Emerging Signaling Mediators in the Anorexia-Cachexia Syndrome of Cancer

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Abstract

The cachexia syndrome in cancer is characterized by weight loss due to the combination of anorexia and atrophy of adipose and skeletal muscle. For decades, inflammatory circulatory factors have been identified to regulate wasting, yet inhibitors of these factors have not yielded the same clinical benefit as in animal models. Therefore, additional mediators of cachexia likely regulate this syndrome, and such factors might be more suitable for targeted intervention. Here, we highlight several anorexia-cachexia signaling mediators, including activin A, myostatin, GDF15, and lipocalin-2. Current evidence is discussed that these factors associate with cachexia in cancer patients and translational efforts including essential early phase clinical trials are summarized. We conclude with thoughts on targeted and personalized approaches for future anti-cachexia treatments.

Keywords

cachexia; anorexia; cytokines; inflammation; pancreatic cancer

The Cancer Cachexia Syndrome

Cachexia is a common clinical syndrome of cancer patients that is characterized by involuntary weight loss due to depletion of skeletal muscle and adipose tissue [1, 2]. Because of the frequency with which cachexia occurs in conjunction with anorexia, or decreased appetite, it is often referred to as the anorexia- cachexia syndrome. Although patients with weight loss greater than 5% are generally considered cachectic, it is not uncommon for patients to lose 20–25% of their pre-illness weight [3, 4]. Continual weight loss associates with a poor prognosis, and patients with cachexia are often weak and prone to fatigue, which lowers their quality of life and complicates their care. Nutritional intervention

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promotes some weight gain in patients, but this weight is mostly transient in the form of adipose tissue, while the loss of lean muscle is thought not to be reversable [5]. Therefore, there remains an urgent need to develop effective cachexia therapies that can translate to better quality of life, improved outcomes, and when given in combination with anti-tumor therapies, increased survival.

The cachexia syndrome does not present equally among tumor types. Pancreatic ductal adenocarcinoma (PDAC) patients have amongst the highest incidence of cachexia, estimated at 70% [1, 6, 7]. In addition, while an increased incidence of cachexia is associated with advanced disease, a significant proportion of PDAC patients already meet cachexia criteria at the time of cancer diagnosis. Other risk groups include esophageal, lung, liver, colon, gastric, and head and neck cancers, while breast, melanoma, prostate, and thyroid cancers present with the lowest incidence [1]. The current basis for these differences remains to be determined.

Over the decades that the cachexia syndrome has been studied in cancer, much attention has been given to the role of pro-inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin-6 (IL-6). Both *in vitro* studies and animal models of cancer cachexia support that these factors can directly promote the catabolism of adipose and skeletal muscle tissues [8]. However, pharmacological inhibitors of these cytokines have yet to prove effective in restoring or maintaining body weight or improving muscle function in cancer patients with cachexia [9–13]. Such outcomes in human studies have led to an appreciation that additional mediators besides TNF and IL-6 are likely to be involved in the regulation of the cancer cachexia syndrome. In this review, we discuss recent studies that have placed new attention on signaling mediators such as activin A and myostatin, and their association with cancer cachexia [14], as well GDF15 and lipocalin-2 which have provided fresh insight on the underlying mechanism of anorexia in response to cancer and the side effects of platinum-based chemotherapeutic drugs [15–17].

Associating cancer cachexia with activin and myostatin in rodents and patients

Activin A and myostatin are members of the tumor growth factor-beta (TGF-β) family of ligands. The signaling of these ligands is controlled through the binding to the type II receptor in skeletal muscle (activin: ACVR2B or ACVR2A; myostatin: ACVR2B predominantly) leading to the phosphorylation and dimerization of SMAD2 and SMAD3 transcription factors that are translocated from the cytoplasm to the nuclei to regulate gene expression [18–20]. Increases in circulating levels of myostatin and activin A are sufficient to induce muscle wasting [21, 22] [Figure 1]. Tumor studies in mice show that elevated levels of activin signaling is associated with increased metastases and shorter survival, and with respect to cancer cachexia, increased weight loss [23, 24]. Consistent with these findings, cancer patients with increases in circulating levels of activin A also present with weight loss [14, 25–27]. Specifically for ovarian and pancreatic cancers, the source of circulating activin A appears to reside within the tumors themselves, perhaps explaining the high rates of cachexia in these cancers [24, 28–30]. With regards to myostatin, the

association between its circulating levels and cachexia is less clear. In fact, Loumaye et. al. reported that circulating levels of myostatin are reduced, not elevated, in colorectal and lung cancer patients with cachexia [14].

Translating activin A and myostatin therapies from mice to cachexia patients

Evidence from a number of studies performed in mouse models of cancer cachexia has demonstrated that reducing activin A and myostatin signaling either through ligand trap or receptor blockade approaches is sufficient to rescue muscle wasting [24, 31–35]. These respective treatments resulted in the downregulation of SMAD2/3 phosphorylation, validating the mechanism of action and suggesting that downstream inhibition of SMAD2/3 can prevent muscle wasting in cancer cachexia [31, 36]. Such studies point to the activin/ myostatin signaling pathways as viable therapeutic targets for the treatment of cancer cachexia. Indeed, clinical trials have been conducted with a series of new compounds specifically aimed at reducing activin A and myostatin activities through either acting as ligand traps for myostatin and activin A or blocking agents for the ACVR2B receptor. Despite the apparent anti-cachectic potential for these compounds, the vast majority of clinical trials have been conducted to treat muscle wasting associated with neuromuscular conditions or sarcopenia [37].

Specific to cancer cachexia, the anti-myostatin antibody Landogrozumab (LY2495655) progressed to a Phase II trial in pancreatic cancer patients (NCT01505530)[i] (Table 1), although it was not deemed to be superior to placebo in improving outcome measures related to muscle wasting [38]. Concerningly, patients treated with the study's higher dose of LY2495655 demonstrated shorter overall survival compared to the placebo-treated group. STM 434, a ligand trap designed for activin A, was recently tested in a Phase I trial (NCT02262455)[ii] (Table 1). In ovarian and other cancer patients, researchers identified some indications of improved lean body mass at higher doses, which were associated with improved 6-minute walk test times in a number of patients [39]. However, very few patients in this study were found to have reductions in tumor burden following treatment, contributing to concerns that activin A inhibition might promote tumor growth. Furthermore, bleeding was a significant complication for a number of patients. Bleeding, particularly of the nose and gums, has been the most consistent and problematic complication of attempts to reduce activin A and myostatin signaling in humans. Bleeding complications have been documented in healthy adult individuals, boys with Duchenne muscular dystrophy, and cancer patients [19, 39]. Because of these complications, in addition to testing different molecules for the current ligand trap and receptor blockade approaches, alternative strategies are currently being pursued to reduce activin A signaling in skeletal muscle without exhibiting similar associated toxicities. One such strategy includes flooding the receptor with inactive propeptide to prevent active activin A from reaching its receptor [21].

GDF15 and GFRAL signaling regulates body weight in cancer cachexia

A recently described cytokine associated with cancer cachexia is Growth Differentiation Factor-15 (GDF15), otherwise referred to macrophage inhibitory cytokine 1 (MIC-1) or

nonsteroidal anti-inflammatory drug activated gene-1 (NAG-1) [17]. GDF15 is a distant member of the TGF-β superfamily of growth factors. Circulating levels of GDF15 are substantially elevated in chronic illnesses such as cardiovascular disease, diabetes, and cancer [17]. Such regulation has led to the classification of GDF15 as a risk factor for cardiac failure and as a potential prognostic marker for certain cancers. Plasma levels of GDF15 are among the highest in PDAC, which is also the population that predominantly suffers from weight loss and cachexia [1, 40].

In animal studies, the administration of recombinant GDF15 promoted weight loss due to anorexia, and implantation of GDF15-producing tumor cells in mice accentuated adipose and skeletal muscle catabolism, together highlighting the multifaceted functions of GDF15 in cancer cachexia [41, 42] [Figure 1]. The mechanism by which GDF15 signals to regulate the anorexia-cachexia syndrome was elucidated in 2017, when several laboratories simultaneously identified the GDF15 receptor, named glial cell-derived neurotrophic factor receptor alpha-like (GFRAL) [43–46].

The GFRAL receptor is expressed in the central nervous system (CNS), specifically in the hindbrain region that controls appetite, and complete signaling activity requires a complex containing the GDF15 ligand, the GFRAL receptor, and the more promiscuously expressed co-receptor, c-Ret. When GFRAL is genetically ablated in mice, animals exposed to a high fat diet gain an excessive amount of weight. Such unambiguous results led to targeting the GDF15/GFRAL signaling axis as a therapeutic strategy for cancer cachexia. Indeed, the generation of separate neutralizing antibodies against GDF15 and GFRAL was efficacious in reversing weight loss in tumor-bearing mice [41, 42], and significantly the GFRAL antibody, NGM120, is currently in a Phase Ia/Ib clinical trial (NCT04068896)[iii] (Table 1) for the treatment of cancer and the cancer anorexia-cachexia syndrome. In mice, the GDF15 antibody, PF-06946860, was recently shown to be effective in attenuating the side effects of platinum-based chemotherapy drugs, including anorexia and nausea [15]. GDF15 antibody therapy is also currently being tested in a Phase I clinical trial (NCT04803305)[iv] (Table 1) to improve cachexia-anorexia symptoms in patients with advanced cancer. Two additional GDF15 antibodies are in earlier phase clinical trials (NCT04815551 and NCT04725474)[v, vi] (Table 1).

Lipocalin 2 and the type 4 melanocortin receptor mediate anorexia in cancer cachexia

Another secreted factor recently described in the cancer cachexia literature that also appears to function as a potent regulator of the feeding response is lipocalin-2 (LCN2). This protein has previously been linked to the innate immune system for its anti-bacterial properties, but recently was shown to function in the CNS and exhibit a neurotoxic activity [47]. In the context of cancer, authors showed that pancreas tumors induced LCN2 production from bone marrow-derived neutrophils [16].These innate immune cells circulated to the CNS and LCN2 bound to the type 4 melanocortin receptor (MC4R), which had previously been shown to be an essential regulator of appetite [48] [Figure 1]. Thus, similar to pharmacological inhibition of the melanocortin receptor that mitigates the anorexic response

in tumor-bearing mice [49, 50], deletion of LCN2 restores appetite in PDAC-induced cachexia. Significantly, LCN2 function in the CNS also regulates the catabolism of adipose and skeletal muscle [16].

This suggests that LCN2 activity extends beyond the regulation of anorexia, which results from clinical trials had previous shown is a process in cachexia that is uncoupled from weight loss induced by chronic peripheral tissue wasting. Thus, LCN2 in addition to MC4R, adds to a list of exciting new therapeutic candidates for the treatment of the anorexia cachexia syndrome in cancer. Although a number of clinical trials have been conducted with agonists of MC4R [51], similar efforts to reduce circulating LCN2 or antagonize MC4R activity remain to be tested in humans.

Implications for future therapeutic approaches

The recently published European Society of Medical Oncology (ESMO) guidelines state: *"Given the complex and multifaceted contributors to cachexia, anti-cachexia treatment must be based on a comprehensive assessment of the patient's situation and an evaluation of reasonable, available treatment options, resulting in a personalised, multitargeted and multimodal approach"* [52]. Emerging evidence suggests that similar to a more personalized treatment approach being pursued in precision oncology, anti-cachexia therapy may also benefit from an individualized treatment strategy. Factors such as age, sex, obesity, performance status, disease stage, or tissue of tumor origin may hold important information that can influence potential strategies to treat cancer-induced cachexia and anorexia. Particularly attractive targets for an individualized treatment are circulating factors that accumulate during cancer, positively associate with weight loss in patients, and whose neutralization in animal studies restores appetite, lean mass, and body weight (see Outstanding Questions Box).

One caveat to targeting circulating factors initially identified in animal models of cancer cachexia is that in many instances, careful attention has not been paid to if the concentrations of circulating factors in rodent models mirror concentrations found in cachectic humans. For example, circulating levels of IL-6 in the Colon-26 tumor model often range from 250 to more than 1000 pg/mL, which 10-fold higher than concentrations measured in cachectic cancer patients [25, 53–56]. Levels of TNF in the Lewis Lung carcinoma model appear to be more in line with humans at 10–40 pg/mL [25, 53, 57], although others have reported much higher concentrations [58]. For activin A, circulating levels in cancer patients that associate with cachexia have been measured between 400 to 650 pg/ml [14, 25]. While also within a comparable range, levels of circulating activin A in mouse cachexia models seem to be two to five times higher, with levels measured in the KPC genetic mouse model of pancreatic cancer at ~2,500 pg/mL and in the Colon-26 mouse model of cancer cachexia at ~1,000 pg/mL [24, 59]. Given that the concentrations of activin A in the circulation in these rodent models of cancer cachexia do not extensively exceed those found in humans, any successful future pre-clinical therapy targeting circulating activin A would have the potential to be translated to patients. Similar comparable serum concentrations were reported with GDF15 between PDAC patients and animal models of cancer cachexia [41, 42], suggesting that neutralization of this circulating signaling mediator

might also be a candidate for individualized therapy. As additional human data are obtained for LCN2, the anticipation is that similar translational strategies can be adapted for this circulating signaling mediator as well.

Concluding Remarks and Future Perspectives

It is evident from recent literature that our understanding of the underlying mechanisms driving weight loss in cancer patients continues to grow. It is also becoming more the norm rather than the exception that studies validate their animal model findings in patient samples. This last point is key, and it is one of the important features we have attempted to highlight in this review. Is it our viewpoint that successful translational studies that will ultimately benefit cancer patients with cachexia will not only depend on elucidating the mechanism of action of a particular signaling mediator, but in addition that animal models used to translate new therapies are able to recapitulate the human phenotype as closely as possible. Inhibition of activin A, GDF15, and LCN2 in various tumor models of cachexia have been efficacious in restoring or maintaining body weight and lean muscle mass, and importantly, the circulating levels of these factors did not dramatically differ between animals and patients, indicating the potential to achieve a therapeutic dose that might exhibit equal efficacy in the clinic. With these thoughts in mind, the serum concentration of a specific signaling mediator of cachexia could be considered in future clinical trials as an inclusion criterion for enrollment.

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Resources

i. This study is registered with ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT01505530)

ii. This study is registered with ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT02262455)

iii. This study is registered with ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT04068896)

iv. This study is registered with ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT04803305)

v. This study is registered with ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT04815551)

vi. This study is registered with ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT04725474)

Outstanding Questions

- Will advanced pre-clinical strategies to modulate circulating levels of activin A, myostatin, GDF15, or LCN2 ultimately translate to more effective treatments to address cancer-associated cachexia or anorexia?

- Would cancer cachexia be best addressed by individualized approaches analogous to current practices in precision oncology?

- What circulating tumor and host factors beyond activin A, myostatin, GDF15, and LCN2 be identified that regulate appetite and tissue catabolism, and serve as therapeutic targets?

Highlights

- Recent findings have revealed new information on the likely roles of activin A and myostatin and identified GDF15 and lipocalin-2 as new signaling mediators of the cancer cachexia syndrome.

- These developments have led to a number of translational efforts including early-phase clinical trials.

- Additional data from cancer patients and late-stage clinical trials are needed to determine if activin A, myostatin, GDF15, or lipocalin-2 will ultimately translate to actionable targets to treat cancer cachexia.

- The future of anti-cachexia treatment may lie in strategies involving more targeted and personalized approaches.
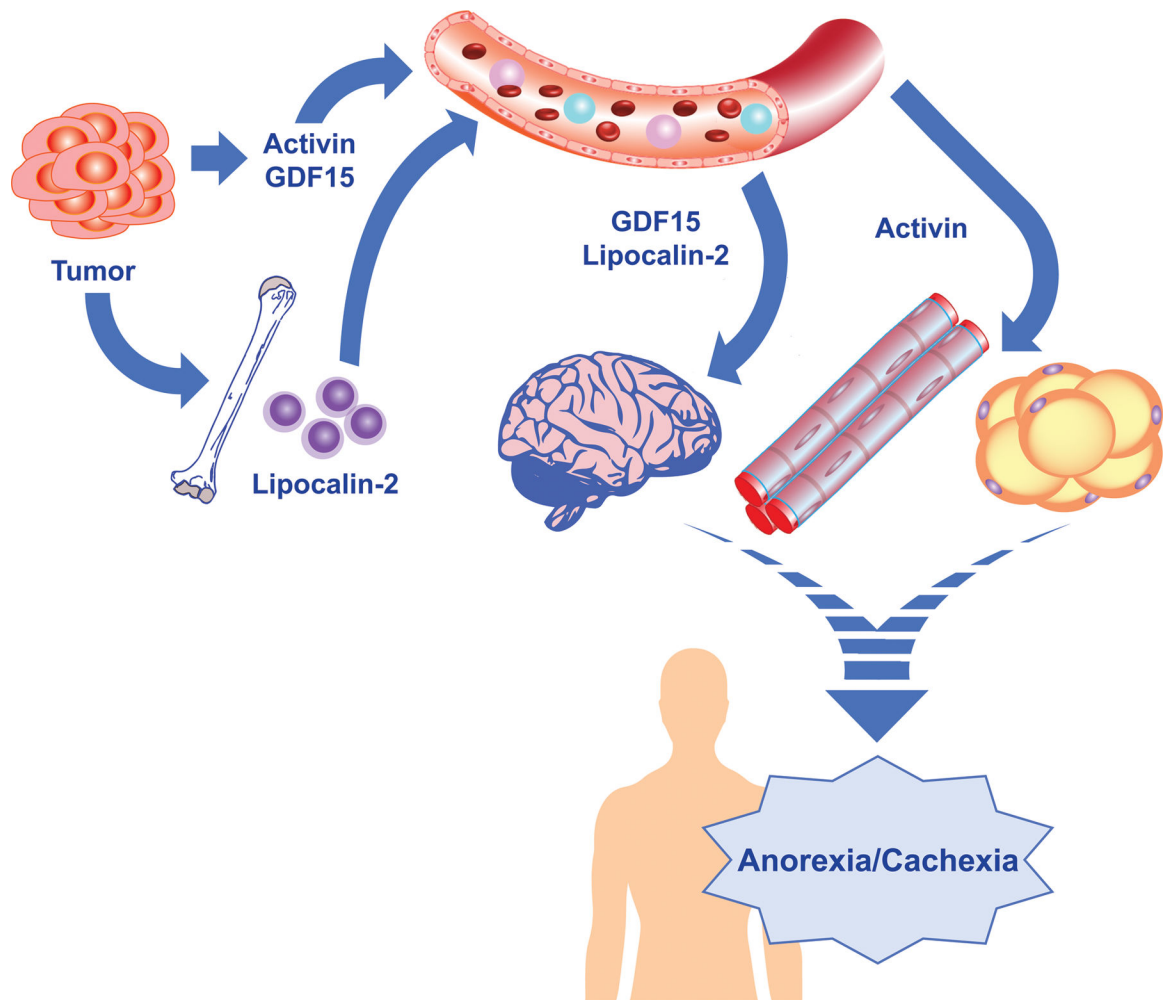
Key Figure. Schematic of emerging signaling mediators in the cancer anorexia-cachexia syndrome.

The signaling mediators activin A, GDF15, and lipocalin-2 and their roles in the cancer anorexia-cachexia syndrome are displayed. Activin and GDF15 are believed to be synthesized and secreted largely from tumors and circulate to peripheral organs to regulate feeding (GDF15), and adipose and skeletal muscle atrophy (activin A). Lipocalin-2 is generated from bone marrow-derived neutrophils and circulates to the brain to regulate anorexia. The human outline is meant to portray the translational potential of targeting these signaling mediators as a therapy for cancer cachexia.

Table 1.

Summary of clinical trials for signaling mediators of cancer cachexia

Clinical Trial	Agent	Target	Population	Phase	Status
NCT01505530 [i]	Landogrozumab (LY2495655)	myostatin	pancreatic cancer patients	II	Completed
NCT02262455 [ii]	STM 434	Activin A	ovarian cancer patients	I	Completed
NCT04068896 [iii]	NGM120	GDF15	advanced solid tumor and pancreatic cancer patients	I/II	Recruiting
NCT04803305 [iv]	PF-06946860	GDF15	certain advanced solid tumor patients with anorexia	I	Recruiting
NCT04815551 [v]	AV-380	GDF15	healthy subjects	I	Active, not recruiting
NCT04725474 [vi]	CTL-002	GDF15	advanced solid tumor patients	I	Recruiting

Roman numerals following the Clinical Trial Identifier refer to additional information under Resources.