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Review

Cachexia: A systemic consequence of progressive, unresolved disease

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SUMMARY

Cachexia, a systemic wasting condition, is considered a late consequence of diseases, including cancer, organ failure, or infections, and contributes to significant morbidity and mortality. The induction process and mechanistic progression of cachexia are incompletely understood. Refocusing academic efforts away from advanced cachexia to the etiology of cachexia may enable discoveries of new therapeutic approaches. Here, we review drivers, mechanisms, organismal predispositions, evidence for multi-organ interaction, model systems, clinical research, trials, and care provision from early onset to late cachexia. Evidence is emerging that distinct inflammatory, metabolic, and neuro-modulatory drivers can initiate processes that ultimately converge on advanced cachexia.

INTRODUCTION

Cachexia, a disabling wasting condition of lean body mass, is one of the most common and challenging whole-body response syndromes and occurs during the progression of many diseases. With the emergence of powerful techniques to capture deep data over time and a resurgence of interest in multi-organ connectivity, research into this complex physiological disease response is ready to turn from a focus on advanced cachexia to the process that initiates the change of a previously healthy organism to a cachectic one. In this review, we aim to summarize the literature on the etiology of cachexia, while also providing an overview of the available model systems and clinical research efforts.

EPIDEMIOLOGY

With an estimated annual death rate of 2 million people worldwide, cachexia is one of the main contributors to human morbidity and mortality.[1] When the term cachexia ("*kakos hexis* = bad state") was first coined in early Greek literature, it was considered a consequence of disease or aging leading to a lack of physical "conditioning" and, therefore, of broad relevance across seemingly different underlying causalities. During

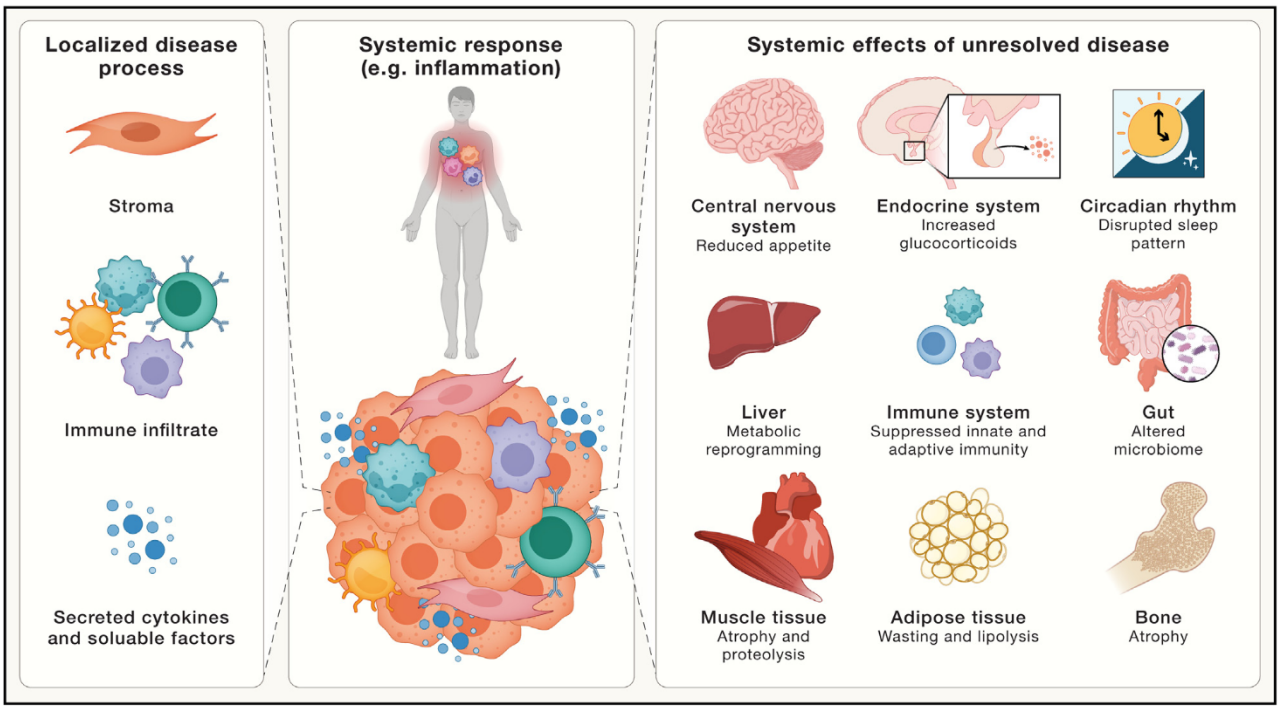

Figure 1. Interconnected causes and consequences of disease- or cancer-associated cachexia at organ level
Examples of host cell contributors to and organ level consequences of cachexia inducing inflammatory and non-inflammatory processes are illustrated.

the 19th century, tuberculosis-induced cachexia became widely recognized with specialist sanatoriums focused on supportive care. Glentworth R. Butler extended cachexia to cancer in 1906, describing "cancer cachexiae" as characterized by "debility, emaciation, anemia, and a dirty yellowish-brown or brown-green complexion."[2] In 1915, Howard C. Taylor highlighted the similarities of cachexia between diseases: "There is however, nothing that is distinctive about cancerous cachexia. Any of the known changes and a similar picture may be produced by other diseases … The symptoms of the cachexia are gradual but progressive … The emaciation is a late symptom … with the loss of appetite, and nausea."[3] In modern biomedical literature, there is no universal definition of cachexia, but in the context of cancer cachexia, it has been defined as "a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment"[4]—a wide definition that may apply to cachexia caused by non-cancer conditions. Recent epidemiological data continue to associate cachexia with several seemingly unrelated but potentially convergent diseases. Patients with cancer, such as lung, colon, and pancreatic cancer, have a high risk of developing cachexia, sometimes estimated to be as high as 80% in pancreatic cancer.[5] Cachexia is also common in patients with end-stage renal failure (ESRF) (25–50%), chronic obstructive pulmonary disease (COPD) (25%), chronic heart failure, AIDS, sepsis, and rheumatologic disorders.[6,7] Given its incidence and prevalence, universally negative impact on prognosis and quality of life (QoL), and contribution to poor tolerance of and reduced response to treatment for the underlying disease, cachexia presents an area of major global public health burden and an urgent unmet need.

What patients with cachexia have in common is an unresolved underlying disease process—a wound that does not heal. They suffer from involuntary weight loss, more specifically muscle and fat loss that may expand to loss of other tissues (e.g., heart and bone), in the context of anorexia, coupled with fatigue and sickness behavior such as anhedonia. The apparent multiplicity of diseases that lead to cachexia suggest that either multiple processes converge on an advanced state or multiple early diseases converge on a common pathway of disease progression to an advanced state. In both cases, an unresolved continued process consequential to one or several distinct disease-mediated systemic perturbations may drive a systemic effect that results in cachexia (Figure 1). The pre-convergence processes could define therapeutically relevant cachexia subtypes. Therefore, the lack of certainty about the underlying mechanisms driving the processes of cachexia requires additional work to identify the initiators and understand how they alter the communication and function within and among multiple organ systems.

DISEASED CELL-, TUMOR-, AND HOST-DERIVED CACHEXIA MEDIATORS

Some features of the cachexia syndrome, such as metabolic, hormonal, behavioral, and inflammatory changes, have been linked to specific molecular mediators. Here, we collate these

mediators and discuss their role during cachexia development and the importance of examining their interconnectivity.

Inflammatory mediators

The process of inflammation has long been associated with cancer cachexia. Injury to a tissue from a variety of insults (e.g., trauma, infection) results in the clinical phenotype of inflammation—features recognized since antiquity that include redness, heat, swelling, pain, and loss of function. The neuro-humoral output from a local injury, including a rapid elevation in circulating cytokines generated by the activated immune system, can progress systemically. This triggers broader molecular, cellular, neuronal, and behavioral responses that result in a more systemic inflammatory phenotype (e.g., fatigue, anhedonia, pain, weight loss).

The evidence that unresolved inflammation is a driver of one type of cachexia[8–11] comes from the detection of multiple inflammatory factors in tissues and the circulation of patients with cachexia (Table 1). These factors have mostly been investigated during periods of detectable weight loss, and their longitudinal trajectories frequently remain unclear. They can be produced directly by disease-driving cells (e.g., infected, damaged, or cancerous cells), by cells recruited to the microenvironment of the cellular lesion (e.g., fibroblasts and/or immune cells), and by other tissues at an organismal level (Figure 2). Given that all these processes may amplify each other, changes in these factors will be dynamic. This is likely relevant to the progression of disease to cachexia.

One of the first factors associated with cachexia was tumor necrosis factor alpha (TNF-α), historically termed *cachexin*, a pro-inflammatory cytokine with muscle and fat tissue catabolic and anorexic effects.[10] TNF-α is associated with cancer cachexia and other cachexia-inducing inflammatory conditions such as rheumatoid arthritis. Trials in patients with cachexia-investigating therapies either blocking the TNF-α receptor or neutralizing TNF-α itself (NCT00046904, NCT00060502, NCT00244192) have not detected clinical benefit.

Interleukin-6 (IL-6) superfamily members, including IL-6 and leukemia inducible factor (LIF), are among the most reported cachexia-inducing factors. Elevated circulating levels of IL-6 and its upstream regulator interleukin 1 (IL-1) have been widely associated with cancer-associated cachexia in both animal models and humans. In mice, IL-6 alters metabolic organ functions in ways such as reducing the liver's ketogenic capacity to respond to diminished food intake[11] and promoting adipose tissue browning.[18] In non-cachectic conditions, IL-6 acts on the brain and influences energy balance.[14] While reversibility of some IL-6 effects has been demonstrated in murine models, a clinical trial in patients with lung cancer and cachexia that blocked IL-6 signaling using ALD518, a humanized anti-IL-6 antibody, showed only mild improvements (NCT00866970), suggesting that late interventions may not be clinically beneficial.

The chemokine CCL2 (monocyte chemoattractant protein-1; MCP-1) that directs CCR2-driven migration of macrophages and can be produced by endothelial cells, fibroblasts, and macrophages has also been linked to cachexia in mice.[48] CCL2 promotes liver inflammation, neuroinflammation, weight loss, and metabolic changes in muscle and white adipose tissue (WAT).[28–31] These reports indicate that persistent CCL2 production may sustain inflammatory changes, resulting in systemic metabolic alterations and reduced food intake that leads to cancer cachexia.

Lipocalin-2 (LCN2), a glycopeptide involved in coordinating the host response to inflammation,[41] has been described in animal models as having an anorexigenic effect by acting through the central melanocortin system within the hypothalamus.[40] Melanocortin 4 receptor antagonists protect from the cachexia of chronic kidney disease and the melanocortin 3 receptor is involved in lean body mass distribution,[40,49] suggesting that the melanocortin pathways may have translational potential for anabolic interventions in cachexia.

This selection of example inflammatory molecules indicates that no single factor is the sole causative agent for cachexia. Different molecules may drive cachexia in different circumstances and/or combinations of molecular factors and their connectivity may be relevant. For example, CCL2 macrophage activation may drive IL-6 production or vice versa, and similar interactions occur with TNF-α. It is, therefore, likely that several upstream inflammatory cascades ultimately converge on the clinical phenotype of cachexia. Reflecting this notion, the JAK 1/2 inhibitor ruxolitinib is currently in a Phase 2 (NCT04906746) clinical trial to assess the efficacy of targeting inflammatory signaling pathways activated in cachexia.

Although there is an array of potential cachexia-inducing factors, no single cell population has emerged as causative in cachexia. Infected cells or cancer cells may directly produce cachexia-inducing factors, and so may immune cells or cells that modulate the immune response. For example, changes in cancer-associated fibroblast (CAFs), such as loss of myofibroblastic CAFs (myCAFs) and enrichment of IL-6 producing CAFs (iCAFs), lead to cachexia in pancreatic cancer mouse models. Since iCAFs are dependent on the activation of the JAK/STAT signaling pathway for their formation in pancreatic ductal adenocarcinoma (PDAC), JAK/STAT inhibitors that cause loss of iCAFs may ameliorate the cachectic phenotype.[50] Similarly, depletion of fibroblast activation protein-α-positive (FAP+) stromal cells leads to loss of muscle mass and cachexia,[51] and genetic depletion of alpha-smooth muscle actin-positive (alphaSMA+) cells, which include myofibroblastic CAFs, following tumor formation leads to a reduction in body weight in mouse models of pancreatic cancer.[52]

Mediators that regulate tissue homeostasis

Apart from inflammatory molecules, multiple important other initiating factors of cachexia have been discovered. These include imbalances between circulating molecules that maintain skeletal muscle mass and mediators that primarily affect the central nervous system (CNS).

Much of the research that has been performed on circulating and local factors focuses on muscle homeostasis. Follistatin deficiency secondary to fibroblast depletion in the muscle is a potent inducer of cachexia.[51] Activation of the activin receptor AcvR2B in skeletal muscle cells by agonists such as activin A or myostatin powerfully induces the catabolic processes of autophagy and proteolysis.[27] Treatment with a soluble activin A decoy receptor has been suggested as a therapeutic intervention in pre-clinical

Table 1. Effect organ matrix for cachexia mediators

Pathway	Soluble factor (mammals/rodents)	*Drosophila* ortholog	Brain	HPA axis	Liver	Muscle	Adipose tissue	Immune system
JAK/STAT	**IFN-gamma**			Food intake[12]		Wasting[13]	Lipolysis[12]	
	IL-6	**Unpaired3 (Upd)**	Energy balance[14]		Metabolic reprogramming,[11] liver growth[15]	Steatosis and wasting,[16] reduced nutrient utilization[17]	Browning,[18] lipolysis,[16] reduced nutrient utilization[17]	Tumor immune escape,[19] inflammation[8]
	Leptin			Appetite and metabolic rate[20]				Immune modulation[21]
	LIF			Appetite suppression		Myogenesis inhibition[22]	Lipolysis[22]	
SMAD	**Activin A**					Atrophy and protein degradation[23]	Adipocyte diameter and fibrotic deposition[24]	Tumorigenic immune microenvironment[25]
	BMP	**Gbb**					Increased lipid catabolism[26]	
	Myostatin					Autophagy and proteolysis[27]		
MAPK	**CCL2**		Neuroinflammation[28] and behavioral adaptation[29]		Inflammation, hepatic steatosis[30]	Metabolic response,[30] adipose tissue/muscle crosstalk[31]	Macrophage infiltration, adipose tissue/muscle crosstalk[31]	
	FGF	**Branchless (bnl)**				Wasting[32]		
	PDGF/VEGF	**Pvf1**				Wasting[32]	Wasting[32]	
PI3/AKT/mTOR	**GDF-15**		Anorectic effect on brainstem[33]	Increased glucocorticoid levels[34]		Atrophy[34,35]	Lipolysis[36]	
	IGFBPs	**ImpL2**				Wasting[37]	Wasting[37]	
	PTHrP					Wasting and fiber atrophy[38]	Browning and wasting[38]	
NF-κβ	**IL-1b**			Appetite suppression[39]		Proteolysis and wasting[39]	Lipolysis[39]	Inflammation[39]
	LCN2			Appetite suppression[40]				Innate immune response and inflammation[41]
	TNF-α	**Eiger (egr)**			Metabolic reprogramming	Wasting[10,13]	Lipolysis[42]	Inflammation[10,13]
β-Catenin	**INSL3**			Food intake[43]				
cAMP/PKA	**ZAG**						Lipolysis and browning[44]	
PLC	**IL-8**					Wasting and myotube atrophy[45]		Tumor immune escape[46]
Renin-angiotensin system	**Angiotensin II**			Appetite suppression[47]		Proteolysis and wasting[47]		

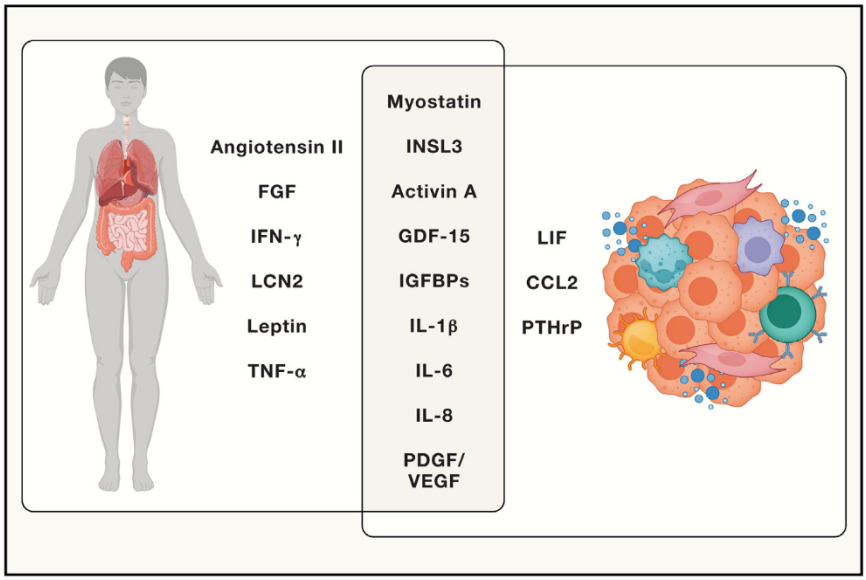

Figure 2. Specific molecular mediators of organ modulation in cancer progression and cachexia

Venn diagram of tumor- or host-derived cachexia mediators.

work,[53] and a human monoclonal anti-ActR2 antibody tested in a clinical study (NCT01433263) led to promising results in preserving lean body mass. However, a clinical trial investigating LY2495655, an anti-myostatin antibody, in patients with pancreatic cancer (NCT01505530) was terminated due to its detrimental effect on survival.[54]

Metabolic mediators

Metabolic mediators may also drive inflammation-independent cachexia subtypes. For example, tumor-secreted insulin growth factor binding proteins (IGFBPs) can stimulate catabolism in nutrient-rich tissues by blocking insulin/IGF-1 signaling and promoting insulin resistance.[55] Among individuals without cancer, insulin resistance reduces metabolic flexibility, impairs muscle protein synthesis, and increases energy expenditure. In cross-sectional studies, patients with lung cancer often have insulin resistance.[56] However, it is unknown how longitudinal changes in insulin resistance, metabolic flexibility, muscle protein synthesis, and energy expenditure relate to changes in muscle mass, muscle quality, and weight loss in patients with cancer.

Cancer also imposes systemic metabolic changes that have not yet been clearly linked to a specific factor. For example, lung cancer can induce diurnal and metabolic changes in the liver that promote gluconeogenesis and inhibit fatty acid metabolism.[57] These effects may be due to hepatic inflammation or could be secondary to elevated levels of catabolic hormones such as glucocorticoids. Furthermore, unbiased metabolomic assessments have identified correlations between weight loss and plasma amino acids and phospholipids of unknown source.[58]

Mediators that target the brain

Centrally acting circulating molecules such as the growth differentiation factor 15 (GDF-15) have been shown to promote cachexia. GDF-15 is produced in response to cell stress and may have evolved to mediate food aversion in response to toxin exposure.[59] It binds mostly to a small number of neurons in the brain stem, outside the blood-brain barrier, that express its specific receptor GFRAL. In some conditions, including numerous cancers, GDF-15 levels are elevated and associated with reduced food intake and body weight in humans and mice.[33] Moreover, GDF-15 potently activates the hypothalamic-pituitary adrenal (HPA) axis and increases circulating glucocorticoid levels.[34] Since glucocorticoids are powerfully catabolic to skeletal muscle, GDF-15 could, via the brain, contribute to the two key features of cachexia, i.e., reduced food intake and selective loss of skeletal muscle. Recently, antibody-mediated blockade of the GDF15-GFRAL pathway has been reported to be efficient in reversing cancer cachexia in pre-clinical murine models.[60] The role GDF-15 plays in anorexia, lipolysis, and muscle wasting has provided a strong rationale to study anti-GDF-15 agents in ongoing human clinical trials (NCT04803305, NCT04068896, NT04725474).

RECIPROCAL INTERACTIONS BETWEEN CACHEXIA-INDUCING DISEASES AND HOST ORGAN SYSTEMS

The physiology of cancer progression may be viewed as a continuously and increasingly perturbed state that involves behavioral changes; dysregulation of the neuroendocrine system, including changes in sleep and circadian rhythm; systemic immune dysregulation; and skeletal muscle and adipose tissue wasting—all of which occur in patients and model systems with cachexia (Figures 1 and 2 and Table 1). While the cachexia-inducing disease process may be locally confined, the hallmarks of cachexia are systemically mediated, indicating that the underlying mechanisms of cause and propagation likely involve modulation of networks that affect all body systems and inter-organ and organ-body communication. One way to approach this connectivity is from the perspective of the energetic imbalance, i.e., a relative lack of energy intake compared to energy expenditure of the system, that ultimately results in overt weight loss during advanced cachexia.

Neuroendocrine interactions

The central nervous system (CNS) makes important contributions to the control of energy homeostasis, and the hypothalamus is widely acknowledged as an area that integrates circulating signals generated in the periphery with potential relevance to cachexia-inducing disease. The hypothalamus's central melanocortinergic system, and specifically MC3R, plays a role in sensing the body's nutritional status. It helps co-coordinate the acquisition and retention of calories and their disposition into processes

such as growth, reproduction, and the acquisition of lean mass.[49] Lack of an appropriate response to peripheral inputs leads to diminished appetite and promotes catabolic stimuli (i.e., reduced energy intake, increased energy expenditure, increased muscle proteolysis, and adipose tissue wasting). Moreover, the CNS regulates endocrine organ function (e.g., the release of hormones). Systemic release of glucocorticoids is a well-described event in cachexia that occurs in response to the activation of the HPA axis by stressors and induces skeletal muscle atrophy and catabolism. Suppression of the hypothalamic–pituitary–gonadal (HPG) axis significantly decreases testosterone levels, contributing to several cachexia-related signs and symptoms like fatigue, weight loss, and muscle catabolism.[61] Additionally, hypogonadism has been linked to systemic inflammation and shortened survival in advanced pancreatic cancer.[62]

Immunological and metabolic interactions

Inflammation and the immune system response in cachexia are host physiological processes directed to targeting the localized disease. However, tumor-infiltrating myeloid cells can differentiate into myeloid-derived suppressor cells (MDSC) and together with tumor-associated macrophages and lymphocytes (TAMs and TILs) promote angiogenesis and metastasis and eventually contribute to an immunosuppressive environment that favors cachexia.[63]

In the periphery, hepatic inflammation and activation of the acute phase response are biosynthetically and bioenergetically costly—when left unresolved, they contribute to systemic metabolic and energetic imbalance. This affects all aspects of intermediary metabolism, including carbohydrate, protein, fat, and energy metabolism. Elevated levels of glucocorticoids and increased gluconeogenesis as well as inhibited fatty acid metabolism and suppressed ketogenesis in the liver are other examples of cancer-induced metabolic changes.[11] Host-produced factors such as the hunger hormone Ghrelin, which originates in the stomach, could counteract anorexia. However, development of resistance to its own function ultimately worsens unresolved anorexia. Cachexia often features insulin resistance leading to reduced metabolic flexibility, impaired muscle protein synthesis, and increased energy expenditure.[56]

Skeletal muscle (SkM) and WAT are the body's main reservoirs for amino acids and lipids, respectively, and both inflammation and imbalances of factors that maintain muscle mass can increase rates of protein breakdown. During times of stress when food intake is low and nutrient demands increase, such as with the reduced caloric intake associated with cancer cachexia, SkM and WAT activate catabolic processes and distribute stored nutrients to the rest of the body so that they can then be used for energy generation and promote survival. Mechanisms underlying SkM wasting may include upregulation of ERK1/2 and p38 MAPKs,[64] activation of autophagy, loss of molecular motor protein MyHC-II,[65] production of reactive oxygen species (ROS) that impair myotube morphometry,[66] systemic inflammation, and production of pro-inflammatory cytokines that induce skeletal muscle atrophy, as well as glucocorticoid release. WAT wasting is caused predominantly by increased lipolysis and reduced fat deposition. Lack of circadian rhythmicity in the expression of transcription factors that regulate fatty acid catabolism during cachexia contributes to lipid metabolism imbalance.[67] If left unresolved, progressive catabolism of SkM and WAT leads to physical deterioration and death. Moreover, tumors seemingly alter host nutrient availability, exchange, and use to favor their own metabolic demands. Identifying the fundamental nature of this tumor-mediated host metabolic reprograming will reveal new tools for the diagnosis and treatment of cachexia.

Interaction with the microbiome

Intestinal microbiota can coordinate hormonal communication between adipose tissue and skeletal muscle to protect from cachexia development during inflammation and infection.[68] Furthermore, changes in the intestinal microbiome ecology, known as dysbiosis, have been shown to influence cachexia due to gut barrier dysfunction,[69] and intestinal pathogens can limit the cachectic response by controlling inflammatory signaling along the gut-brain axis to regulate feeding behavior.[70] Thus, manipulation of beneficial bacteria in the gut microbiota has been explored as treatment.[71]

Taken together, these findings suggest a potential sequence of events which lends itself to systematic scientific study: a local insult promotes a systemic response that would normally lead to its resolution, but if the original insult is not cleared (e.g., advanced cancer), this persistent systemic response becomes destructive. It promotes central reduction in nutrient intake behavior and altered peripheral nutrient processing, leading to changes in body composition, fatigue, and functional decline, which in turn diminish tolerance to therapeutic interventions targeting the underlying disease and, ultimately, to cachexia and death (Figure 3).

HOST AND IATROGENIC CONTRIBUTORS TO CACHEXIA

The interaction between cachexia molecular drivers and organ responsiveness occurs in a host organism. Individuals may have genetic or acquired characteristics that protect from or predispose to cachexia. This is an important dimension for understanding cachexia, because genetic or acquired cachexia-related traits will synergize or antagonize with the progression of disease-induced cachexia. Some genetic signatures related to inflammation and the renin-angiotensin system have been linked to cachexia susceptibility.[72] Moreover, experiments in cachectic animals treated with dextran sulfate sodium to cause intestinal injury have demonstrated that strains purchased from different suppliers or vivarium rooms have more or less rapid onset of body weight loss and variations in the degree of skeletal muscle atrophy.[68] Variations in the intestinal microbiota ecology are sufficient to generate differences in cachexia onset and severity, while the specific contribution of genetic differences remains unknown.

Sex-based differences

Distinct body composition, fat distribution, insulin sensitivity, glucose and lipid metabolism, and energy substrate utilization are biological differences between male and female metabolism. Innate metabolic divergences such as these may well influence the susceptibility and development of metabolic syndromes

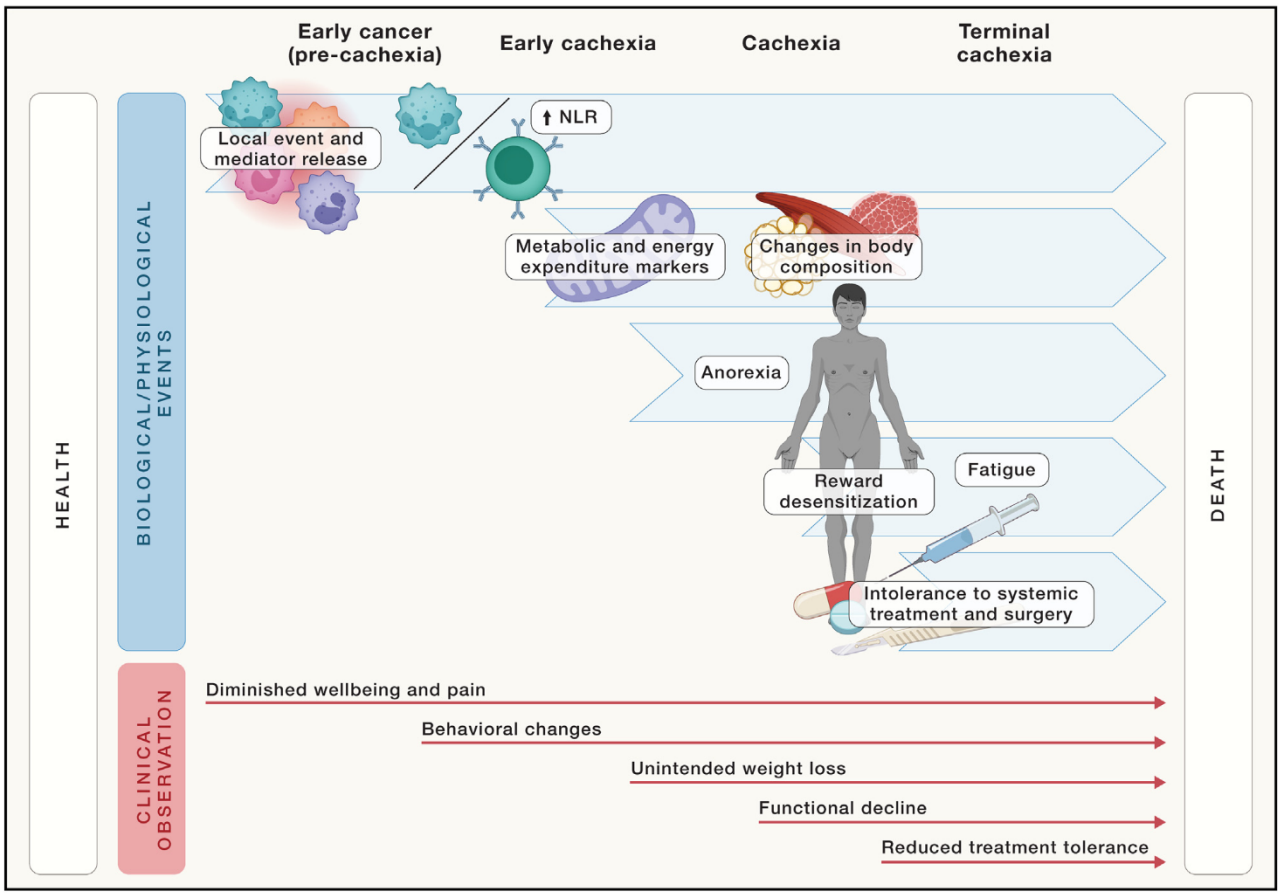

Figure 3. Longitudinal progression of biological phenomena and clinical observations from early cancer to advanced cachexia

such as cachexia. Nevertheless, much of the pre-clinical and clinical research of cachexia has focused on its consequences in skeletal muscle tissue. Muscle depletion is more prevalent in males than in females with cancer,[73] and cachectic male patients have increased muscle fatigue and greater reduction in handgrip strength compared to cachectic female patients.[74] This difference could be attributed to estrogen status, since estrogen signaling is a regulator of muscle contractility and anabolism, and can impact morphology, fatigability, and function of myofibers. Hormone replacement therapy can mitigate strength loss in postmenopausal females.[75] In addition, estrogens modulate inflammation, and while pro-inflammatory cytokines such as IL-6 induce and accelerate cachexia in tumor-bearing male mice, IL-6 does not impact tumor-bearing female mice.[76] Estrogens have a direct effect on hypothalamic neurons regulating physical activity and energy expenditure in females.[77] Furthermore, hypogonadism has been associated with cachexia development.[62] Testosterone is a potent anabolic factor contributing to muscle mass, and its therapeutic potential for cancer-related weight loss has been assessed in a randomized trial, demonstrating improved lean body mass without an effect on survival.[78]

However, differences between the male and female cachectic phenotype may also be due to variations in the distribution and metabolic preference of muscle fiber types. Type II muscle fibers account for the majority of male muscle mass and have a glycolytic phenotype, whereas females have predominantly Type I muscle fibers that are oxidative. Data from pre-clinical models and patients with cancer suggest that Type II glycolytic myofibers are more sensitive to cancer-induced muscle wasting than Type I myofibers.[79] Thus, this inherent fiber difference is associated with differential fatigue susceptibility in males and females, and although direct causality has not been established, it may drive some of the sex-dependent differential responses during muscle wasting and cachexia.

Sex-driven differences lead to some treatments being only effective in males or females in pre-clinical models.[53] This is potentially relevant for differential outcome in clinical interventions in patients with cancer. A better understanding of how sex-based differences impact cachexia is needed and would benefit the development of therapeutics that improve quality of life and survival.

Aging

A gradual decrease in muscle mass and strength is estimated to start at the age of 30, with the rate of decline increasing after 60 years of age, and by the age of 80, 30% of muscle mass is estimated to be lost.[80] Moreover, decrease in appetite and anhedonia are associated with aging and could be explained by

changes in various neurotransmitters and brain circuitry, and hormones, which may then result in the frequently observed food intake decline.[81]

A major feature of aging is a loss of physiological reserve and coordinated tuning of the organism, which would synergize with the predisposition to cachexia. This is perhaps captured in the concept of "inflammaging", the sustained increased levels of circulating pro-inflammatory molecules, which is associated with diminishing organ function, and progressive sarcopenia (loss of muscle: from Greek *sarx*: flesh, *penia*: poverty). In murine models, aging causes an energetic imbalance toward catabolism that interferes with homeostatic signaling and ultimately causes high susceptibility to chronic morbidity, disability, frailty, and premature death. Data from the Rotterdam Study demonstrate that the neutrophil-to-lymphocyte ratio (NLR) is an independent risk indicator for survival in the elderly, and even in the general population over the age of 45. This highlights the clinical value of NLR as an early marker of disease progression and suggests that it may be a proxy measure of the aging process.[9] Recent studies link metabolic dysregulation and chronic aging-associated inflammation in a reversible manner,[82] opening new interventional avenues for anti-aging treatments.

Other factors, including reduced peripheral or central responsiveness for nutritional and lean body homeostasis may synergize with disease processes in aging and cachexia. Altogether, the phenotype and processes associated with old age mirrors those observed in patients with end-stage cachexia, pointing to convergent biological phenomena and underlying mechanisms that occur at different rates and may potentiate each other, an area that warrants further research.

Anti-cancer therapy-induced cachexia

Physical barriers that impede the digestion and absorption of food may directly contribute to cachexia. Anatomical obstructions of the gastrointestinal tract secondary to tumor progression, malabsorption due to infections or treatment side effects, surgical- or radiotherapy-induced alterations of the digestive system that result in strictures, anatomical removal of organ parts that aid nutrient uptake, and neurohormonal imbalances may all contribute to whole-body wasting from caloric deficiency. These disease- or treatment-related developments may negatively synergize with the molecular mechanisms that cause cachexia.

Some anti-cancer treatments, such as chemotherapy, can cause muscle wasting, weakness, and fatigue in patients, thus exacerbating cachexia and worsening prognosis. A chemotherapy-induced increase in circulating GDF-15 peptide causes anorexia, nausea, and emesis.[83] These symptoms may be exacerbated by an underlying decreased glomerular filtration rate (GFR) in chronic kidney disease (CKD) or organ failure in the elderly. For example, endogenous formaldehyde toxicity-induced GDF-15 production in the proximal renal tubule promotes cachexia in a murine model of Cockayne syndrome A.[84] Moreover, dexamethasone, a synthetic glucocorticoid prescribed as a supportive care co-medication for patients with cancer, induces muscle atrophy and dysfunction when used long-term.[85] While dexamethasone is a well-established effective antiemetic drug for patients receiving chemotherapy, it induces a positive feedback loop that accelerates wasting. However, administration of dexamethasone reduces IL-6 secretion, ameliorates inflammation in muscle cells, and promotes appetite.[86] This warrants further investigation, as glucocorticoids may have a dose-dependent and dose-scheduling-dependent effect on skeletal muscle and the cachectic phenotype.

Cachexia and, more specifically, lean muscle mass depletion is associated with worse immunotherapy responses and increased treatment-related toxicities.[87] For example, a Phase 2 clinical trial assessing the efficacy of lenalidomide, an immunomodulatory drug, on lean body mass and handgrip strength in advanced solid tumor patients with inflammatory cachexia showed no treatment response (NCT01127386). Moreover, systemic inflammation and cancer-induced release of pro-inflammatory cytokines may not only directly contribute to muscle breakdown but also influence immune response and, consequently, immunotherapy effectiveness.[88]

EARLY DISEASE PROGRESSION TO ADVANCED CACHEXIA

To date, perhaps led by the literal interpretation of *hexis* (state), definitions and research of cachexia focus on contrasting health with advanced cachexia. More recently, the pre-cachectic state has been recognized as a state when early clinical and metabolic signs are present in the absence of weight loss.[4] However, a successive chain of events must occur that connects the healthy state with advanced cachexia. Molecular, organ-, and host-level contributory factors and aspects continue to emerge. A better understanding of the exact hierarchical sequence of events and functional roles is necessary to guide attempts to treat cachexia successfully or prevent its onset. The early dynamics of tumor-host interaction, the pattern of change for circulating cachectogenic factors and metabolites, longitudinal organ-specific changes, and causal relationships must be characterized over the disease's course and progression to cachexia (Figure 3). For example, early markers of protein breakdown, namely branched chain amino acids (BCAA), have been identified in patients with pancreatic cancer, who are at very high risk of developing cachexia, and could therefore be useful biomarkers to identify groups at risk of developing cachexia.[89]

In the clinic and in mice, evidence of the liver's acute phase response can be detected long before overt weight loss and development of cachexia is observed. In some patients who eventually develop cachexia, elevations of circulating C-reactive protein (CRP), a key marker of systemic inflammation and a response gene of IL-6, are detected at earlier stages of cancer and show a strong relationship with functional decline during cachexia development. Likewise, an elevated NLR is an early biological event in cancer, and neutrophilia may play an adaptive role in host metabolic homeostasis during cancer progression to directly influence weight loss.[9]

Modest increases in glucose oxidation and desensitization to insulin have also been frequently observed in patients with cancer and can become more notable with cancer progression toward cachexia.[56] These processes are driven by cytokines such as TNF-α, IL-1, and IL-6 and hormones such as glucocorticoids, which accelerate whole-body catabolism and lead to changes in body composition.

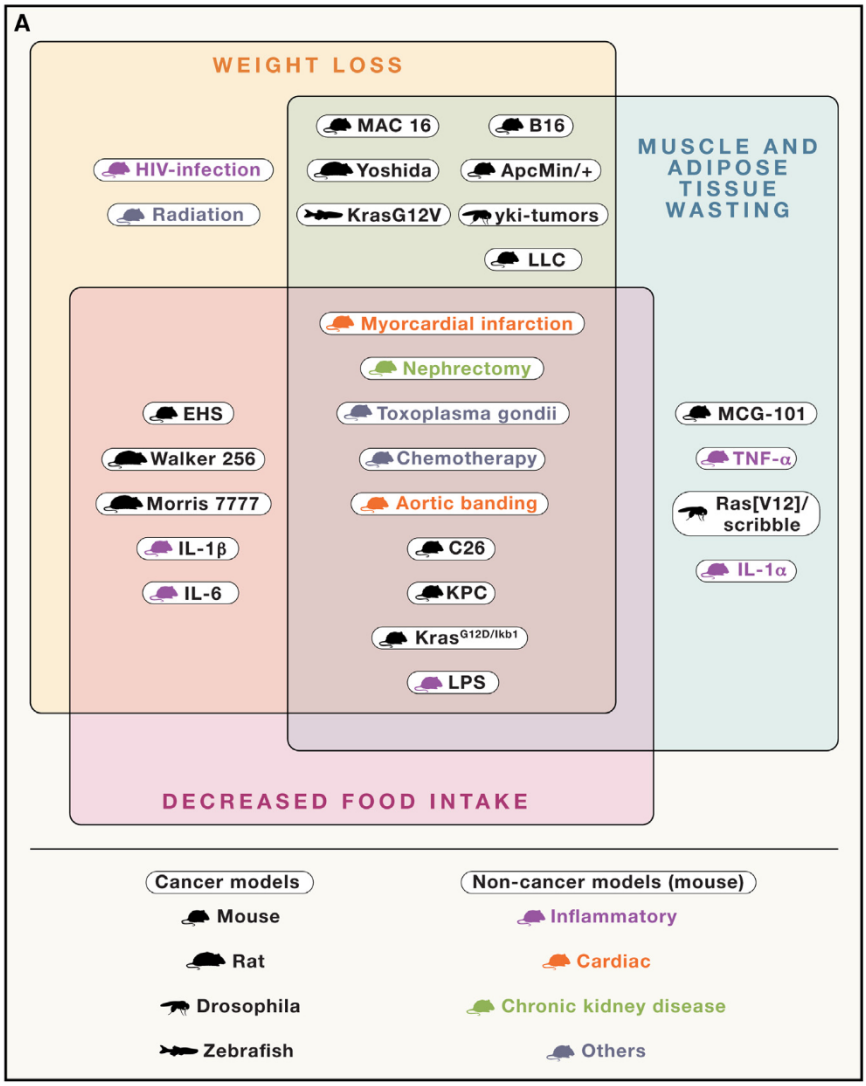

Figure 4. Key examples of established pre-clinical model systems for systemic inflammation predisposing or leading to cachexia

Venn diagram of physiological cachexia defining aspects of different cancer and non-cancer model systems. Note: The assignment of model systems is based on assessment of consensus from the current literature. It is likely that future characterization of model systems will lead to refined allocations.

The patterns of progression for inflammation-independent cachexia are not established. However, they are likely to contribute to the increase over time of fatigue, depression, and anhedonia, a cluster of symptoms and behavioral changes in the cachectic syndrome that contribute to diminished patient well-being. Understanding the progressive sequence of events that lead to cachexia as well as their relationship to the normal biology of the body, dynamics, and effect on the causal disease state are essential for diagnosis, stratification, prevention, and therapy of cachexia.

Established model systems for cachexia research

While human sampling cannot capture the gradual transition from early stages of diseases to advanced cachexia, research using pre-clinical models can be used for that purpose. Well-characterized animal models are needed to demonstrate the efficacy of prospective treatments and to continue to explore etiologies of disease, potentially identifying new therapeutic targets (Figure 4 and Table 2).

Thus far, *in vivo* pre-clinical models of cachexia have been used to investigate multiple aspects of the syndrome, such as higher energy expenditure, which has been extensively described in the C26 mouse model of colorectal cancer cachexia,[99] and brown adipose tissue (BAT) thermogenic activity, which despite being present in only 7% of patients with cancer, is greater in cachectic rats with Yoshida sarcoma.[118] Muscle and WAT wasting, as well as browning of WAT, have been described in multiple mouse models, including genetically engineered mouse models (GEMMs) of lung, pancreatic, and skin cancer, diethylnitrosamine (DEN)-induced models of liver cancer, and subcutaneous models of melanoma (B16), lung (LLC), and colorectal (C26) cancers.[24,119,120] IL-6 inhibition prevents browning and weight loss in the K5-SOS and the C26 models.[18,38] Measurements of glucose uptake flux by tumors and tissues in the MAC16 model led to identification of the tumor as the second major consumer of glucose, only after the brain. MAC16 tumors also have a higher cycling flux through the triglyceride-fatty acid cycle, but protein synthesis rates are unchanged.[121,122] These findings demonstrate a direct impact of the tumor on host nutrition in animal models, but their relevance in comparatively smaller human tumors is not yet clear.

Studies in various *in vivo* models describe severe systemic hypoglycemia; impaired hepatic ketogenesis; increased plasma triglycerides, VLDL, and LDL; and modified ceramides as the main metabolic consequences of cancer cachexia in the host, making them potential therapeutic targets for prevention and reversal of cancer cachexia.[11,123,124] In addition, patient-derived xenograft (PDX) and organoid models created from surgically resected tumors from cachectic patients recapitulate both local and systemic aspects of the wasting syndrome and are valuable models to investigate heterogeneity in cachexia.

The fruit fly *Drosophila* has emerged as an attractive model to address some of the outstanding questions in cachexia research because of (1) the conservation of signaling pathways and hormonal control of metabolism, (2) the tools available, and (3) the availability of organ wasting/cachexia models.[125,126] A wealth

Table 2. Summary categorization of model systems

Cancer-associated						Non-cancer-associated			
Mouse			Rat	Drosophila	Zebrafish	Inflammatory	Cardiac	Chronic kidney disease	Other
Subcutaneous	GEMMs		Yoshida AH-130 (Hepatoma)[90]	Yki-tumors (gut)[17]	KrasG12V (Hepatocellular carcinoma)[91]	LPS[92]	Myocardical infarction[93]	5/6 Nephrectomy[94]	Short-term model of radiation-induced injury[95]
LLC (Lewis Lung Carcinoma)[96]	**Pancreatic adenocarcinoma**	**Lung and colorectal cancer**	Walker 256 (Carcinosarcoma)[97]			TNF-α[98]			
C26 (Colorectal Carcinoma)[99]	KPC (Kras+/LSL-G12D; Trp53+/R270H; Pdx1+/Cr)[100]	KG12; p53[101]				IL-6[8]			
B16 (Melanoma)[102]						IL-1a[103]			Chemotherapy[104]
MAC16 (Colon adenocarcinoma)[105]	PKT (Ptf1acre/+; LSL-KrasG12D/+; Tgfbr2flox/flox)[52]	KrasG12D/lkb1 (non-small cell lung cancer – NSCLC)[57]	Morris 7777 (Hepatoma)[106]	Ras[V12]/scribble (eye disc)[107]			Aortic banding[108]		
EHS (Chondrosarcoma)[109]						IL-1b[110]			
MCG-101 (Methylcholanthrene-induced sarcoma)[111]	Kras+/G12D; Ptf1a+/ER-Cre; Ptenf/f[112]	ApcMin/+ (colorectal cancer)[113]	Prostate carcinoma[114]						Toxoplasma gondii[115]
Cross-species cell lines used in immuno-compromised mice[116]						HIV infection[117]			

of genetic tools is available for *Drosophila* studies of organ wasting. In particular, new cachectic factors can be identified using genome-wide tissue-specific RNAi or CRISPR screens. In addition, tissue-specific proximity labeling methods using biotin ligases can identify secreted factors from various tissues.[127] Importantly, several Drosophila tumor models, based on the expression of oncogenes or loss of tumor suppressors in tissues such as the gut or imaginal discs, in either larvae or adults, are available.[125,126] Already, studies of these models have identified tumor-derived factors involved in wasting and have provided insights into their roles in tumor-induced metabolic dysregulation. Among them are insulin-binding protein (ImpL2), receptor tyrosine kinase ligands (Pvf1/PDGF-VEGF, Bnl/FGF), matrix metallopeptidase (MMP1), and inflammatory cytokines (Unpaireds/IL-6, Eiger/TNF-α).[125,126] Studies from flies support the emerging concept that cachexia is more than one disease, as the nature of cachectic factors in many cases depends on the type of tumors analyzed. Moving forward, fly models will not only help obtain a system-level understanding of cachectic factors throughout the entire organism, but also allow various studies such as characterization of the role of microbiota in cachexia and how tumors affect feeding, olfactory and gustatory behaviors.

Observations of animal responses to non-cancer-associated cachexia have informed our understanding of the pathophysiology of this wasting syndrome, highlighting inflammation as one of the most relevant aspects of cachexia. Pre-clinical models of acute or chronic inflammation, such as injection of lipopolysaccharide (LPS) or specific inflammatory cytokines (TNF-α, IL-6, or IL-1) exhibit an intense decrease in food intake and increase in resting energy expenditure as seen in disease-associated cachexia (Figure 3). Cardiac cachexia is often a comorbidity in heart failure patients,[128] partly caused by the release of inflammatory mediators in response to bacterial toxins absorbed through an edematous bowel wall. The use of surgical techniques either to cause cardiac muscle infarction or limit left ventricular output allow for the replication of the main clinical findings of cardiac cachexia. As with heart failure, cachexia in patients with chronic kidney disease (CKD) is thought to be due to increased inflammation. Animal models of CKD focus on surgical approaches that increase uremia as a means of inducing changes in food intake and body composition. Models of both cardiac cachexia and CKD-associated cachexia, as well as models of radiation- and chemotherapy-induced cachexia, have been used to demonstrate the efficacy of melanocortin-inhibitors and ghrelin on improving appetite, weight gain and lean body mass.[104]

The mechanism of muscle protein catabolism in cachexia has been studied *in vitro* using C2C12 myoblasts and myotubes,[129] muscle stem cells derived from C26 tumor-bearing mice,[130] and engineered skeletal muscle.[131] These models show great potential for research aimed to enhance regenerative processes in the muscle.

The pre-clinical model systems mentioned above—despite being useful, informative, and instrumental in advancing cachexia research—have restrictions that may contribute to the unsuccessful clinical translation of some treatment approaches. These limitations include the inability to fully recapitulate the human disease (nonspontaneous development or lack of a tumor microenvironment), the fact that the tumor models often reach large tumor sizes (sometimes >10% of the entire body mass), the absence of an adaptive immune system in case of PDX models, or induction of cachexia on a rapid timescale (e.g., a few weeks).

PREVENTION AND REVERSAL OF CACHEXIA

Cachexia is preventable and potentially reversible. In murine models, treatments that reverse muscle mass loss and anorexia significantly prolong survival.[53] Patients with early-stage cancer or with infections do not develop cachexia if they are cured. Occasionally, patients with cachexia who respond strongly to treatment of the underlying disease or undergo surgical resection of the cachexia-inducing tumor demonstrate recovery of lean body mass.[132] However, as seen in clinical trials to date (Table 3), reversibility of cachexia, especially if the treatment is aimed at preventing the end organ damage of body fat loss and skeletal muscle atrophy, is a great challenge.

Cachexia prevents patients with advanced cancer from getting adequate treatments, thus, early intervention in cachexia would be highly advantageous. Most patients with advanced cachexia are too weak to tolerate standard doses of anti-cancer therapies and instead, succumb to accelerated death resulting from respiratory and cardiac failure due to weakened diaphragm and cardiac muscles. Consequently, a substantial portion of deaths in advanced cancer stem not necessarily from cancer itself, but from cachexia (Figure 3). Anti-cachexia treatments may synergize with cancer-directed treatments to the benefit of patients. A specific therapeutic example could be the synergy of patient reconditioning and normalization of HPA axis function in the context of cancer immunotherapy.

The multiple triggers of cancer cachexia and the amalgam of metabolic conditions that result from a tumor-initiated imbalance in whole body metabolism also suggest some value in exploring diet. Clinical guidelines for nutrition support during cachexia mostly focus on the later and end stages of disease and research approaches to nutrition and cachexia typically test a defined meal or supplement strategy. A better understanding of the early dynamics in tumor versus host metabolism is thus vital to the design of optimally targeted nutrition support earlier in disease process. Some nutritional interventions, such as a ketogenic diet, may disrupt tumor metabolism or synergize with chemotherapy but, on the other hand, may challenge host metabolism.[11] Enteral nutrition may result in weight stability of patients with pancreatic cancer, but its feasibility is unclear.[139] Total parental nutrition has had minimal or no effect in delaying cachexia in small trials,[140] perhaps indicating that nutrient utilization is impaired in addition to nutrient uptake. Building on a Phase 2 feasibility trial, the MENAC trial (NCT02330926) is an active Phase 3 randomized-controlled trial (RCT) investigating the use of a home-based exercise routine, nutritional supplementation, and anti-inflammatories (EPA/NSAID). Additional clarity with respect to nutrient-gene interactions, the gut microbiota, the circadian clock, and biological rhythms in feeding and metabolism must be established to facilitate best deployment of nutritional strategies.

Table 3. Selected ongoing and completed clinical trials for patients with cachexia

Clinical trial	Drug/treatment	Mechanism	Phase	Population		Endpoint	Results
				Underlying disease	Stage		
POWER (NCT00467844)[133]	Enobosarm	Selective androgen receptor modulator	Phase 2	Non-obese male (>45 years) and female (postmenopausal) patients with cancer	≥2% weight loss in the previous 6 months	Change in total lean body mass from baseline, assessed by dual-energy X-ray absorptiometry	Significant increases in total lean body mass by day 113 or end of study (enobosarm 1mg median 1.5 kg, range 2.1–12.6, p = −0.0012; enobosarm 3 mg median 1kg, 4.8–11.5, p = 0.046)
ROMANA (NCT00219817 and NCT00267358)[134]	Anamorelin	Ghrelin receptor agonist	Phase 2	Patients with advanced or incurable cancer	Weight loss ≥5%	Lean body mass changes by dual-energy X-ray absorptiometry over the 12-week treatment period	Lean body mass increased by a least-squares mean of 1.89 kg (95% CI 0.84–2.95)
NCT03743064, NCT03743051			Phase 3	Patients with advanced Non-Small Cell Lung Cancer (NSCLC)	Body mass index <20 kg/m^2 with involuntary weight loss of >2% within 6 months prior to screening	Changes in weight and 5-item Anorexia Symptom Subscale	*Active. Not recruiting.*
Loprinzi et al.[135]	Dexamethasone Fluoxymesterone Megestrol acetate	Corticosteroid Synthetic testosterone Synthetic progesterone	Phase 3	Patients with advanced incurable cancer	Weight loss of ≥5 pounds withing the previous 2 months or estimated daily caloric intake of less than 20 cal/kg	O'Brien global test	Patients treated with megestrol acetate improved on more variables than patients in the other treatment arms
Nelson et al.[136]	Dronabinol	Orexigenic agent	Phase 2	Patients with incurable cancer	Loss of 5 pounds or more during 2 months and/or a daily intake of less than 20 cal/kg	Changes in weight and appetite	Weight not improves compared to megestrol acetate arm
Fearon et al.[137]	Eicosapentaenoic acid diester	Pure omega-3 fatty acid	Phase 2	Clinical diagnosis of gastrointestinal or lung cancer	5% or more loss of pre-illness stable weight	Survival, weight, and other nutritional variables	No statistically significant improvements. Relative to placebo, mean weight increased by 1.2 kg with 2 g EPA (95% CI, 0 kg–2.3 kg) and by 0.3 kg with 4 g EPA (≥0.9 kg–1.5 kg)

(*Continued on next page*)

Table 3. ***Continued***

Clinical trial	Drug/treatment	Mechanism	Phase	Population		Endpoint	Results
				Underlying disease	Stage		
NCT01127386[138]	Lenalidomide	Immune-modulator	Phase 2	Advances and incurable solid tumor with inflammatory cachexia	Weight loss ≥2% in 2 months or ≥5% in 6 months, CRP ≥30 mg/L, Granul. ≥ 1.5 x 10^9/L, platelet ≥100 x 10^9/L, serum creatinine ≤2 mg/dL	Lean body mass and handgrip strength	No treatment response on muscle mass and muscle strength was observed with lenalidomide
NCT04803305	anti-GDF-15	Growth/ differentiation factor-15 blockade	Phase 1	Patients with advanced non-small cell lung, pancreatic, colorecta, prostate, breast or ovarian cancer	Anorexia as defined by a score of ≤ in the Cancer-Related Cachexia Symptom Assessment Appetite 7-day recall scale	Changes in appetite	*Completed. No results published.*
PINNACLES (NCT04725474)			Phase 2	Patients with metastatic pancreatic adenocarcinoma		Incidence and Severity of Treatment-Emergent Adverse Events	*Recruitment ongoing*
GDFATHER (NCT04725474)			Phase 2	Patients with advanced-stage or recurrent pancreatic adenocarcinoma	Life expectancy >3 months	Adverse Events, determination of dose-limiting toxicity (DLT) and MTD, assessment of toxicities	
MENAC (NCT02330926)	Exercise routine, nutritional supplementation and anti-inflammatory	Multimodal intervention	Phase 3	Patients with lung, pancreatic, non-small cell lung (stage III or IV), or pancreatic (stage III or IV) cancer	Karnofsky Performance Status >70	Changes in body weight	*Active. Not recruiting*
NCT04906746	Ruxolitinib	JAK1/2 inhibitor	Phase 1	Patietns with non-small cell lung cancer and cachexia	Stage IV	Identification of any DLT	*Recruitment ongoing*

Table 4. Monitoring and measuring approaches for pathophysiological parameters in cachexia

Parameter	Clinical test	Pre-clinical test
Functional impairment		
Cardiorespiratory fitness	6-min walk test	Calorimetry and telemetry
Mobility balance	Timed up and go (TUG)	Rotarod performance test
Leg strength and speed	Short physical performance battery (SPPB) test	Whole-limb grip strength and treadmill speed
Upper extremity strength	30-s arm curl test	Forelimb grip strength
Free-living activity and behavior	Triaxial actigraph	IR photocell technology for axis detection of animal motion in cage
Anorexia		
Calories, protein intake and diet quality	Food frequency questionnaires	Food intake monitoring and access control
Quality of life		
Fatigue, pain, anxiety and depression	Patient-reported outcomes (PROs)	Treadmill fatigue test
Body composition		
Skeletal muscle and adipose tissue density	Longitudinal CT scans	Longitudinal CT scans
Biomarkers		
Blood markers for metabolic, endocrine and inflammatory state	Standardized panel of markers	Standardized panel of markers

DIMENSIONS FOR ENHANCED CLINICAL CACHEXIA RESEARCH AND PATIENT CARE

Cachexia therapeutic development is at a critical juncture. Despite 60 years of investigation, there are no effective U.S Food and Drug Administration (FDA)-approved treatments for cachexia. Early cachexia clinical trials focused on evaluating drugs that simply stimulated appetite but did not significantly improve other aspects of this wasting syndrome. The past decade has seen advances in our understanding of cachexia pathophysiology, resulting in the development of drugs targeting presumed cachectogenic mechanisms. Unfortunately, these more recent strategies have still proven only partially effective or led to unsuccessful clinical trials (Table 3).

Gaps in our understanding of mechanisms and longitudinal courses of cachexia are likely to be the root of suboptimal endpoints, enrollment, and dosing of patients in failed clinical trials. Cachexia manifests non-uniformly across patients, and there may be multiple cachexia subtypes. Mechanistic biomarker-driven patient stratification, better longitudinal understanding of the processes leading to advanced cachexia, and refined trial design may improve therapeutic developments and lead to impactful clinical management guidelines (Table 4). For example, emerging circulating molecules, such as PLA2G7, may have potential as biomarkers for standardized early detection of cachexia, therapeutic efficacy, and patient stratification.[141]

Imaging utilization

In addition to longitudinal tracking of circulating molecules and underlying disease with repeat sampling, the distribution and utilization of nutrients and the composition of lean body mass and organs can be monitored longitudinally in pre-clinical and clinical research using radiological methods. Utilizing this approach for research and care in cancer cachexia is prudent because, in the clinic, computed tomography (CT) is used for routine surveillance of tumor burden in cancer care and for diagnoses of non-cancerous cachexia inducing diseases. From routine scans, cross-sectional muscle area size at the height of third lumbar vertebra (L3) correlate with whole-body muscle and adipose tissue volumes—their analyses can be automated for reproducible routine measurement and identification of high-risk groups in trials and care.[142] Dynamic metabolic tracking offered by magnetic resonance imaging (MRI) and by positron emission tomography (PET) offers further research and care advances. Functional brain MRI has been used to demonstrate that pre-treatment dysfunction in executive networks is associated with post-treatment fatigue and cognitive dysfunction more strongly than receipt of chemotherapy.[143] MRI and PET have also been used to track choline and glucose uptake in the brain and lungs and depletion of triglycerides as well as altered liver gluconeogenesis in murine cancer models. In patients, tumor glucose uptake positively correlates with energy expenditure and weight loss,[144] while low liver uptake of glucose associates with poor cachexia-associated survival.[145] New and sensitive (x40-fold improvement) total-body PET scanners that can image the full body in a single scan and measure multiple metabolic substrates bring new possibilities to image dynamic metabolic networks and identify interactions between organs, with examples including tumor-liver-muscle or brain-gut axes, as well as to image other metabolic pathways such as beta-oxidation in BAT, fatty acid synthesis in the tumor and liver, and the Cori and Cahill cycles in the liver and muscle. Radiological imaging, therefore, has potential for early detection of the metabolic alterations that precede changes in body composition. These new imaging

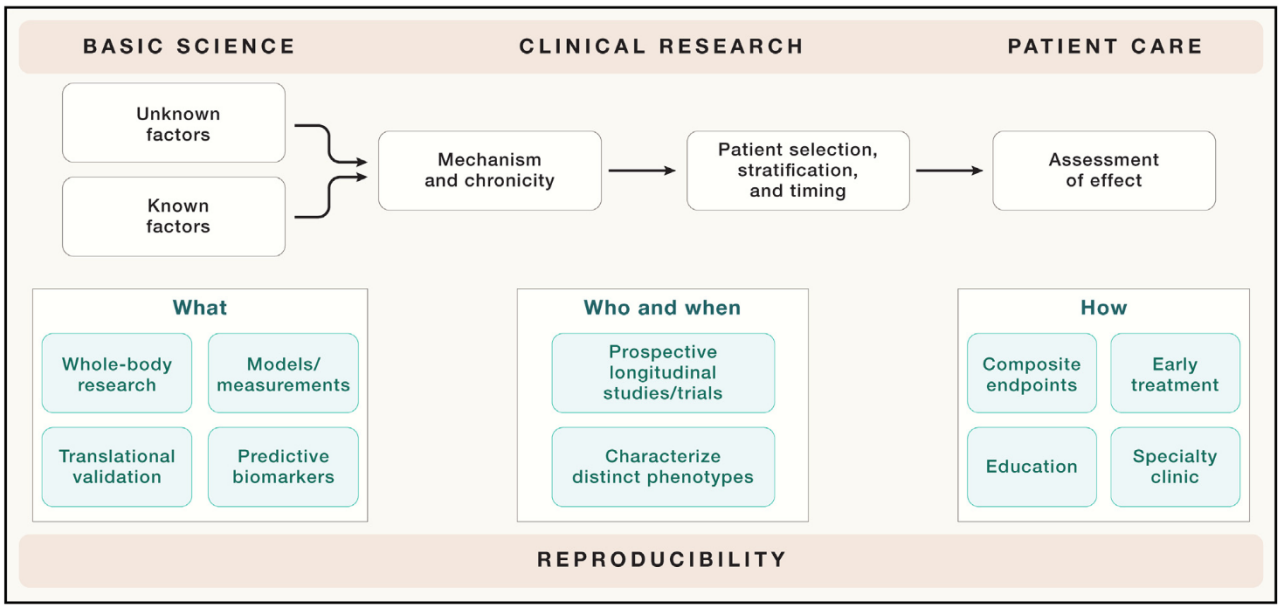

Figure 5. Potential and established contributory areas for the advancement of cachexia research and care
Selected aspects relating to the full translational research enterprise from pre-clinical mechanistic work to clinical team building and trial design are listed.

approaches may also be applied to monitoring the effectiveness of new interventions in cachexia.

Patient stratification and trial enrollment

Patients have been traditionally dichotomized into either the presence or absence of cachexia. However, the view that all cachexia can be treated with one standard approach is likely oversimplified. Data from cross-sectional and retrospective studies suggest that distinct subtypes of cachexia with variable clinical phenotypes exist. Recently, Gagnon et al. demonstrated that there are at least two clinical subtypes of cancer cachexia, based on each patient's inflammation and anorexic symptoms.[146] The inflammatory-necrotic/anorexic group had shorter median survival (13.9 vs. 27.7 months) than the non-inflammatory/non-anorexic group. Other studies have used clustering approaches to describe body composition changes observed in patients with cachexia, and three distinct descriptive clusters were found[147]: muscle and fat wasting, fat wasting alone, and no wasting. Those with no wasting had the best survival outcomes, followed by those with fat wasting alone. Those with both muscle and fat wasting had the least favorable outcomes.

In addition to specific and concrete categorization of cachexia populations and a deeper understanding of the molecular and physiologic underpinnings of each cachexia subtype, evidence of how clinical and functional metrics change over time are urgently needed to advance the field. Large prospective observational trials in the clinic as well as correlative deep phenotyping and mechanistic sequential research in pre-clinical models, both focused on understanding the natural trajectory of cachexia, would meet this unmet need and inform future more targeted, precise, and, hopefully, positive cachexia clinical trials (Figure 5). For example, the REVOLUTION study is a longitudinal observational study recruiting patients from a palliative care service with advanced cancer following changes in body composition, function, quality of life, and inflammatory markers.[148]

A further challenge is that cachexia clinically resembles the consequences of other clinical entities that affect the whole organism, such as malnutrition, sarcopenia, or frailty of old age. Therefore, more specific and concrete categorization of cachexia populations, a deeper understanding of the molecular and physiologic underpinnings of each cachexia subtype (genetic, microenvironmental, and histologic), and evidence of how clinical and functional metrics change over time are urgently needed to advance the field. Rather than broadening the scope of cachexia trials, cachexia intervention trials should perhaps focus more on the target population and trial endpoints.

In terms of trial operation, most cachexia clinical trial programs enroll patients who have experienced >5% body weight loss. Weight loss, however, does not fully correlate with skeletal muscle loss,[149] nor does it fully characterize the effect of cachexia on physical functioning, quality of life, and overall survival.[150] Moreover, cachexia-induced weight loss is a late manifestation of the wasting syndrome; therefore, the whole-body's metabolism is likely to have already reprogrammed at the time of enrollment. Interventions most likely to succeed may have to be delivered sooner, perhaps at cancer diagnosis when patients are in the early stages of cachexia; however, there continues to be no effective biomarkers for this state. The modified Glasgow Prognostic Score (mGPS) is a relevant tool that may help clinical identification and staging of cachexia in patients with cancer.[151]

Trial endpoints

An additional clinical trial challenge is a lack of agreement on the endpoints for cancer cachexia treatments. It remains uncertain if

bodyweight per se represents an endpoint that is sufficiently clinically meaningful. Notably, in one study using CT, the traditional definition of >5% body weight loss underestimated cachexia at 56.6%, while CT-based body composition analysis detected tissue loss of >5% in 81% of patients.[147] Endpoints that directly reflect how patients feel, function, or survive are most informative. Historically, regulatory agencies have required co-primary endpoints that quantify lean tissue and objectively measure physical functioning for cancer cachexia treatment indications. Enobosarm (POWER; NCT00467844) and anamorelin (ROMANA; NCT00219817 and NCT00267358) are examples of drugs that showed improved lean body mass but no changes in physical function and were consequently not approved by the FDA. Anamorelin has been approved for use in treating cancer cachexia in Japan but not in the U.S. and continues to be evaluated in Phase 3 clinical trials (NCT03743064 and NCT03743051), though its primary endpoints have shifted to focus more on weight and anorexia. Recently, a composite endpoint approach has been adopted that combines a measure of body habitus (e.g., body weight or body composition) with a patient-reported outcome (NCT02138422).[152] Such a composite endpoint approach could enable the quantification of clinical benefit across various types of interventions (e.g., lifestyle, pharmacotherapy, etc.) in a clinically meaningful manner.

Robustly addressing these challenges and coupling endpoints to mechanistic studies will reduce common barriers to developing and approving effective interventions for cachexia prevention and treatment (Figure 5). These discoveries would dramatically enhance the provision of evidence-based, patient-oriented cancer care. The foundation research is instrumental, but not sufficient. Outcome work in chronic disease management has demonstrated benefit from involvement of an informed care team in patient support. Thus, a cachexia-focused clinical effort should not solely focus on interventions. Education of a multidisciplinary team, awareness of malnutrition and other conditions that could mimic or exacerbate cachexia, and close collaborations with the teams that address the underlying diseases that drive cachexia, as well as involvement and support of patient caregivers and social networks of patients are essential for best care.

Conclusion

Cachexia is the ultimate consequence of a variety of unresolved diseases, including infections, chronic inflammatory diseases, and cancers. Distinct causes for cachexia suggest cachexia subtypes driven by inflammatory mechanisms, imbalances of molecules that maintain tissue homeostasis, and suppression of appetite and nutrient intake. In addition, multi-organ interaction, organismal predisposition to cachexia due to genetics, age, sex, and treatments are emerging as relevant contributors to cachexia.

The robust research foundation on advanced cachexia and the availability of model systems that allow longitudinal tracking of specific molecular processes across organs together open the door to expand our understanding of the processes that lead to the development of cachexia. The combination of pre-clinical and clinical research and a comprehensive understanding of the unifying and distinct processes that drive earlier cachexia events, such as initiation and progression, will enable better clinical intervention and patient-centered care in the years to come.

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AUTHOR CONTRIBUTIONS

Conceptualization, M.F. and T.J.; Methodology and Writing – Original Draft, M.F. and T.J.; Writing – Review & Editing, all authors.; Funding Acquisition and Supervision, T.J.

DECLARATION OF INTERESTS

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REFERENCES

1. Farkas, J., von Haehling, S., Kalantar-Zadeh, K., Morley, J.E., Anker, S.D., and Lainscak, M. (2013). Cachexia as a major public health problem: Frequent, costly, and deadly. J. Cachexia Sarcopenia Muscle *4*, 173–178. https://doi.org/10.1007/s13539-013-0105-y.
2. Butler, G. (1906). The Diagnostics of Internal Medicine, 2nd editio (D Appleton & Co).
3. Taylor, H. (1915). Cancer: Its Study and Prevention (Lea & Febiger).
4. Fearon, K., Strasser, F., Anker, S.D., Bosaeus, I., Bruera, E., Fainsinger, R.L., Jatoi, A., Loprinzi, C., MacDonald, N., Mantovani, G., et al. (2011). Definition and classification of cancer cachexia: An international consensus. Lancet Oncol. *12*, 489–495. https://doi.org/10.1016/S1470-2045(10)70218-7.
5. Bachmann, J., Heiligensetzer, M., Krakowski-Roosen, H., Büchler, M.W., Friess, H., and Martignoni, M.E. (2008). Cachexia worsens prognosis in patients with resectable pancreatic cancer. J. Gastrointest. Surg. *12*, 1193–1201. https://doi.org/10.1007/s11605-008-0505-z.
6. Wagner, P.D. (2008). Possible mechanisms underlying the development of cachexia in COPD. Eur. Respir. J. *31*, 492–501. https://doi.org/10.1183/09031936.00074807.
7. Zanders, L., Kny, M., Hahn, A., Schmidt, S., Wundersitz, S., Todiras, M., Lahmann, I., Bandyopadhyay, A., Wollersheim, T., Kaderali, L., et al. (2022). Sepsis induces interleukin 6, gp130/JAK2/STAT3, and muscle wasting. J. Cachexia Sarcopenia Muscle *13*, 713–727. https://doi.org/10.1002/jcsm.12867.
8. Oldenburg, H.S., Rogy, M.A., Lazarus, D.D., van Zee, K.J., Keeler, B.P., Chizzonite, R.A., Lowry, S.F., and Moldawer, L.L. (1993). Cachexia and the acute-phase protein response in inflammation are regulated by interleukin-6. Eur. J. Immunol. *23*, 1889–1894. https://doi.org/10.1002/eji.1830230824.
9. Petruzzelli, M., Ferrer, M., Schuijs, M.J., Kleeman, S.O., Mourikis, N., Hall, Z., Perera, D., Raghunathan, S., Vacca, M., Gaude, E., et al. (2022). Early Neutrophilia Marked by Aerobic Glycolysis Sustains Host

Metabolism and Delays Cancer Cachexia. Cancers *14*, 963. https://doi.org/10.3390/cancers14040963.

10. Schakman, O., Dehoux, M., Bouchuari, S., Delaere, S., Lause, P., Decroly, N., Shoelson, S.E., and Thissen, J.P. (2012). Role of IGF-I and the TNFα/NF-κB pathway in the induction of muscle atrogenes by acute inflammation. Am. J. Physiol. Endocrinol. Metab. *303*, E729–E739. 2012. https://doi.org/10.1152/ajpendo.00060.2012.
11. Flint, T.R., Janowitz, T., Connell, C.M., Roberts, E.W., Denton, A.E., Coll, A.P., Jodrell, D.I., and Fearon, D.T. (2016). Tumor-Induced IL-6 Reprograms Host Metabolism to Suppress Anti-tumor Immunity. Cell Metab. *24*, 672–684. https://doi.org/10.1016/j.cmet.2016.10.010.
12. Matthys, P., Dijkmans, R., Proost, P., Van Damme, J., Heremans, H., Sobis, H., and Billiau, A. (1991). Severe cachexia in mice inoculated with interferon-γ-producing tumor cells. Int. J. Cancer *49*, 77–82. https://doi.org/10.1002/ijc.2910490115.
13. Chiappalupi, S., Sorci, G., Vukasinovic, A., Salvadori, L., Sagheddu, R., Coletti, D., Renga, G., Romani, L., Donato, R., and Riuzzi, F. (2020). Targeting RAGE prevents muscle wasting and prolongs survival in cancer cachexia. J. Cachexia Sarcopenia Muscle *11*, 929–946. https://doi.org/10.1002/jcsm.12561.
14. Dickson, S.L., Wallenius, K., Ahrén, B., Rudling, M., Carlsten, H., Wallenius, V., Ohlsson, C., and Jansson, J.O. (2002). Interleukin-6-deficient mice develop mature-onset obesity. Nat. Med. *8*, 75–79.
15. Zimmers, T.A., McKillop, I.H., Pierce, R.H., Yoo, J.Y., and Koniaris, L.G. (2003). Massive liver growth in mice induced by systemic interleukin 6 administration. Hepatology *38*, 326–334. https://doi.org/10.1053/jhep.2003.50318.
16. Rupert, J.E., Narasimhan, A., Jengelley, D.H.A., Jiang, Y., Liu, J., Au, E., Silverman, L.M., Sandusky, G., Bonetto, A., Cao, S., et al. (2021). Tumor-derived IL-6 and trans-signaling among tumor, fat, and muscle mediate pancreatic cancer cachexia. J. Exp. Med. *218*, e20190450. https://doi.org/10.1084/jem.20190450.
17. Ding, G., Xiang, X., Hu, Y., Xiao, G., Chen, Y., Binari, R., Comjean, A., Li, J., Rushworth, E., Fu, Z., et al. (2021). Coordination of tumor growth and host wasting by tumor-derived Upd3. Cell Rep. *36*, 109553. https://doi.org/10.1016/j.celrep.2021.109553.
18. Petruzzelli, M., Schweiger, M., Schreiber, R., Campos-Olivas, R., Tsoli, M., Allen, J., Swarbrick, M., Rose-John, S., Rincon, M., Robertson, G., et al. (2014). A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. Cell Metab. *20*, 433–447. https://doi.org/10.1016/j.cmet.2014.06.011.
19. Mace, T.A., Bloomston, M., and Lesinski, G.B. (2013). Pancreatic cancer-associated stellate cells: A viable target for reducing immunosuppression in the tumor microenvironment. OncoImmunology *2*, e24891–e24897. https://doi.org/10.4161/onci.24891.
20. Engineer, D.R., and Garcia, J.M. (2012). Leptin in anorexia and cachexia syndrome. Int. J. Pept. *2012*, 287457. 2012. https://doi.org/10.1155/2012/287457.
21. Tanaka, M., Suganami, T., Kim-Saijo, M., Toda, C., Tsuiji, M., Ochi, K., Kamei, Y., Minokoshi, Y., and Ogawa, Y. (2011). Role of central Leptin signaling in the starvation-induced alteration of B-cell development. J. Neurosci. *31*, 8373–8380. https://doi.org/10.1523/JNEUROSCI.6562-10.2011.
22. Kandarian, S.C., Nosacka, R.L., Delitto, A.E., Judge, A.R., Judge, S.M., Ganey, J.D., Moreira, J.D., and Jackman, R.W. (2018). Tumour-derived leukaemia inhibitory factor is a major driver of cancer cachexia and morbidity in C26 tumour-bearing mice. J. Cachexia Sarcopenia Muscle *9*, 1109–1120. https://doi.org/10.1002/jcsm.12346.
23. Walton, K.L., Chen, J.L., Arnold, Q., Kelly, E., La, M., Lu, L., Lovrecz, G., Hagg, A., Colgan, T.D., Qian, H., et al. (2019). Activin A-Induced Cachectic Wasting Is Attenuated by Systemic Delivery of Its Cognate Propeptide in Male Mice. Endocrinology *160*, 2417–2426. https://doi.org/10.1210/en.2019-00257.
24. Xu, P.C., You, M., Yu, S.Y., Luan, Y., Eldani, M., Caffrey, T.C., Grandgenett, P.M., O'Connell, K.A., Shukla, S.K., Kattamuri, C., et al. (2022). Visceral adipose tissue remodeling in pancreatic ductal adenocarcinoma cachexia: the role of activin A signaling. Sci. Rep. *12*, 1659. https://doi.org/10.1038/s41598-022-05660-7.
25. Antsiferova, M., Huber, M., Meyer, M., Piwko-Czuchra, A., Ramadan, T., MacLeod, A.S., Havran, W.L., Dummer, R., Hohl, D., and Werner, S. (2011). Activin enhances skin tumourigenesis and malignant progression by inducing a pro-tumourigenic immune cell response. Nat. Commun. *2*, 576. https://doi.org/10.1038/ncomms1585.
26. Lodge, W., Zavortink, M., Golenkina, S., Froldi, F., Dark, C., Cheung, S., Parker, B.L., Blazev, R., Bakopoulos, D., Christie, E.L., et al. (2021). Tumor-derived MMPs regulate cachexia in a Drosophila cancer model. Dev. Cell *56*, 2664–2680.e6. https://doi.org/10.1016/j.devcel.2021.08.008.
27. Busquets, S., Toledo, M., Orpí, M., Massa, D., Porta, M., Capdevila, E., Padilla, N., Frailis, V., López-Soriano, F.J., Han, H.Q., and Argiles, J.M. (2012). Myostatin blockage using actRIIB antagonism in mice bearing the Lewis lung carcinoma results in the improvement of muscle wasting and physical performance. J. Cachexia Sarcopenia Muscle *3*, 37–43. https://doi.org/10.1007/s13539-011-0049-z.
28. Bose, S., and Cho, J. (2013). Role of chemokine CCL2 and its receptor CCR2 in neurodegenerative diseases. Arch Pharm. Res. (Seoul) *36*, 1039–1050. https://doi.org/10.1007/s12272-013-0161-z.
29. Le Thuc, O., Cansell, C., Bourourou, M., Denis, R.G., Stobbe, K., Devaux, N., Guyon, A., Cazareth, J., Heurteaux, C., Rostène, W., et al. (2016). Central CCL2 signaling onto MCH neurons mediates metabolic and behavioral adaptation to inflammation. EMBO Rep. *17*, 1738–1752. https://doi.org/10.15252/embr.201541499.
30. Luciano-Mateo, F., Cabré, N., Fernández-Arroyo, S., Baiges-Gaya, G., Hernández-Aguilera, A., Rodríguez-Tomàs, E., Muñoz-Pinedo, C., Menéndez, J.A., Camps, J., and Joven, J. (2020). Chemokine C–C motif ligand 2 overexpression drives tissue-specific metabolic responses in the liver and muscle of mice. Sci. Rep. *10*, 11954. https://doi.org/10.1038/s41598-020-68769-7.
31. Sell, H., Dietze-Schroeder, D., Kaiser, U., and Eckel, J. (2006). Monocyte chemotactic protein-1 is a potential player in the negative cross-talk between adipose tissue and skeletal muscle. Endocrinology *147*, 2458–2467. https://doi.org/10.1210/en.2005-0969.
32. Song, W., Kir, S., Hong, S., Hu, Y., Wang, X., Binari, R., Tang, H.W., Chung, V., Banks, A.S., Spiegelman, B., and Perrimon, N. (2019). Tumor-derived ligands trigger tumor growth and host wasting via differential MEK activation. Dev. Cell *48*, 277–286.e6. https://doi.org/10.1016/j.devcel.2018.12.003.Tumor-derived.
33. Lockhart, S.M., Saudek, V., and O'Rahilly, S. (2020). Gdf15: A hormone conveying somatic distress to the brain. Endocr. Rev. *41*. bnaa007–642. https://doi.org/10.1210/ENDREV/BNAA007.
34. Cimino, I., Kim, H., Tung, Y.C.L., Pedersen, K., Rimmington, D., Tadross, J.A., Kohnke, S.N., Neves-Costa, A., Barros, A., Joaquim, S., et al. (2021). Activation of the hypothalamic-pituitary-adrenal axis by exogenous and endogenous GDF15. Proc. Natl. Acad. Sci. USA *118*. 21068681188. https://doi.org/10.1073/pnas.2106868118.
35. Garfield, B.E., Crosby, A., Shao, D., Yang, P., Read, C., Sawiak, S., Moore, S., Parfitt, L., Harries, C., Rice, M., et al. (2019). Growth/differentiation factor 15 causes TGFβ-activated kinase 1-dependent muscle atrophy in pulmonary arterial hypertension. Thorax *74*, 164–176. https://doi.org/10.1136/thoraxjnl-2017-211440.
36. Laurens, C., Parmar, A., Murphy, E., Carper, D., Lair, B., Maes, P., Vion, J., Boulet, N., Fontaine, C., Marquès, M., et al. (2020). Growth and differentiation factor 15 is secreted by skeletal muscle during exercise and promotes lipolysis in humans. JCI Insight *5*, e131870. https://doi.org/10.1172/jci.insight.131870.
37. Kwon, Y., Song, W., Droujinine, I.A., Hu, Y., Asara, J.M., and Perrimon, N. (2015). Systemic Organ Wasting Induced by Localized Expression of the

Secreted Insulin/IGF Antagonist ImpL2. Dev. Cell *176*, 139–148. https://doi.org/10.1016/j.devcel.2015.02.012.Systemic.

38. Kir, S., White, J.P., Kleiner, S., Kazak, L., Cohen, P., Baracos, V.E., and Spiegelman, B.M. (2014). Tumor-derived PTH-related Protein Triggers Adipose Tissue Browning and Cancer Cachexia. Nature *513*, 100–104. https://doi.org/10.1038/nature13528.Tumor-derived.
39. Laird, B.J., McMillan, D., Skipworth, R.J.E., Fallon, M.T., Paval, D.R., McNeish, I., and Gallagher, I.J. (2021). The Emerging Role of Interleukin 1β (IL-1β) in Cancer Cachexia. Inflammation *44*, 1223–1228. https://doi.org/10.1007/s10753-021-01429-8.
40. Mosialou, I., Shikhel, S., Liu, J.-M., Maurizi, A., Luo, N., He, Z., Huang, Y., Zong, H., Friedman, R.A., Barasch, J., et al. (2017). MC4R-dependent suppression of appetite by bone-derived lipocalin 2. Nature *543*, 385–390. https://doi.org/10.1016/b978-0-12-820649-2.00156-x.
41. Flo, T.H., Smith, K.D., Sato, S., Rodriguez, D.J., Holmes, M.A., Strong, R.K., Akira, S., and Aderem, A. (2004). Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. Nature *432*, 917–921. https://doi.org/10.1038/nature03104.
42. Fried, S.K., and Zechner, R. (1989). Cachectin/tumor necrosis factor decreases human adipose tissue lipoprotein lipase mRNA levels, synthesis, and activity. J. Lipid Res. *30*, 1917–1923. https://doi.org/10.1016/s0022-2275(20)38211-0.
43. Yeom, E., Shin, H., Yoo, W., Jun, E., Kim, S., Hong, S.H., Kwon, D.W., Ryu, T.H., Suh, J.M., Kim, S.C., et al. (2021). Tumour-derived Dilp8/INSL3 induces cancer anorexia by regulating feeding neuropeptides via Lgr3/8 in the brain. Nat. Cell Biol. *23*, 172–183. https://doi.org/10.1038/s41556-020-00628-z.
44. Elattar, S., Dimri, M., and Satyanarayana, A. (2018). The tumor secretory factor ZAG promotes white adipose tissue browning and energy wasting. FASEB J *32*, 4727–4743. https://doi.org/10.1096/fj.201701465RR.
45. Callaway, C.S., Delitto, A.E., Patel, R., Nosacka, R.L., D'Lugos, A.C., Delitto, D., Deyhle, M.R., Trevino, J.G., Judge, S.M., and Judge, A.R. (2019). IL-8 released from human pancreatic cancer and tumor-associated stromal cells signals through a CXCR2-ERK1/2 axis to induce muscle atrophy. Cancers *11*, 1863. https://doi.org/10.3390/cancers11121863.
46. Schalper, K.A., Carleton, M., Zhou, M., Chen, T., Feng, Y., Huang, S.-P., Walsh, A.M., Baxi, V., Pendya, D., Baradet, T., et al. (2020). Elevated serum interleukin-8 is associated with enhanced intratumor neutrophils and reduced clinical benefit of immune- checkpoint inhibitors. Nat. Med. *26*, 688–692. https://doi.org/10.1038/s41591-020-0856-x.
47. Yoshida, T., Tabony, A.M., Galvez, S., Mitch, W.E., Higashi, Y., Sukhanov, S., and Delafontaine, P. (2013). Molecular mechanisms and signaling pathways of angiotensin II- induced muscle wasting: potential therapeutic targets for cardiac cachexia. Int. J. Biochem. Cell Biol. *23*, 1–7. https://doi.org/10.1016/j.biocel.2013.05.035.Molecular.
48. Burfeind, K.G., Zhu, X., Norgard, M.A., Levasseur, P.R., Huisman, C., Buenafe, A.C., Olson, B., Michaelis, K.A., Torres, E.R., Jeng, S., et al. (2020). Circulating myeloid cells invade the central nervous system to mediate cachexia during pancreatic cancer. Elife *9*, 540955. https://doi.org/10.7554/eLife.54095.
49. Lam, B.Y.H., Williamson, A., Finer, S., Day, F.R., Tadross, J.A., Gonçalves Soares, A., Wade, K., Sweeney, P., Bedenbaugh, M.N., Porter, D.T., et al. (2021). MC3R links nutritional state to childhood growth and the timing of puberty. Nature *599*, 436–441. https://doi.org/10.1038/s41586-021-04088-9.
50. Biffi, G., Oni, T.E., Spielman, B., Hao, Y., Elyada, E., Park, Y., Preall, J., and Tuveson, D.A. (2019). IL-1-induced JAK/STAT Signaling Is Antagonized by TGF-β to Shape CAF Heterogeneity in Pancreatic Ductal Adenocarcinoma. Cancer Discov *9*, 282–301..
51. Roberts, E.W., Deonarine, A., Jones, J.O., Denton, A.E., Feig, C., Lyons, S.K., Espeli, M., Kraman, M., McKenna, B., Wells, R.J.B., et al. (2013). Depletion of stromal cells expressing fibroblast activation protein-α from skeletal muscle and bone marrow results in cachexia and anemia. J. Exp. Med. *210*, 1137–1151. https://doi.org/10.1084/jem.20122344.
52. Ozdemir, B.C., Pentcheva-Hoang, T., Carstens, J.L., Zheng, X., Wu, C.-C., Simpson, T.R., Laklai, H., Sugimoto, H., Kahlert, C., Novitskiy, S.V., et al. (2014). Depletion of Carcinoma-Associated Fibroblasts and Fibrosis Induces Immunosuppression and Accelerates Pancreas Cancer with reduced Survival. Cancer Cell *25*, 719–734. https://doi.org/10.1016/j.ccr.2014.04.005.Depletion.
53. Queiroz, A.L., Dantas, E., Ramsamooj, S., Murthy, A., Ahmed, M., Zunica, E.R.M., Liang, R.J., Murphy, J., Holman, C.D., Bare, C.J., et al. (2022). Blocking ActRIIB and restoring appetite reverses cachexia and improves survival in mice with lung cancer. Nat. Commun. *13*, 4633. https://doi.org/10.1038/s41467-022-32135-0.
54. Golan, T., Geva, R., Richards, D., Madhusudan, S., Lin, B.K., Wang, H.T., Walgren, R.A., and Stemmer, S.M. (2018). LY2495655, an antimyostatin antibody, in pancreatic cancer: a randomized, phase 2 trial. J. Cachexia Sarcopenia Muscle *9*, 871–879. https://doi.org/10.1002/jcsm.12331.
55. Ding, G., Li, X., Hou, X., Zhou, W., Gong, Y., Liu, F., He, Y., Song, J., Wang, J., Basil, P., et al. (2021). Rev-erb in GABAergic Neurons Controls Diurnal Hepatic Insulin Sensitivity. Nature *592*, 763–767. https://doi.org/10.1038/s41586-021-03358-w.Rev-erb.
56. Winter, A., MacAdams, J., and Chevalier, S. (2012). Normal protein anabolic response to hyperaminoacidemia in insulin-resistant patients with lung cancer cachexia. Clin. Nutr. *31*, 765–773. https://doi.org/10.1016/j.clnu.2012.05.003.
57. Goncalves, M.D., Hwang, S.K., Pauli, C., Murphy, C.J., Cheng, Z., Hopkins, B.D., Wu, D., Loughran, R.M., Emerling, B.M., Zhang, G., et al. (2018). Fenofibrate prevents skeletal muscle loss in mice with lung cancer. Proc. Natl. Acad. Sci. USA *115*, E743–E752. https://doi.org/10.1073/pnas.1714703115.
58. Miller, J., Alshehri, A., Ramage, M.I., Stephens, N.A., Mullen, A.B., Boyd, M., Ross, J.A., Wigmore, S.J., Watson, D.G., and Skipworth, R.J.E. (2019). Plasma metabolomics identifies lipid and amino acid markers of weight loss in patients with upper gastrointestinal cancer. Cancers *11*, 1594. https://doi.org/10.3390/cancers11101594.
59. Patel, S., Alvarez-Guaita, A., Melvin, A., Rimmington, D., Dattilo, A., Miedzybrodzka, E.L., Cimino, I., Maurin, A.C., Roberts, G.P., Meek, C.L., et al. (2019). GDF15 Provides an Endocrine Signal of Nutritional Stress in Mice and Humans. Cell Metab. *29*, 707–718.e8. https://doi.org/10.1016/j.cmet.2018.12.016.
60. Suriben, R., Chen, M., Higbee, J., Oeffinger, J., Ventura, R., Li, B., Mondal, K., Gao, Z., Ayupova, D., Taskar, P., et al. (2020). Antibody-mediated inhibition of GDF15–GFRAL activity reverses cancer cachexia in mice. Nat. Med. *26*, 1264–1270. https://doi.org/10.1038/s41591-020-0945-x.
61. Burney, B.O., and Garcia, J.M. (2012). Hypogonadism in male cancer patients. J. Cachexia Sarcopenia Muscle *3*, 149–155. https://doi.org/10.1007/s13539-012-0065-7.
62. Skipworth, R.J.E., Moses, A.G.W., Sangster, K., Sturgeon, C.M., Voss, A.C., Fallon, M.T., Anderson, R.A., Ross, J.A., and Fearon, K.C.H. (2011). Interaction of gonadal status with systemic inflammation and opioid use in determining nutritional status and prognosis in advanced pancreatic cancer. Support. Care Cancer *19*, 391–401. https://doi.org/10.1007/s00520-010-0832-y.
63. Miller, M., Laird, B.J.A., and Skipworth, R.J.E. (2019). The immunological regulation of cancer cachexia and its therapeutic implications. J. Cancer Metastasis Treat *2019*, 1–11. 2019. https://doi.org/10.20517/2394-4722.2019.001.
64. Barreto, R., Waning, D.L., Gao, H., Liu, Y., Zimmers, T.A., and Bonetto, A. (2016). Chemotherapy-related cachexia is associated with mitochondrial depletion and the activation of ERK1/2 and p38 MAPKs. Oncotarget *7*, 43442–43460. https://doi.org/10.18632/oncotarget.9779.
65. Amrute-Nayak, M., Pegoli, G., Holler, T., Lopez-Davila, A.J., Lanzuolo, C., and Nayak, A. (2021). Chemotherapy triggers cachexia by deregulating synergetic function of histone-modifying enzymes. J. Cachexia Sarcopenia Muscle *12*, 159–176. https://doi.org/10.1002/jcsm.12645.

66. Rybalka, E., Timpani, C.A., Cheregi, B.D., Sorensen, J.C., Nurgali, K., and Hayes, A. (2018). Chemotherapeutic agents induce mitochondrial superoxide production and toxicity but do not alter respiration in skeletal muscle in vitro. Mitochondrion *42*, 33–49. https://doi.org/10.1016/j.mito.2017.10.010.

67. Tsoli, M., Schweiger, M., Vanniasinghe, A.S., Painter, A., Zechner, R., Clarke, S., and Robertson, G. (2014). Depletion of white adipose tissue in cancer cachexia syndrome is associated with inflammatory signaling and disrupted circadian regulation. PLoS One *9*, e92966. https://doi.org/10.1371/journal.pone.0092966.

68. Schieber, A.M.P., Lee, Y.M., Chang, M.W., Leblanc, M., Collins, B., Downes, M., Evans, R.M., and Ayres, J.S. (2015). Disease tolerance mediated by microbiome E. coli involves inflammasome and IGF-1 signaling. Science *80*, 558–563. https://doi.org/10.1126/science.aac6468.Disease.

69. Ni, Y., Lohinai, Z., Heshiki, Y., Dome, B., Moldvay, J., Dulka, E., Galffy, G., Berta, J., Weiss, G.J., Sommer, M.O.A., and Panagiotou, G. (2021). Distinct composition and metabolic functions of human gut microbiota are associated with cachexia in lung cancer patients. ISME J. *15*, 3207–3220. https://doi.org/10.1038/s41396-021-00998-8.

70. Rao, S., Schieber, A.M.P., O'Connor, C.P., Leblanc, M., Michel, D., and Ayres, J.S. (2017). Pathogen-mediated inhibition of anorexia promotes host survival and transmission. Cell *168*, 503–516.e12. https://doi.org/10.1016/j.cell.2017.01.006.Pathogen-mediated.

71. Varian, B.J., Gourishetti, S., Poutahidis, T., Lakritz, J.R., Levkovich, T., Kwok, C., Teliousis, K., Ibrahim, Y.M., Mirabal, S., and Erdman, S.E. (2016). Beneficial bacteria inhibit cachexia. Oncotarget *7*, 11803–11816. https://doi.org/10.18632/oncotarget.7730.

72. Johns, N., Stretch, C., Tan, B.H.L., Solheim, T.S., Sørhaug, S., Stephens, N.A., Gioulbasanis, I., Skipworth, R.J.E., Deans, D.A.C., Vigano, A., et al. (2017). New genetic signatures associated with cancer cachexia as defined by low skeletal muscle index and weight loss. J. Cachexia Sarcopenia Muscle *8*, 122–130. https://doi.org/10.1002/jcsm.12138.

73. Wallengren, O., Iresjö, B.M., Lundholm, K., and Bosaeus, I. (2015). Loss of muscle mass in the end of life in patients with advanced cancer. Support. Care Cancer *23*, 79–86. https://doi.org/10.1007/s00520-014-2332-y.

74. Stephens, N.A., Gray, C., MacDonald, A.J., Tan, B.H., Gallagher, I.J., Skipworth, R.J.E., Ross, J.A., Fearon, K.C.H., and Greig, C.A. (2012). Sexual dimorphism modulates the impact of cancer cachexia on lower limb muscle mass and function. Clin. Nutr. *31*, 499–505. https://doi.org/10.1016/j.clnu.2011.12.008.

75. Pöllänen, E., Ronkainen, P.H.A., Horttanainen, M., Takala, T., Puolakka, J., Suominen, H., Sipilä, S., and Kovanen, V. (2010). Effects of combined hormone replacement therapy or its effective agents on the IGF-1 pathway in skeletal muscle. Growth Horm. IGF Res. *20*, 372–379. https://doi.org/10.1016/j.ghir.2010.07.003.

76. Hetzler, K.L., Hardee, J.P., Puppa, M.J., Narsale, A.A., Sato, S., Davis, J.M., and Carson, J.A. (2015). Sex differences in the relationship of IL-6 signaling to cancer cachexia progression. Biochim. Biophys. Acta *1852*, 816–825. https://doi.org/10.1016/j.bbadis.2014.12.015.

77. Krause, W.C., Rodriguez, R., Gegenhuber, B., Matharu, N., Rodriguez, A.N., Padilla-Roger, A.M., Toma, K., Herber, C.B., Correa, S.M., Duan, X., et al. (2021). Oestrogen engages brain MC4R signalling to drive physical activity in female mice. Nature *599*, 131–135. https://doi.org/10.1038/s41586-021-04010-3.

78. Wright, T.J., Dillon, E.L., Durham, W.J., Chamberlain, A., Randolph, K.M., Danesi, C., Horstman, A.M., Gilkison, C.R., Willis, M., Richardson, G., et al. (2018). A randomized trial of adjunct testosterone for cancer-related muscle loss in men and women. J. Cachexia Sarcopenia Muscle *9*, 482–496. https://doi.org/10.1002/jcsm.12295.

79. Wang, Y., and Pessin, J.E. (2013). Mechanisms for fiber-type specificity of skeletal muscle atrophy. Curr. Opin. Clin. Nutr. Metab. Care *16*, 243–250. https://doi.org/10.1097/MCO.0b013e328360272d.

80. Frontera, W.R., Hughes, V.A., Fielding, R.A., Fiatarone, M.A., Evans, W.J., and Roubenoff, R. (2000). Aging of skeletal muscle: A 12-yr longitudinal study. J. Appl. Physiol. *88*, 1321–1326. https://doi.org/10.1152/jappl.2000.88.4.1321.

81. Leibowitz, S.F. (1988). Brain neurotransmitters and eating behavior in the elderly. Neurobiol. Aging *9*, 20–22. https://doi.org/10.1016/S0197-4580(88)80007-1.

82. He, M., Chiang, H.-H., Luo, H., Zheng, Z., Qiao, Q., Wang, L., Tan, M., Ohkubo, R., Mu, W.-C., Zhao, S., et al. (2020). An Acetylation Switch of the NLRP3 Inflammasome Regulates Aging-associated Chronic Inflammation and Insulin Resistance. Cell Metab. *31*, 580–591.e5. https://doi.org/10.1016/j.cmet.2020.01.009.An.

83. Breen, D.M., Kim, H., Bennett, D., Calle, R.A., Collins, S., Esquejo, R.M., He, T., Joaquim, S., Joyce, A., Lambert, M., et al. (2020). GDF-15 Neutralization Alleviates Platinum-Based Chemotherapy-Induced Emesis, Anorexia, and Weight Loss in Mice and Nonhuman Primates. Cell Metab. *32*, 938–950.e6. https://doi.org/10.1016/j.cmet.2020.10.023.

84. Mulderrig, L., Garaycoechea, J.I., Tuong, Z.K., Millington, C.L., Dingler, F.A., Ferdinand, J.R., Gaul, L., Tadross, J.A., Arends, M.J., O'Rahilly, S., et al. (2021). Aldehyde-driven transcriptional stress triggers an anorexic DNA damage response. Nature *600*, 158–163. https://doi.org/10.1038/s41586-021-04133-7.

85. Cea, L.A., Balboa, E., Puebla, C., Vargas, A.A., Cisterna, B.A., Escamilla, R., Regueira, T., and Sáez, J.C. (2016). Dexamethasone-induced muscular atrophy is mediated by functional expression of connexin-based hemichannels. Biochim. Biophys. Acta *1862*, 1891–1899. https://doi.org/10.1016/j.bbadis.2016.07.003.

86. Chang, W.T., Hong, M.Y., Chen, C.L., Hwang, C.Y., Tsai, C.C., and Chuang, C.C. (2021). Mutant glucocorticoid receptor binding elements on the interleukin-6 promoter regulate dexamethasone effects. BMC Immunol. *22*. 24–11. https://doi.org/10.1186/s12865-021-00413-z.

87. Daly, L.E., Power, D.G., O'Reilly, Á., Donnellan, P., Cushen, S.J., O'Sullivan, K., Twomey, M., Woodlock, D.P., Redmond, H.P., and Ryan, A.M. (2017). The impact of body composition parameters on ipilimumab toxicity and survival in patients with metastatic melanoma. Br. J. Cancer *116*, 310–317. https://doi.org/10.1038/bjc.2016.431.

88. Muhammed, A., Fulgenzi, C.A.M., Dharmapuri, S., Pinter, M., Balcar, L., Scheiner, B., Marron, T.U., Jun, T., Saeed, A., Hildebrand, H., et al. (2021). The systemic inflammatory response identifies patients with adverse clinical outcome from immunotherapy in hepatocellular carcinoma. Cancers *14*, 186. https://doi.org/10.3390/cancers14010186.

89. Mayers, J.R., Wu, C., Clish, C.B., Kraft, P., Torrence, M.E., Fiske, B.P., Yuan, C., Bao, Y., Townsend, M.K., Tworoger, S.S., et al. (2014). Elevation of circulating branched chain amino acids is an early event in human pancreatic adenocarcinoma development. Nat. Med. *20*, 1193–1198. https://doi.org/10.1038/nm.3686.Elevated.

90. Tessitore, L., Bonelli, G., and Baccino, F.M. (1987). Early development of protein metabolic perturbations in the liver and skeletal muscle of tumour-bearing rats. A model system for cancer cachexia. Biochem. J. *241*, 153–159. https://doi.org/10.1042/bj2410153.

91. Yang, Q., Yan, C., Wang, X., and Gong, Z. (2019). Leptin induces muscle wasting in a zebrafish kras-driven hepatocellular carcinoma (HCC) model. Dis. Model. Mech. *12*, dmm038240. https://doi.org/10.1242/dmm.038240.

92. O'Reilly, B., Vander, A.J., and Kluger, M.J. (1988). Effects of chronic infusion of lipopolysaccharide on food intake and body temperature of the rat. Physiol. Behav. *42*, 287–291. https://doi.org/10.1016/0031-9384(88)90084-4.

93. Gould, K.E., Taffet, G.E., Michael, L.H., Christie, R.M., Konkol, D.L., Pocius, J.S., Zachariah, J.P., Chaupin, D.F., Daniel, S.L., Sandusky, G.E., et al. (2002). Heart failure and greater infarct expansion in middle-aged mice: A relevant model for postinfarction failure. Am. J. Physiol. Heart Circ. Physiol. *282*, H615–H621. https://doi.org/10.1152/ajpheart.00206.2001.

94. Cheung, W., Yu, P.X., Little, B.M., Cone, R.D., Marks, D.L., and Mak, R.H. (2005). Role of leptin and melanocortin signaling in uremia-

associated cachexia. J. Clin. Invest. *115*, 1659–1665. https://doi.org/10.1172/JCI22521.

95. Nelson, K., Walsh, D., and Sheehan, F. (2002). Cancer and chemotherapy-related upper gastrointestinal symptoms: The role of abnormal gastric motor function and its evaluation in cancer patients. Support. Care Cancer *10*, 455–461. https://doi.org/10.1007/s00520-002-0340-9.

96. Ohe, Y., Podack, E.R., Olsen, K.J., Miyahara, Y., Miura, K., Saito, H., Koishihara, Y., Ohsugi, Y., Ohira, T., Nishio, K., et al. (1993). Interleukin-6 cdna transfected lewis lung carcinoma cells show unaltered net tumour growth rate but cause weight loss and shorten survival in syngenic mice. Br. J. Cancer *67*, 939–944. https://doi.org/10.1038/bjc.1993.174.

97. Morrison, S.D. (1972). Feeding Response to Change in Absorbable Food Fraction During Growth of Walker 256 Carcinosarcoma. Cancer Res. *32*, 968–972.

98. Plata-Salamán, C.R., Oomura, Y., and Kai, Y. (1988). Tumor necrosis factor and interleukin-1β: suppression of food intake by direct action in the central nervous system. Brain Res. *448*, 106–114. https://doi.org/10.1016/0006-8993(88)91106-7.

99. Tanaka, Y., Eda, H., Tanaka, T., Udagawa, T., Ishikawa, T., Horii, I., Ishitsuka, H., Kataoka, T., and Taguchi, T. (1990). Experimental Cancer Cachexia Induced by Transplantable Colon 26 Adenocarcinoma in Mice. Cancer Res. *50*, 2290–2295.

100. Hingorani, S.R., Wang, L., Multani, A.S., Combs, C., Deramaudt, T.B., Hruban, R.H., Rustgi, A.K., Chang, S., and Tuveson, D.A. (2005). Trp53R172H and KrasG12D cooperate to promote chromosomal instability and widely metastatic pancreatic ductal adenocarcinoma in mice. Cancer Cell *7*, 469–483. https://doi.org/10.1016/j.ccr.2005.04.023.

101. Wang, G., Biswas, A.K., Ma, W., Kandpal, M., Coker, C., Grandgenett, P.M., Hollingsworth, M.A., Jain, R., Tanji, K., López-Pintado, S., et al. (2018). Metastatic cancers promote cachexia through ZIP14 upregulation in skeletal muscle. Nat. Med. *24*, 770–781. https://doi.org/10.1038/s41591-018-0054-2.

102. Voltarelli, F.A., Frajacomo, F.T., Padilha, C.d.S., Testa, M.T.J., Cella, P.S., Ribeiro, D.F., de Oliveira, D.X., Veronez, L.C., Bisson, G.S., Moura, F.A., and Deminice, R. (2017). Syngeneic B16F10 melanoma causes cachexia and impaired skeletal muscle strength and locomotor activity in mice. Front. Physiol. *8*, 715. https://doi.org/10.3389/fphys.2017.00715.

103. Fong, Y., Moldawer, L.L., Marano, M., Wei, H., Barber, A., Manogue, K., Tracey, K.J., Kuo, G., Fischman, D.A., and Cerami, A. (1989). Cachectin/TNF redistribution or IL-1alpha induces cachexia with redistribution of body proteins. Am. J. Physiol. *256*, R659–R665.

104. Liu, Y.L., Malik, N.M., Sanger, G.J., and Andrews, P.L.R. (2006). Ghrelin alleviates cancer chemotherapy-associated dyspepsia in rodents. Cancer Chemother. Pharmacol. *58*, 326–333. https://doi.org/10.1007/s00280-005-0179-0.

105. Bibby, M.C., Double, J.A., Ali, S.A., Fearon, K.C., Brennan, R.A., and Tisdale, M.J. (1987). Characterization of a transplantable adenocarcinoma of the mouse colon producing cachexia in recipient animals. J. Natl. Cancer Inst. *78*, 539–546.

106. Grubbs, B., Rogers, W., and Cameron, I. (1979). Total parenteral nutrition and inhibition of gluconeogenesis on tumor-host responses. Oncology *36*, 216–223. https://doi.org/10.1159/000225345.

107. Figueroa-Clarevega, A., and Bilder, D. (2015). Malignant Drosophila tumors interrupt signaling to induce cachexia-like wasting. Dev. Cell *176*, 139–148. https://doi.org/10.1016/j.devcel.2015.03.001.Malignant.

108. Scarlett, J.M., Bowe, D.D., Zhu, X., Batra, A.K., Grant, W.F., and Marks, D.L. (2010). Genetic and pharmacologic blockade of central melanocortin signaling attenuates cardiac cachexia in rodent models of heart failure. J. Endocrinol. *206*, 121–130. https://doi.org/10.1677/JOE-09-0397.

109. Marks, D.L., Ling, N., and Cone, R.D. (2001). Role of the central melanocortin system in cachexia. Cancer Res. *61*, 1432–1438.

110. Kent, S., Rodriguez, F., Kelley, K.W., and Dantzer, R. (1994). Reduction in food and water intake induced by microinjection of interleukin-1β in the ventromedial hypothalamus of the rat. Physiol. Behav. *56*, 1031–1036. https://doi.org/10.1016/0031-9384(94)90339-5.

111. Lonnroth, C., Svaninger, G., Gelin, J., Cahlin, C., Iresjo, B., Cvetkovska, E., Edstrom, S., Andersson, M., Svanberg, E., and Lundholm, K. (1995). Effects related to indomethacin prolonged survival and decreased tumor growth in a mouse tumor model with cytokine dependent cancer cachexia. Int. J. Oncol. *7*, 1405–1413. https://doi.org/10.3892/ijo.7.6.1405.

112. Talbert, E.E., Cuitino, M.C., Ladner, K.J., Rajasekerea, P.V., Siebert, M., Shakya, R., Leone, G.W., Ostrowski, M.C., Paleo, B., Weisleder, N., et al. (2017). Modeling Human Cancer-Induced Cachexia. Physiol. Behav. *176*, 139–148. Modeling. https://doi.org/10.1016/j.celrep.2019.07.016.

113. White, J.P., Puppa, M.J., Narsale, A., and Carson, J.A. (2013). Characterization of the male ApcMin/+ mouse as a hypogonadism model related to cancer cachexia. Biol. Open *2*, 1346–1353. https://doi.org/10.1242/bio.20136544.

114. Wisse, B.E., Frayo, R.S., Schwartz, M.W., and Cummings, D.E. (2001). Reversal of cancer anorexia by blockade of central melanocortin receptors in rats. Endocrinology *142*, 3292–3301. https://doi.org/10.1210/endo.142.8.8324.

115. Hatter, J.A., Kouche, Y.M., Melchor, S.J., Ng, K., Bouley, D.M., Boothroyd, J.C., and Ewald, S.E. (2018). Toxoplasma gondii infection triggers chronic cachexia and sustained commensal dysbiosis in mice. PLoS One *13*, 02048955. https://doi.org/10.1371/journal.pone.0204895.

116. Hanada, T., Toshinai, K., Kajimura, N., Nara-Ashizawa, N., Tsukada, T., Hayashi, Y., Osuye, K., Kangawa, K., Matsukura, S., and Nakazato, M. (2003). Anti-cachectic effect of ghrelin in nude mice bearing human melanoma cells. Biochem. Biophys. Res. Commun. *301*, 275–279. https://doi.org/10.1016/S0006-291X(02)03028-0.

117. Rytik, P.G., Kutcherov, I.I., Muller, W.E.G., Poleschuk, N.N., Duboiskaya, G.P., Kruzo, M., and Podolskaya, I.A. (2004). Small animal model of HIV-1 infection. J. Clin. Virol. *31*, 83–87. https://doi.org/10.1016/j.jcv.2004.09.010.

118. Oudart, H., Calgari, C., Andriamampandry, M., Le Maho, Y., and Malan, A. (1995). Stimulation of brown adipose tissue activity in tumor-bearing rats. Can. J. Physiol. Pharmacol. *73*, 1625–1631. https://doi.org/10.1139/y95-724.

119. Rohm, M., Schäfer, M., Laurent, V., Üstünel, B.E., Niopek, K., Algire, C., Hautzinger, O., Sijmonsma, T.P., Zota, A., Medrikova, D., et al. (2016). An AMP-activated protein kinase-stabilizing peptide ameliorates adipose tissue wasting in cancer cachexia in mice. Nat. Med. *22*, 1120–1130. https://doi.org/10.1038/nm.4171.

120. Tsoli, M., Moore, M., Burg, D., Painter, A., Taylor, R., Lockie, S.H., Turner, N., Warren, A., Cooney, G., Oldfield, B., et al. (2012). Activation of thermogenesis in brown adipose tissue and dysregulated lipid metabolism associated with cancer cachexia in mice. Cancer Res. *72*, 4372–4382. https://doi.org/10.1158/0008-5472.CAN-11-3536.

121. Plumb, J.A., Fearon, K.C., Carter, K.B., and Preston, T. (1991). Energy expenditure and protein synthesis rates in an animal model of cancer cachexia. Clin. Nutr. *10*, 23–29. https://doi.org/10.1016/0261-5614(91)90077-.

122. Beck, S.A., and Tisdale, M.J. (2004). Effect of cancer cachexia on triacylglycerol/fatty acid substrate cycling in white adipose tissue. Lipids *39*, 1187–1189. https://doi.org/10.1007/s11745-004-1346-8.

123. O'Connell, T.M., Ardeshirpour, F., Asher, S.A., Winnike, J.H., Yin, X., George, J., Guttridge, D.C., He, W., Wysong, A., Willis, M.S., and Couch, M.E. (2008). Metabolomic analysis of cancer cachexia reveals distinct lipid and glucose alterations. Metabolomics *4*, 216–225. https://doi.org/10.1007/s11306-008-0113-7.

124. Morigny, P., Zuber, J., Haid, M., Kaltenecker, D., Riols, F., Lima, J.D.C., Simoes, E., Otoch, J.P., Schmidt, S.F., Herzig, S., et al. (2020). High levels of modified ceramides are a defining feature of murine and human cancer cachexia. J. Cachexia Sarcopenia Muscle *11*, 1459–1475. https://doi.org/10.1002/jcsm.12626.

125. Bilder, D., Ong, K., Hsi, T.C., Adiga, K., and Kim, J. (2021). Tumour–host interactions through the lens of Drosophila. Nat. Rev. Cancer *21*, 687–700. https://doi.org/10.1038/s41568-021-00387-5.

126. Liu, Y., Li, J.S.S., Rodiger, J., Comjean, A., Attrill, H., Antonazzo, G., Brown, N.H., Hu, Y., and Perrimon, N. (2022). FlyPhoneDB: an integrated web-based resource for cell–cell communication prediction in Drosophila. Genetics *220*, iyab235. https://doi.org/10.1093/genetics/iyab235.

127. Droujinine, I.A., Meyer, A.S., Wang, D., Udeshi, N.D., Hu, Y., Rocco, D., McMahon, J.A., Yang, R., Guo, J., Mu, L., et al. (2021). Proteomics of protein trafficking by in vivo tissue-specific labeling. Nat. Commun. *12*, 2382. https://doi.org/10.1038/s41467-021-22599-x.

128. Christensen, H.M., Kistorp, C., Schou, M., Keller, N., Zerahn, B., Frystyk, J., Schwarz, P., and Faber, J. (2013). Prevalence of cachexia in chronic heart failure and characteristics of body composition and metabolic status. Endocrine *43*, 626–634. https://doi.org/10.1007/s12020-012-9836-3.

129. Gomes-Marcondes, M.C.c., Smith, H.J., Cooper, J.C., and Tisdale, M.J. (2002). Development of an in-vitro model system to investigate the mechanism of muscle protein catabolism induced by proteolysis-inducing factor. Br. J. Cancer *86*, 1628–1633. https://doi.org/10.1038/sj.bjc.6600236.

130. Inaba, S., Hinohara, A., Tachibana, M., Tsujikawa, K., and Fukada, S.I. (2018). Muscle regeneration is disrupted by cancer cachexia without loss of muscle stem cell potential. PLoS One *13*, 02054677. https://doi.org/10.1371/journal.pone.0205467.

131. Shahriyari, M., Islam, M.R., Sakib, S.M., Rinn, M., Rika, A., Krüger, D., Kaurani, L., Gisa, V., Winterhoff, M., Anandakumar, H., et al. (2022). Engineered skeletal muscle recapitulates human muscle development, regeneration and dystrophy. J. Cachexia Sarcopenia Muscle *13*, 3106–3121. https://doi.org/10.1002/jcsm.13094.

132. Williams, J.P., Phillips, B.E., Smith, K., Atherton, P.J., Rankin, D., Selby, A.L., Liptrot, S., Lund, J., Larvin, M., and Rennie, M.J. (2012). Effect of tumor burden and subsequent surgical resection on skeletal muscle mass and protein turnover in colorectal cancer patients. Am. J. Clin. Nutr. *96*, 1064–1070. https://doi.org/10.3945/ajcn.112.045708.

133. Crawford, J., Prado, C.M.M., Johnston, M.A., Gralla, R.J., Taylor, R.P., Hancock, M.L., and Dalton, J.T. (2016). Study Design and Rationale for the Phase 3 Clinical Development Program of Enobosarm, a Selective Androgen Receptor Modulator, for the Prevention and Treatment of Muscle Wasting in Cancer Patients (POWER Trials). Curr. Oncol. Rep. *18*, 37. https://doi.org/10.1007/s11912-016-0522-0.

134. Temel, J.S., Abernethy, A.P., Currow, D.C., Friend, J., Duus, E.M., Yan, Y., and Fearon, K.C. (2016). Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. Lancet Oncol. *17*, 519–531. https://doi.org/10.1016/S1470-2045(15)00558-6.

135. Loprinzi, C.L., Kugler, J.W., Sloan, J.A., Mailliard, J.A., Krook, J.E., Wilwerding, M.B., Rowland, K.M., Camoriano, J.K., Novotny, P.J., Christensen, B.J., et al. (1999). Randomized Comparison of Megestrol Acetate Versus Dexamethasone Versus Fluoxymesterone for the Treatment of Cancer Anorexia/Cachexia. J. Clin. Oncol. *17*, 3299–3306.

136. Nelson, K., Walsh, D., Deeter, P., and Sheehan, F. (1994). A phase II study of delta-9-tetrahydrocannabinol for appetite stimulation in cancer-associated anorexia. J. Palliat. Care *10*, 14–18. https://doi.org/10.1177/082585979401000105.

137. Fearon, K.C.H., Barber, M.D., Moses, A.G., Ahmedzai, S.H., Taylor, G.S., Tisdale, M.J., and Murray, G.D. (2006). Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. J. Clin. Oncol. *24*, 3401–3407. https://doi.org/10.1200/JCO.2005.04.5724.

138. Blum, D., Hertler, C., Oberholzer, R., Wolf-Linder, S., Joerger, M., Driessen, C., and Strasser, F. (2022). Lenalidomide in cancer cachexia: a randomized trial of an anticancer drug applied for anti-cachexia. JCSM Rapid Communications *5*, 68–76. https://doi.org/10.1002/rco2.54.

139. Gresham, G., Placencio-Hickok, V.R., Lauzon, M., Nguyen, T., Kim, H., Mehta, S., Paski, S., Pandol, S.J., Osipov, A., Gong, J., et al. (2021). Feasibility and efficacy of enteral tube feeding on weight stability, lean body mass, and patient-reported outcomes in pancreatic cancer cachexia. J. Cachexia Sarcopenia Muscle *12*, 1959–1968. https://doi.org/10.1002/jcsm.12799.

140. Amano, K., Maeda, I., Ishiki, H., Miura, T., Hatano, Y., Tsukuura, H., Taniyama, T., Matsumoto, Y., Matsuda, Y., Kohara, H., et al. (2021). Effects of enteral nutrition and parenteral nutrition on survival in patients with advanced cancer cachexia: Analysis of a multicenter prospective cohort study. Clin. Nutr. *40*, 1168–1175. https://doi.org/10.1016/j.clnu.2020.07.027.

141. Morigny, P., Kaltenecker, D., Zuber, J., Machado, J., Mehr, L., Tsokanos, F.F., Kuzi, H., Hermann, C.D., Voelkl, M., Monogarov, G., et al. (2021). Association of circulating PLA2G7 levels with cancer cachexia and assessment of darapladib as a therapy. J. Cachexia Sarcopenia Muscle *12*, 1333–1351. https://doi.org/10.1002/jcsm.12758.

142. Cespedes Feliciano, E.M., Popuri, K., Cobzas, D., Baracos, V.E., Beg, M.F., Khan, A.D., Ma, C., Chow, V., Prado, C.M., Xiao, J., et al. (2020). Evaluation of automated computed tomography segmentation to assess body composition and mortality associations in cancer patients. J. Cachexia Sarcopenia Muscle *11*, 1258–1269. https://doi.org/10.1002/jcsm.12573.

143. Askren, M.K., Jung, M., Berman, M.G., Zhang, M., Therrien, B., Peltier, S., Ossher, L., Hayes, D.F., Reuter-Lorenz, P.A., and Cimprich, B. (2014). Neuromarkers of Fatigue and Cognitive Complaints Following Chemotherapy for Breast Cancer: A Prospective fMRI Investigation. Breast Cancer Res. Treat. *147*, 445–455. https://doi.org/10.1007/s10549-014-3092-6.Neuromarkers.

144. Mitamura, A., Kaneta, T., Miyata, G., Takanami, K., Hiraide, T., Fukuda, H., Takahashi, S., and Satomi, S. (2011). Positive correlations between tumor uptake on FDG PET and energy expenditure of patients with esophageal cancer. Ann. Nucl. Med. *25*, 241–246. https://doi.org/10.1007/s12149-010-0456-9.

145. Nakamoto, R., Okuyama, C., Ishizu, K., Higashi, T., Takahashi, M., Kusano, K., Kagawa, S., and Yamauchi, H. (2019). Diffusely Decreased Liver Uptake on FDG PET and Cancer-Associated Cachexia With Reduced Survival. Clin. Nucl. Med. *44*, 634–642. https://doi.org/10.1097/RLU.0000000000002658.

146. Murphy, J., Simonyan, D., and Penafuerte, C. (2021). Cancer anorexia-cachexia syndrome is characterized by more than one inflammatory pathway. Poster Present. 6th Annu. Cancer Cachexia Conf. Bridg. Mol. Adv. to Clin. Care.

147. Kays, J.K., Shahda, S., Stanley, M., Bell, T.M., O'Neill, B.H., Kohli, M.D., Couch, M.E., Koniaris, L.G., and Zimmers, T.A. (2018). Three cachexia phenotypes and the impact of fat-only loss on survival in FOLFIRINOX therapy for pancreatic cancer. J. Cachexia Sarcopenia Muscle *9*, 673–684. https://doi.org/10.1002/jcsm.12307.

148. Patton, R., Cook, J., Haraldsdottir, E., Brown, D., Dolan, R.D., McMillan, D.C., Skipworth, R.J.E., Fallon, M., and Laird, B.J.A. (2021). REVOLUTION (Routine EValuatiOn of people LivIng with caNcer)—Protocol for a prospective characterisation study of patients with incurable cancer. PLoS One *16*, e0261175–e0261179. https://doi.org/10.1371/journal.pone.0261175.

149. Roeland, E.J., Ma, J.D., Nelson, S.H., Seibert, T., Heavey, S., Revta, C., Gallivan, A., and Baracos, V.E. (2017). Weight loss versus muscle loss: re-evaluating inclusion criteria for future cancer cachexia interventional

trials. Support. Care Cancer *25*, 365–369. https://doi.org/10.1007/s00520-016-3402-0.

150. Fearon, K.C., Voss, A.C., and Hustead, D.S.; Cancer Cachexia Study Group (2006). Definition of cancer cachexia: Effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am. J. Clin. Nutr. *83*, 1345–1350. https://doi.org/10.1093/ajcn/83.6.1345.

151. Silva, G.A.d., Wiegert, E.V.M., Calixto-Lima, L., and Oliveira, L.C. (2020). Clinical utility of the modified Glasgow Prognostic Score to classify cachexia in patients with advanced cancer in palliative care. Clin. Nutr. *39*, 1587–1592. https://doi.org/10.1016/j.clnu.2019.07.002.

152. Hickish, T., Andre, T., Wyrwicz, L., Saunders, M., Sarosiek, T., Kocsis, J., Nemecek, R., Rogowski, W., Lesniewski-Kmak, K., Petruzelka, L., et al. (2017). MABp1 as a novel antibody treatment for advanced colorectal cancer: a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. *18*, 192–201. https://doi.org/10.1016/S1470-2045(17)30006-2.