety and tolerability in clinical trials on rheumatoid arthritis (GSK315234), systemic sclerosis (GSK2330811) and metastatic solid tumors (AZD0171) [138–140]. Such therapeutic tools can potentially be repurposed to test their efficacy in the reversal of symptoms of cachexia in cancer patients.

It is possible that all of IL-6, LIF, OSM and other family members are involved in the development of cancer cachexia. Their contribution is likely determined by their relative tumor-induced expression in immune cells or their relative secretion by tumors. Future studies should test circulating levels of these cytokines in clinical samples to assess their potential involvement in weight loss. Furthermore, some of these cytokines were found to enhance the expression of other members of the IL-6 family, including LIF- and OSM-mediated IL-6 induction [101,141]. A therapeutic approach targeting a common downstream element of these cytokine pathways could yield more effective clinical outcomes. For instance, inhibition of JAK1/2 by the administration of ruxolitinib and tofacitinib in mice was shown to suppress tumor-induced anorexia and adipose tissue wasting [98]. In a clinical trial involving ruxolitinib, increased body weight was reported in myelofibrosis patients in response to the administration of this drug [142]. In fact, ruxolitinib is currently tested in a clinical trial for its efficacy in preventing cachexia and anorexia in NSCLC patients (NCT04906746). However, it should be noted that various cytokines and hormones signal through the JAK/STAT pathway and the inhibition of JAK1/2 will likely cause undesired side effects. In previous trials, patients receiving JAK inhibitors experienced a broad spectrum of side effects due to the varying specificity of the inhibitors for different JAKs [35]. These side



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effects ranged from various types of infections to anemia, altered blood cell counts, gastrointestinal issues, and neurotoxicity [143]. A therapeutic agent more specific for the IL-6 family cytokines could have gp130 as the primary target [144]. In fact, gp130 blockade mediated by a specific antibody was shown to inhibit myeloma growth more efficiently compared with IL-6 and IL-6Rα antibodies [145]. It is imperative that the redundant roles of IL-6 family cytokines in cancer cachexia be considered when designing novel therapeutics against this syndrome.

## Acknowledgements

This work was supported by the European Molecular Biology Organization (EMBO) installation grant (#4162) and the Scientific and Technological Research Council of Turkiye (TUBITAK) grant (118C014 and 118Z791) to SK. Figures were created with BioRender.com.

## Conflict of interest

The authors declare no conflict of interest.

## Author contributions

SA and SK jointly wrote the manuscript.

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