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Review

Cancer cachexia: A tumor-driven disorder of whole-body homeostasis

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SUMMARY

Cancer cachexia is a systemic metabolic syndrome driven by tumor-induced disruption of whole-body homeostasis. Characterized by skeletal muscle atrophy and adipose tissue loss, cachexia leads to functional decline, impaired quality of life, reduced treatment tolerance, and poor survival across multiple malignancies. Emerging evidence indicates that cachexia arises from complex and dynamic interactions between tumors and host organ systems, including immune, metabolic, endocrine, and neural networks, that collectively reshape energy balance, immune function, and tissue integrity. Despite its profound clinical impact, effective therapies remain limited, reflecting incomplete mechanistic understanding and the absence of integrated clinical frameworks. Here, we review recent advances in cachexia biology, including tumor-host signaling, multiorgan metabolic remodeling, and neuroendocrine regulation. We further propose a tumor-centric framework in which cachexia represents a progressive collapse of systemic homeostasis and outline translational strategies to guide mechanism-informed therapeutic interventions.

INTRODUCTION: CANCER CACHEXIA AS A DISORDER OF WHOLE-BODY HOMEOSTASIS

Cancer cachexia is a multifactorial metabolic syndrome affecting up to 80% of patients with advanced malignancies and contributing to approximately 20%–30% of cancer-related deaths.[1,2] Beyond involuntary weight loss or malnutrition, cachexia is increasingly recognized as a tumor-driven disorder of whole-body homeostasis, characterized by progressive skeletal muscle wasting, adipose tissue loss, anorexia, systemic inflammation, and global metabolic reprogramming.[3] These systemic alterations drive functional decline, impair quality of life, limit tolerance to anticancer therapies, compromise immunity, and accelerate mortality across multiple cancer types.[4,5] Unlike starvation or age-related muscle atrophy, cancer cachexia arises from active tumor-host signaling networks that disrupt physiological regulatory systems across multiple organs.[6] Tumors secrete inflammatory cytokines, hormones, metabolites, and extracellular vesicles (EVs) that perturb central and peripheral control of energy balance and tissue integrity.[7] In response, host tissues, including skeletal muscle, adipose tissue, liver, immune system, and central nervous system (CNS), enter maladaptive states that amplify catabolic signaling and propagate systemic metabolic instability, reinforcing a cycle of progressive homeostatic failure.[8]

Despite the prevalence and profound clinical consequences, cancer cachexia remains underdiagnosed and largely untreatable in routine oncology practice.[9] Therapeutic limitations partially reflect the historical tendency to study cachexia through isolated organs or single pathways, rather than as an integrated systemic disorder.[1] Recent advances in tumor-host interaction biology, neuroendocrine regulation, immunometabolism, and spatial and multi-omics technologies now enable a more comprehensive understanding of how tumors orchestrate multiorgan dysfunction at the systemic level.[10] Importantly, although the clinical presentation and severity of cachexia vary across malignancies, many cachexia-prone tumors share inflammatory, metabolic, and endocrine programs that predispose them to drive systemic catabolic stress.

In this review, we present a tumor-centric, systems-level framework for cancer cachexia as a disorder of whole-body homeostasis (Figure 1). We first examine how tumor-derived signals initiate systemic metabolic and inflammatory dysregulation, followed by discussion of how these signals reshape host metabolic, immune, and neuroendocrine networks across organs. Finally, we highlight emerging biomarkers, therapeutic strategies, and translational opportunities that may enable earlier detection and more effective intervention in cancer-associated cachexia.

TUMOR AS THE PRIMARY DRIVER OF SYSTEMIC DYSREGULATION

Cancer cachexia is increasingly recognized as a tumor-initiated systemic disorder rather than just a secondary consequence of malnutrition or advanced disease.[11] Cachexia-inducing tumors

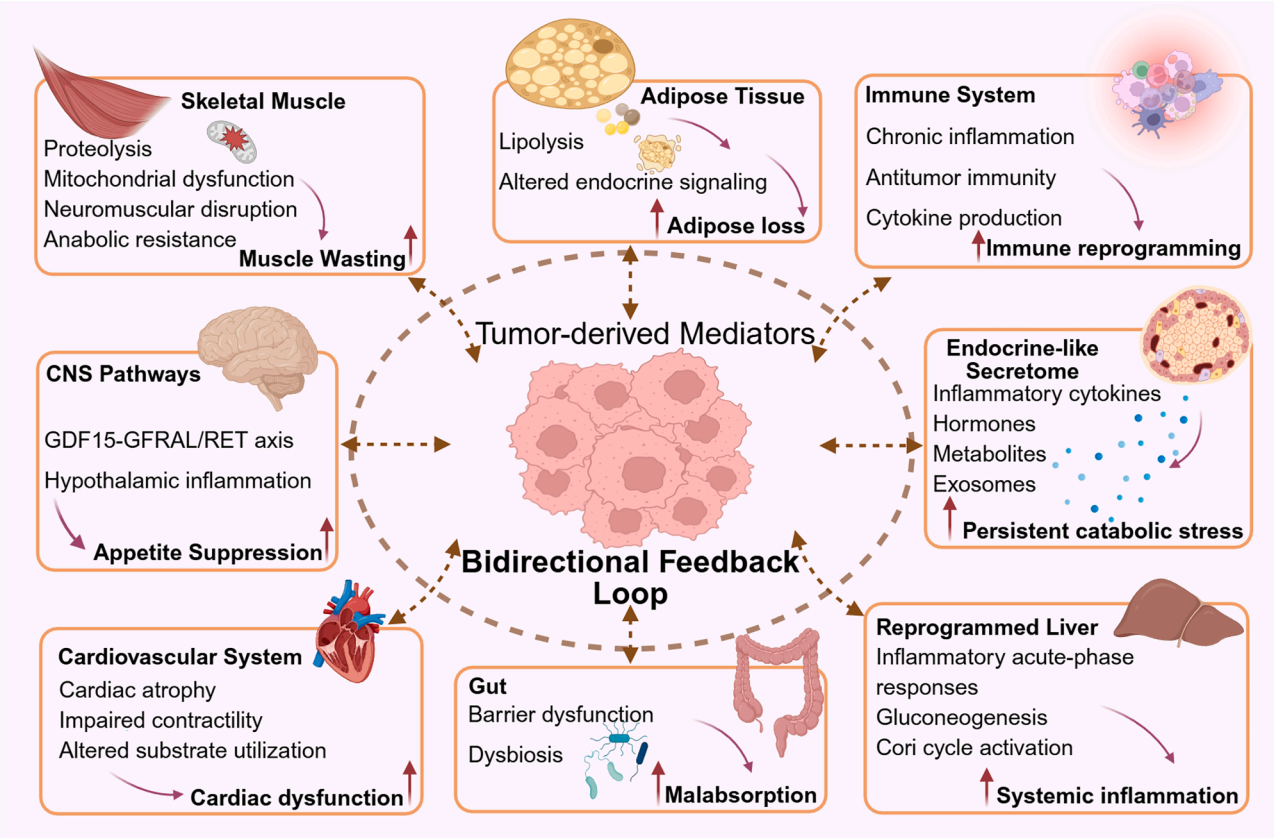

Figure 1. Tumor-driven multiorgan circuits underlying cancer cachexia

This schematic illustrates cancer cachexia as a tumor-driven disorder of whole-body homeostasis resulting from coordinated dysfunction across multiple host organ systems. Tumors act as central signaling hubs, releasing cytokines, hormones, metabolites, and extracellular vesicles (EVs) that impose persistent systemic stress. In response, organs including skeletal muscle, adipose tissue, liver, immune system, central nervous system (CNS), digestive system, and cardiovascular system undergo maladaptive changes that disrupt circuits regulating appetite, energy balance, and metabolism. These tumor-induced, maladaptive organ responses interact through bidirectional feedback loops that reinforce systemic inflammation, metabolic instability, and tissue wasting. Collectively, these multiorgan circuits drive the progressive collapse of physiological homeostasis that defines cancer cachexia.

actively disrupt metabolic, immune, and neuroendocrine homeostasis through coordinated secretion of catabolic mediators and profound metabolic rewiring.[1,12] In this context, the tumor functions as an aberrant endocrine and metabolic organ, imposing organism-wide stress that initiates and sustains progressive tissue wasting, inflammation, and functional decline.

Tumor-derived catabolic factors: A multifaceted secretome

A defining feature of cachexia-prone tumors is the production of a complex and biologically potent catabolic secretome.[13] Pro-inflammatory cytokines, including members of the interleukin 6 (IL-6) family, tumor necrosis factor-alpha (TNF-α), and interleukin 1β (IL-1β), are central drivers of systemic inflammation, promoting hepatic acute-phase responses (APRs), adipose lipolysis, and skeletal muscle proteolysis in preclinical models or in patients with cancer cachexia.[14–20] Beyond soluble cytokines, tumor-derived extracellular stress mediators represent an additional mechanism of systemic signaling in cancer cachexia. Danger-associated molecular pattern (DAMP) proteins such as HSP70 and HSP90 can activate innate immune pathways and induce skeletal muscle proteolysis through toll-like receptor 4 (TLR4) signaling in experimental systems.[21–25] These mediators have also been identified within EV-enriched fractions from tumor-bearing models. For example, ZIP4-driven pancreatic ductal adenocarcinoma (PDAC) promotes RAB27B-dependent release of EV-associated HSP70 and HSP90 capable of activating TLR4-dependent muscle catabolic signaling.[21] Similar wasting phenotypes can be reproduced using purified DAMP proteins, suggesting that while the biological activity of the cargo is clearly established, EVs likely represent an important and physiologically relevant delivery platform, although their quantitative and context-specific contribution requires further investigation.

Tumors also secrete endocrine-like mediators that couple peripheral catabolism to central neuroendocrine dysregulation. Growth differentiation factor 15 (GDF15) induces anorexia through activation of hindbrain GDNF family receptor alpha-like (GFRAL) signaling pathways.[26,27] Additionally, members of the transforming growth factor β (TGF-β) superfamily, such as activin A, promote muscle wasting by suppressing anabolic signaling and activating proteolytic pathways.[16,28] GDF15 is a stress-induced hormone that promotes adipose lipolysis and increases energy expenditure by enhancing fatty acid oxidation in white adipose tissue, often through β-adrenergic signaling and muscle-fat metabolic

crosstalk.[29–31] Many systemic effects are mediated through the canonical GFRAL pathway, linking central appetite regulation to whole-body metabolic adaptation. GDF15 can also regulate hepatic sympathetic outflow and triglyceride metabolism during inflammatory stress, connecting it to peripheral fuel handling.[32] Additionally, muscle-derived GDF15 drives systemic metabolic remodeling during mitochondrial stress, influencing adipose metabolism and insulin sensitivity, with some endocrine effects potentially occurring independently of GFRAL.[33,34] Non-receptor-mediated mechanisms, including activation of the hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoid release, have also been suggested in animal models.[35] However, further work is required to clarify the physiological relevance and alternative mechanisms underlying these observations in human disease.

Leukemia inhibitory factor (LIF), an IL-6 family cytokine, contributes to inflammatory signaling that promotes adipose tissue lipolysis and systemic metabolic remodeling in cancer cachexia.[36] While parathyroid hormone-related protein (PTHrP) induces adipose tissue browning and thermogenic activation, increasing whole-body energy expenditure in tumor-bearing Lewis lung carcinoma mouse models of cancer cachexia.[37] However, the relevance of this mechanism in humans remains uncertain, as a retrospective analysis of cancer patients using F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging found that brown adipose tissue was not associated with cachexia or increased mortality.[38] Collectively, these tumor-derived signals impose persistent systemic stress in which normally adaptive inflammatory and metabolic pathways become chronically activated and maladaptive. Mechanistically, pro-inflammatory cytokines, EV-mediated signaling, and TGF-β superfamily pathways converge on shared intracellular catabolic networks. Cytokines such as IL-6 activate Janus Kinase (JAK)-Signal Transducer and Activator of Transcription 3 (STAT3) signaling to drive skeletal muscle wasting, whereas TNF-α and related inflammatory cytokines activate NF-κB-dependent catabolic programs in skeletal muscle; IL-6 has also been causally linked to experimental cancer cachexia and systemic inflammation.[14,20,39] Tumor-derived EVs further propagate cachectic signaling by transferring bioactive cargo to distant tissues, promoting muscle catabolism and adipose metabolic remodeling.[21] In parallel, TGF-β superfamily ligands such as activins and myostatin activate SMAD2/3 signaling that suppresses insulin growth factor (IGF)-1-AKT-mTOR anabolic pathways and promotes muscle atrophy.[40] Convergence of STAT3, NF-κB, and SMAD transcriptional programs creates feedforward signaling loops that stabilize the systemic catabolic state characteristic of cancer cachexia. Importantly, cachexia-inducing secretomes differ substantially across cancer types. For example, pancreatic, lung, and gastric cancers are enriched for catabolic mediators, including inflammatory cytokines and cachexia-associated factors such as IL-6 family cytokines, GDF15, and LIF. Pan-cancer transcriptomic and functional studies indicate that these tumors exhibit stronger cachexia-associated secretory programs, reflecting intrinsic differences in oncogenic signaling, stromal composition, and inflammatory pathways.[41,42] Proteomic, single-cell, and spatial transcriptomic analyses further show that cachexia-prone tumors contain distinct fibroblast and immune subpopulations that amplify cytokine production and systemic metabolic stress.[43,44] Tumor-specific genetic and epigenetic features, together with distinct secretory and microenvironmental programs, influence cachexia susceptibility and highlight cancer cell-autonomous determinants that predispose certain tumor types to drive systemic catabolism.[41,45]

Tumor metabolism and nutrient competition

Tumor-intrinsic metabolic rewiring is a defining feature of cancer biology and contributes to systemic metabolic stress in cancer cachexia. Cancer cells exhibit heightened glycolysis, altered lipid metabolism, and increased amino acid consumption, reshaping systemic nutrient flux and diverting energy substrates toward tumor growth.[46] Amplification of the Cori cycle, whereby tumor-derived lactate is reconverted to glucose in the liver at substantial energetic cost, further exacerbates whole-body energy inefficiency and accelerates metabolic exhaustion.[47] Tumor uptake of glucose, branched-chain amino acids, and lipids may deprive skeletal muscle and adipose tissue of substrates required for tissue maintenance and repair.[48] Recent studies further demonstrate that tumor metabolic stress can induce acetyl-Coenzyme A synthetase 2 (ACSS2), enhancing tumor nutrient scavenging via macropinocytosis while simultaneously promoting skeletal muscle wasting, thereby coupling host tissue catabolism to tumor metabolic fitness.[49]

However, despite these mechanistic observations, quantitative human evidence demonstrating that tumor metabolic demand alone accounts for the magnitude of systemic weight and muscle loss remains limited.[50,51] Imaging-based metabolic measurements, including PET, reflect regional substrate uptake but do not directly establish organism-level caloric drain or distinguish direct energetic competition from host-mediated metabolic responses to inflammation and neuroendocrine stress.[52–54] A conservative interpretation is therefore that tumor metabolism functions as a context-dependent modifier of cachexia, particularly in settings of high tumor burden or rapidly progressive disease, where it may amplify systemic metabolic inefficiency and accelerate wasting once catabolic pathways are established.

By contrast, the most consistent clinical evidence indicates that negative energy balance, frequently driven by reduced nutritional intake, represents a common early manifestation of cancer cachexia.[1,55] Reduced intake often emerges early during disease progression and temporally parallels weight loss across multiple cachexia-prone malignancies. Even modest caloric deficits can be compounded by inflammation-associated anabolic resistance and altered substrate utilization, leading to progressive tissue catabolism.[56] Importantly, these host metabolic disturbances arise within the broader context of tumor-driven systemic signaling. Thus, current evidence supports a model in which tumor-initiated inflammatory, neuroendocrine, and metabolic reprogramming promotes reduced intake and impaired energy utilization. While tumor metabolic rewiring further amplifies systemic energy imbalance rather than serving as a universal primary trigger of cachexia initiation. Notably, the degree of reduced energy intake is variable and dependent on tumor type, stage, and symptom burden in clinical studies of cancer patients.[57]

Tumor-driven immune reprogramming

Tumor-driven immune reprogramming represents a central mechanism linking local malignancy to the systemic metabolic collapse characteristic of cancer cachexia. Cachexia-inducing tumors

reshape the immune landscape toward a myeloid-dominant inflammatory state, with increased recruitment and activation of monocytes and macrophages that amplify tumor-associated inflammation rather than simply responding to tissue wasting.[58,59] In PDAC, this process has been defined more directly, as tumor cells recruit macrophages through the CCL2-CCR2 axis, and these macrophages in turn stimulate tumor-cell TWEAK production through CCL5/TRAF6/NF-κB signaling, establishing a feedforward tumor-macrophage circuit that promotes cachexia progression.[44] Tumor-driven immune reprogramming also extends beyond the tumor microenvironment. In cancer cachexia, increased hepatic myeloid-cell infiltration and activation of the inflammasome/IL-1β pathway have been observed in rodent models and human liver samples, indicating that immune remodeling in peripheral metabolic organs contributes to systemic inflammation.[60] In addition to soluble chemokines and cytokines, tumor-derived EVs provide a second route for immune activation.[25] Together, these studies support a concise model in which tumor-driven immune reprogramming sustains cachexia through a limited set of interacting mechanisms, such as myeloid-cell recruitment, macrophage-tumor feedforward signaling, peripheral immune remodeling, and EV-mediated innate immune activation.

Importantly, immune dysfunction acts as both a cause and a consequence of cachexia. While tumor-driven immune activation initiates catabolic signaling, progressive loss of muscle and adipose mass feeds back to impair immune cell metabolic fitness, limiting the energetic capacity required for effective T cell responses and promoting immune exhaustion.[61] This reciprocal relationship establishes a feedforward loop in which immune suppression facilitates tumor progression, further intensifying tumor-derived inflammatory and catabolic signaling and reinforcing sustained metabolic decline in the host.

Tumor-type heterogeneity in cancer cachexia

Cancer cachexia displays substantial heterogeneity across malignancies in prevalence, timing, and dominant biological drivers, reflecting differences in tumor secretory programs, metabolic wiring, and tumor-host organ interactions.[62] PDAC represents a prototypical cachexia-prone malignancy characterized by early and severe wasting driven by a potent inflammatory and endocrine secretome, stromal-immune amplification, and extensive tumor metabolic rewiring.[63,64] Lung cancers similarly exhibit high cachexia prevalence associated with inflammatory signaling and neuroendocrine dysregulation of appetite and energy balance.[65–68] In contrast, upper gastrointestinal cancers often combine tumor-derived inflammatory signaling with impaired nutrient intake,[69,70] whereas colorectal cancer shows more heterogeneous cachexia linked to systemic inflammation and metastatic burden.[71,72] Despite these differences, cachexia-prone tumors commonly display strong inflammatory signaling, metabolic stress, and interactions with metabolically critical organs, collectively overwhelming host homeostatic capacity and driving systemic tissue wasting.[3]

MULTIORGAN RESPONSE: UNRAVELING OF HOMEOSTASIS

Cancer cachexia arises not from failure of a single organ, but from coordinated dysfunction across multiple host systems responding to persistent tumor-derived stress. Skeletal muscle, adipose tissue, liver, CNS, immune compartments, heart, and the gut undergo maladaptive remodeling that collectively drives collapse of systemic homeostasis. Each organ contributes distinct metabolic and functional derangements, yet these responses are highly interconnected, forming an integrated catabolic network that accelerates clinical decline signals.[73] Understanding cachexia through this multiorgan lens is essential for developing effective, system-level therapeutic strategies.

Skeletal muscle: A central effector of systemic catabolism

Skeletal muscle wasting is often the most prominent and clinically debilitating feature of cancer cachexia. Clinically, muscle atrophy/loss corresponds with worsening physical function, higher symptom burden, and impaired quality of life.[4,5] Muscle loss reflects an imbalance between protein degradation and synthesis, driven predominantly by activation of the ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway.[74] E3 ubiquitin ligases, such as MuRF1 and atrogin-1, promote targeted proteolysis, while autophagy contributes to clearance of proteins and damaged organelles.[75] Tumor-derived cytokines, activin A, and inflammatory signals converge on transcriptional regulators including FoxO, NF-κB, C/EBPβ, and STAT3 to activate these catabolic programs.[76] Concurrently, mitochondrial dysfunction is an early feature of cancer cachexia, characterized by impaired oxidative phosphorylation, altered mitochondrial dynamics, and increased oxidative stress that reduce ATP production and sensitize muscle to catabolic signaling. In tumor-bearing mice, skeletal muscle shows mitochondrial respiratory defects and reduced electron transport chain activity before overt atrophy, indicating early metabolic stress.[77] Cachectic muscle also exhibits impaired mitochondrial quality control and mitophagy, leading to accumulation of dysfunctional mitochondria and activation of proteolytic pathways.[78] Inflammatory signaling further aggravates these defects; IL-6 suppresses mitochondrial biogenesis and oxidative metabolism through inhibition of PGC-1α and mitochondrial fusion pathways.[79] Importantly, similar abnormalities have been observed in patients with cancer-associated weight loss, whose skeletal muscle displays reduced oxidative capacity and impaired ATP production, supporting the clinical relevance of mitochondrial dysfunction in cachexia.[80] Collectively, these findings position mitochondrial impairment as a key contributor to energetic stress and activation of muscle proteolysis in cancer cachexia.

In addition, PDAC-associated muscle wasting is mediated by local complement (C3) activation in skeletal muscle, which drives immune cell infiltration, fibrotic remodeling, and activation of proteolytic pathways culminating in myofiber atrophy and dysfunction.[81] Notably, C3 and TLR4 exhibit significant functional crosstalk within the innate immune response.[82] Disruption of neuromuscular junction (NMJ) integrity, impaired satellite cell regeneration, and restricted amino acid availability further exacerbate muscle atrophy, leading to progressive loss of strength and functional capacity.[83,84] The complex array of extracellular mediators of cancer cachexia converges in muscle cells to activate transcription factor C/EBPβ that has the unique capacity to

upregulate multiple rate-limiting genes in the proteolytic pathways, including those encoding E3 ligases atrogin1/MAFbx and UBR2, as well as autophagy-related genes LC3b and Gabarapl1, resulting in increased protein degradation.[85–87] UBR2 specifically ubiquitylates the fast isoforms of myosin heavy chain (fMHC), MHC-IIb, and MHC-IIx, for degradation by the 26S proteasome, which is responsible for the preferential loss of fast muscle fibers induced by a cancer burden.[88] C/EBPβ is specifically activated by p38β mitogen-activated protein kinase (MAPK) in cooperation with p300.[89–91] In addition, p38β MAPK activates autophagy by phosphorylating ULK1 independent of AMPK.[85] These signaling events of p38β MAPK have been verified in the cachectic muscle of cancer patients.[92,93] Consequently, selective inhibition of p38β MAPK with nilotinib attenuates muscle wasting and prolongs survival in murine models of cancer cachexia.[91] Therefore, highly specific p38β MAPK inhibitors may provide a unique therapeutic opportunity for cancer-induced muscle wasting.

Adipose tissue: Lipolysis, browning, and thermogenic stress

Adipose tissue loss often represents an early event in cancer cachexia and can precede overt skeletal muscle wasting, reflecting an early shift toward systemic negative energy balance and altered fuel partitioning.[1] Tumor- and host-derived inflammatory cues, together with increased sympathetic β-adrenergic signaling, activate the canonical lipolytic machinery in adipocytes, particularly adipose triglyceride lipase (ATGL/PNPLA2) and hormone-sensitive lipase (HSL/LIPE). This activation accelerates triglyceride breakdown, releasing free fatty acids and glycerol that fuel hepatic gluconeogenesis and exacerbate systemic metabolic stress.[94]

Beyond lipolysis, a hallmark metabolic feature in many cachexia models is "browning" of white adipose tissue, characterized by induction of a beige/thermogenic program with UCP1 expression and mitochondrial biogenesis in cachectic mice, which increases energy expenditure and amplifies host energy wasting.[37,95] Tumor-induced metabolic reprogramming of adipocytes can further promote energy-wasting cycles, Röhm et al. reported that tumor-associated signaling activates futile metabolic cycling and AMPK-dependent energy stress in adipocytes, contributing to adipose tissue loss during cancer cachexia.[96] However, evidence for adipose browning in human cachexia remains limited and inconsistent. Imaging-based studies have produced mixed results, Becker et al., using longitudinal FDG-PET/computed tomography (CT) analyses, found that brown adipose tissue activity in cancer patients was largely associated with environmental temperature and patient characteristics rather than cancer-associated weight loss,[97] while Eljalby et al. reported in a retrospective FDG-PET cohort that brown adipose tissue presence was not associated with cachexia or mortality in patients.[38] These findings highlight important species- and context-dependent differences between experimental models and human disease. Cachexia-associated adipose remodeling also alters endocrine output, including leptin, adiponectin, and broader adipokine networks, contributing to insulin resistance and reinforcing adipose-liver-muscle crosstalk that sustains systemic catabolism.[98–100]

Liver and systemic metabolism: Energy drain and acute-phase bias

The liver serves as a central metabolic hub in cancer cachexia, integrating tumor- and host-derived inflammatory signals with systemic nutrient flux. Tumor-induced cytokines, particularly IL-6 family members, drive a sustained hepatic APR, redirecting hepatic protein synthesis toward acute-phase reactants, such as C-reactive protein (CRP), fibrinogen, and serum amyloid A, at the expense of constitutive protein production. Although adaptive during acute infection or injury, chronic APR activation in cancer cachexia imposes a substantial energetic and nitrogen burden, reinforcing systemic inflammation and accelerating skeletal muscle proteolysis to supply hepatic amino acids.[101] Concurrently, hepatic gluconeogenesis is increased in cancer cachexia, supported by enhanced delivery of substrates from peripheral tissues, including alanine and glutamine from muscle proteolysis, glycerol from adipose lipolysis, and lactate recycled through the Cori cycle.[46] Hepatic conversion of lactate to glucose consumes more ATP than is generated by tumor glycolysis, and the sustained Cori-cycle flux creates a net energetic drain on the host and contributes to negative energy balance and progressive wasting. Additional hepatic alterations, including mitochondrial dysfunction, dysregulated lipid handling, impaired ketogenesis, and insulin resistance, further destabilize whole-body metabolic homeostasis and link liver inflammation to multiorgan catabolic progression in cancer cachexia.[101]

CNS: Neuroendocrine influence on appetite and energy balance

The CNS integrates peripheral inflammatory and metabolic cues to help coordinate appetite, energy expenditure, autonomic output, and sickness/motivational behaviors.[102] In cachexia, circulating cytokines and tumor-derived inflammatory signals trigger hypothalamic neuroinflammation, particularly within mediobasal hypothalamic circuits, characterized by microglial activation and cytokine induction. These changes disrupt the balance between orexigenic (Agouti-Related Peptide [AgRP]/Neuropeptide Y [NPY]) and anorexigenic (Pro-opiomelanocortin [POMC]/Cocaine- and amphetamine-regulated transcript [CART]) pathways while activating neuroendocrine stress programs, including the HPA axis, which increases glucocorticoid signaling and reinforces peripheral catabolism and muscle wasting in animal models.[103,104] Additionally, central inflammatory signaling involving TNF-α can directly regulate hypothalamic pathways controlling energy expenditure and feeding; Arruda et al. showed that hypothalamic TNF-α signaling increases thermogenesis and suppresses food intake, linking inflammatory signaling to metabolic dysregulation in cachexia.[105]

A cachexia-associated anorexia pathway involves GDF15 signaling through GFRAL-Rearranged during Transfection(RET) receptor complex in the area postrema and nucleus tractus solitarius, where activation suppresses feeding and drives persistent anorexia.[106,107] In addition to hypothalamic neuroendocrine pathways, tumor-derived inflammatory signals reshape broader CNS metabolic regulatory networks. Huisman et al. demonstrated that tumor-associated signals induce transcriptional remodeling and inflammatory activation in hypothalamic cell

populations, supporting a role for brain-periphery crosstalk in coordinating systemic metabolic dysfunction during cachexia.[108] Alongside this, inflammation alters mesolimbic dopamine and reward circuitry, reducing food-seeking behavior and contributing to the motivational deficits characteristic of cachexia.[109]

Heart and cardiovascular system: Cardiac atrophy and functional consequences

Cardiac involvement is an under-recognized but clinically significant component of cancer cachexia. Tumor-derived cytokines and inflammatory mediators activate proteolytic pathways in cardiomyocytes, leading to cardiac atrophy, impaired contractility, mitochondrial dysfunction, and altered substrate utilization. These changes compromise cardiac performance, exacerbate fatigue, reduce exercise tolerance, and may limit tolerance to anticancer therapies, thereby contributing to worse quality of life and increased mortality.[110]

Gut and microbiome: Barrier dysfunction and metabolic signaling

The gut contributes to systemic catabolism through impaired barrier integrity, altered nutrient absorption, and microbiome dysbiosis. Tumor-induced inflammation disrupts epithelial tight junctions, permitting microbial translocation and systemic endotoxemia that amplify inflammatory signaling.[111] Cachexia-associated dysbiosis alters microbiota-derived metabolites, including short-chain fatty acids and bile acids, which influence immune tone, hepatic metabolism, and skeletal muscle function.[112] Through gut-brain and gut-liver axes, microbial signals further shape appetite regulation and systemic metabolism, reinforcing multiorgan dysfunction.

BIOMARKERS AND CLINICAL ASSESSMENT OF SYSTEMIC HOMEOSTASIS FAILURE

Timely clinical diagnosis of cancer cachexia remains challenging due to the multifactorial biologic nature and the absence of universally accepted biomarkers. Current diagnostic criteria rely heavily on weight loss, which captures only late manifestations of a progressive, multiorgan syndrome and fails to identify patients in early or mechanistically distinct stages.[11,12,113] Consequently, opportunities for early intervention are frequently missed. Importantly, biomarkers differ substantially in their biological specificity as some are enriched in particular tumor contexts, some represent generalized host responses that are nonspecific or confounded by infection or treatment effects, and others are strongly context- or stage-dependent.[27,37,114] A modern framework for cachexia assessment requires integrative tools capable of detecting early catabolic activity, quantifying tissue-specific remodeling, and stratifying patients based on biological drivers rather than relying on weight loss alone.[115] Circulating, imaging, and functional biomarkers together provide complementary approaches for assessing systemic homeostasis failure in cancer cachexia and for identifying patients at risk for progressive metabolic decline. Below, we summarize biomarkers and clinical assessment tools in cancer cachexia (Table 1).

Body composition imaging: Quantifying muscle and adipose loss

Cross-sectional imaging provides an objective and reproducible assessment of cachexia-related tissue remodeling.[115,125] CT, routinely obtained in oncology care, enables precise quantification of skeletal muscle area and radiodensity at the L3 vertebral level, as well as visceral and subcutaneous adipose depots.[126] These measurements allow identification of reduced muscle area and low muscle radiodensity (myosteatosis), both of which consistently predict poorer survival, increased chemotherapy toxicity, and impaired functional outcomes across multiple malignancies.[127,128] However, a single CT measurement reflects body composition at a specific time point and does not establish whether progressive muscle atrophy is occurring. Longitudinal analysis of serial imaging studies is therefore required to distinguish active catabolic decline from stable low muscle mass. Because imaging measures tissue quantity rather than biological drivers, these approaches are broadly tumor-agnostic but require longitudinal assessment to distinguish active catabolism from stable low muscle mass.[121,129] Magnetic resonance imaging (MRI) and dual-energy X-ray absorptiometry (DXA) provide complementary longitudinal assessments. MRI allows detailed characterization of skeletal muscle and adipose distribution and has been used to predict cachexia risk in clinical cohorts,[130] while DXA offers practical, low-burden measurements of lean and fat mass in cancer patients.[131] Improving methods to detect true muscle atrophy, particularly through longitudinal imaging and more sensitive biomarkers, may help refine cachexia diagnosis and enable earlier intervention before advanced wasting develops. Beyond conventional body composition metrics, emerging computational approaches are expanding the clinical utility of imaging. Radiomics and deep machine learning approaches further extend the utility of imaging by capturing subtle, preclinical alterations in muscle quality and fat-muscle distribution before overt wasting becomes apparent, offering promise for early detection and risk stratification.[132]

Circulating biomarkers: Tumor-derived and host-response signals

Circulating biomarkers relevant to cancer cachexia can be broadly grouped into two complementary biological categories: tumor-derived mediators that initiate systemic catabolic signaling and host-response markers that reflect downstream inflammatory and metabolic consequences of tumor-host interactions.

Tumor-derived biomarkers are tumor-secreted endocrine and inflammatory mediators, which represent proximal drivers of cachexia and may serve as biologically informative biomarkers in selected tumor contexts. GDF15, for example, has emerged as a key mediator of cancer-associated anorexia and weight loss.[106,107] Similarly, PTHrP promotes adipose tissue browning and increased energy expenditure in experimental models of lung cancer cachexia.[37] Additional tumor-associated factors such as activin A and myostatin contribute to skeletal muscle wasting through ActRIIB-SMAD signaling pathways.[116] Importantly, expression of these endocrine mediators varies across cancer types, indicating that tumor-derived biomarkers may show tumor-type enrichment rather than universal applicability.

Table 1. Biomarkers and clinical assessment tools in cancer cachexia

Biomarker category	Examples	Biological interpretation	Clinical utility	Key references
Tumor-derived biomarkers	GDF15	tumor-derived endocrine mediator that suppresses appetite through hindbrain GFRAL signaling	potential early indicator of tumor-driven anorexia and systemic metabolic stress	Emmerson et al.[106]; Yang et al.[107]
	PTHrP	tumor-secreted factor promoting adipose tissue browning and increased energy expenditure	tumor-type enriched biomarker linked to hypermetabolism in some cancers	Kir et al.[37]
	activin A/myostatin	TGF-β family ligands promoting muscle wasting via ActRIIB-SMAD signaling	potential indicators of tumor-driven muscle catabolism	Goodman et al.[116]
Host response biomarkers	IL-6	systemic inflammatory cytokine driving APRs and muscle wasting	indicator of inflammatory cachexia phenotype and poor prognosis	Bonetto et al.[114]
	CRP	acute-phase protein reflecting systemic inflammation	clinically accessible surrogate marker of inflammatory burden	O'Riordain et al.[117]; Wigmore et al.[118]
	metabolic markers (amino acids, lactate, acylcarnitines)	reflect altered nutrient flux and tumor-host metabolic competition	may detect systemic metabolic stress during early cachexia	Falconer et al.[119]; Fujiwara et al.[120]
Imaging biomarkers	CT-derived skeletal muscle area (L3)	quantifies sarcopenia and muscle depletion	predicts survival, treatment toxicity, and postoperative outcomes	Martin et al.[121]
	muscle radiodensity (myosteatosis)	reflects fatty infiltration of muscle	associated with impaired physical function and worse outcomes	Martin et al.[121]
Functional biomarkers	handgrip strength	global indicator of muscle strength and physiologic reserve	predicts survival and treatment tolerance	Kilgour et al.[122]
	6-min walk test	integrates muscle, cardiovascular, and metabolic function	functional assessment of physical capacity in cancer patients	Jones et al.[123]
Composite biomarkers (emerging)	multi-omics signatures	integrated inflammatory, endocrine, and metabolic profiles	may enable precision stratification of cachexia subtypes	Muqaku et al.[124]

Overview of representative biomarker categories used to detect, stratify, and monitor cancer cachexia, including tumor-derived factors, host inflammatory responses, metabolic markers, imaging-based measurements, and functional assessments. The table summarizes key examples, their biological interpretation in the pathophysiology of cachexia, and potential clinical applications such as early detection, risk stratification, and evaluation of disease severity or treatment response. Emerging composite approaches integrating multi-omics profiling may further enable precision classification of cachexia subtypes.

Interpretation of these markers should therefore consider tumor biology, disease stage, and the broader clinical context.

In contrast to tumor-derived factors, host-response biomarkers are many circulating biomarkers, which reflect systemic host responses to tumor-induced metabolic and inflammatory stress. Among these, inflammatory mediators are the most extensively studied. Elevated IL-6 and acute-phase proteins such as CRP correlate with systemic inflammation, weight loss, and poorer outcomes in patients with cancer cachexia.[114,117,118] Because these markers reflect generalized inflammatory activation rather than tumor-specific signaling, they must be interpreted cautiously in the presence of infection, treatment toxicity, or other inflammatory conditions.

Metabolic biomarkers provide additional insight into systemic metabolic stress. Alterations in circulating amino acids, lactate, acylcarnitines, and albumin levels may reflect tumor-host nutrient competition and altered substrate utilization. However, these metabolic signatures are strongly context dependent and may vary according to tumor burden, hepatic function, treatment exposure, or disease stage.[119,120] For this reason, single metabolic markers rarely capture the full biological complexity of cachexia progression. Multi-omics approaches integrating inflammatory, endocrine, and metabolic signals are therefore being explored as composite biomarkers capable of improving risk stratification and monitoring disease trajectory. Notably, multi-omics platforms integrating inflammatory, hormonal, and metabolic features show promise as composite biomarkers of cachexia severity and trajectory.[133] However, these approaches require validation in large, longitudinal clinical cohorts before routine clinical implementation.

Functional biomarkers: Measuring physiologic capacity

Functional assessments capture the individual-level consequences of cachexia and often correlate more closely with outcomes than weight change alone.[4,134] Unlike molecular biomarkers, functional measures are largely tumor-agnostic but integrate the cumulative physiological impact of muscle wasting, systemic inflammation, and metabolic stress.[122,123] Handgrip strength is a simple, reproducible metric that predicts survival, chemotherapy tolerance, and postoperative outcomes across cancer types.[135] Measures, such as the 6-min walk test integrate muscular, cardiovascular, and metabolic function, and have demonstrated reliability and prognostic value in cancer populations.[136] Performance status scales, such as the Eastern Cooperative Oncology Group (ECOG) and Karnofsky classifications, though subjective, remain widely used in clinical trials to capture broad functional impairment and correlate with treatment tolerance and survival.[134] Combining functional measures with molecular and imaging biomarkers may substantially improve early risk stratification and longitudinal monitoring of cachexia progression.

Molecular stratification, early detection, and biomarker-guided trials in cancer cachexia

Accumulating transcriptomic, proteomic, and metabolomic evidence indicates that cancer cachexia is not a uniform entity but consists of multiple molecular and physiological subtypes driven by dominant inflammatory, neuroendocrine, and metabolic programs. Inflammation-dominant cachexia is characterized by sustained IL-6/STAT3 signaling and systemic acute-phase activation.[39] Neuroendocrine-dominant cachexia is driven by GDF15 signaling through the hindbrain GFRAL-RET axis. Metabolic-dominant cachexia is marked by systemic energy inefficiency, in which heightened tumor glycolysis and excessive lactate production increase Cori-cycle flux. This futile hepatic gluconeogenesis imposes a substantial energetic burden and elevates resting energy expenditure.[137] This metabolic phenotype aligns conceptually with the framework proposed by Petruzzelli and Wagner, which emphasizes tumor-driven metabolic reprogramming and maladaptive host responses as central drivers of whole-body energy dissipation in cachexia.[6] At the tissue level, integrative RNAome profiling of human skeletal muscle biopsies by Bhatt et al. identified a cachexia-associated muscle molecular subtype characterized by profound fiber atrophy, inflammatory and metabolic reprogramming, and markedly reduced survival, providing the first human molecular taxonomy of muscle-intrinsic dysfunction in cancer cachexia.[138] Additional subtypes involving mitochondrial depletion, impaired oxidative capacity, and defective regenerative responses further exacerbate functional decline. Recognition of these biologically distinct patterns may improve patient stratification and enable mechanism-matched therapeutic interventions.

A critical translational challenge in cancer cachexia is the early identification of this condition before irreversible tissue loss occurs. Pre-cachexia represents a clinically important stage in which metabolic, inflammatory, and neuroendocrine disturbances precede overt weight loss and functional deterioration.[11] Timing is therefore a central consideration for biomarker interpretation, as several circulating markers emerge only after significant systemic catabolism has already begun. Early detection signals in the circulation indicate that subclinical PDAC induces whole-body protein breakdown, reflected by early elevations in muscle-derived metabolites such as methyl-histidine years before clinical diagnosis.[139] As disease progresses, additional candidate indicators may emerge, including rising circulating GDF15 or activin A, low-grade increases in CRP or IL-6 in the absence of infection, declining muscle radiodensity despite stable body weight, subtle reductions in strength or endurance, and metabolomic signatures consistent with hepatic or mitochondrial stress.[26,140,141] Detecting these changes before advanced tissue wasting develops could enable earlier intervention and improve preservation of metabolic and functional reserve.

A phenotype- or subtype-oriented framework is most valuable when operationalized clinically. Cachexia evaluation can be conceptualized as a stepwise workflow linking screening, staging, subtype assignment, and longitudinal monitoring. Screening may begin with weight trajectory and reported food intake, as reduced intake frequently precedes overt wasting. Staging can incorporate inflammatory surrogates, such as CRP, together with opportunistic CT-based body composition and at least one functional or patient-reported outcome measure. Subtype assignment can then be guided by the dominant biological pattern across these domains, enabling stratification into inflammation-, neuroendocrine-, or metabolism-dominant phenotypes. This pragmatic framework strengthens the linkage between mechanistic biology, measurable clinical variables, and precision therapeutic intervention.

Despite substantial biological insight, most cachexia clinical trials to date have lacked biomarker-based stratification, contributing to heterogeneous patient populations and inconsistent therapeutic outcomes. Incorporating inflammatory profiles, body-composition metrics, neuroendocrine markers, and molecular subtypes into trial design has the potential to improve patient selection, enable mechanism-matched therapies, and distinguish responders from non-responders.[113] Biomarker-guided approaches are therefore essential for translating mechanistic understanding of cachexia into effective, personalized clinical interventions and for advancing the field toward precision oncology-aligned trial paradigms.

THERAPEUTIC LANDSCAPE: RESTORING SYSTEMIC HOMEOSTASIS

Despite extensive research, effective therapies for cancer cachexia remain limited, largely because most interventions have targeted isolated pathways within a biologically complex, multiorgan syndrome. Conceptualizing cachexia as a tumor-driven disorder of whole-body homeostasis emphasizes the need for integrated strategies that simultaneously address tumor biology, systemic inflammation, host metabolic dysregulation, and central control of appetite and energy balance.[1,11,70,142,143] Below, we summarize current and emerging therapeutic approaches, highlighting mechanistic rationales, clinical experience, and lessons from past trials.

Targeting tumor-derived factors and tumor-intrinsic drivers

Tumor-intrinsic signaling programs the systemic inflammatory and metabolic disturbances that drive cancer cachexia, positioning the tumor secretome as a central therapeutic target.[39,144] Tumor-derived cytokines and endocrine-like mediators promote hepatic APRs, skeletal muscle proteolysis, adipose remodeling, anorexia, and neuroendocrine dysregulation. Among these, IL-6 has emerged as a dominant mediator linking tumor burden to systemic catabolism. Pharmacologic inhibition of IL-6 or downstream JAK/STAT signaling has shown benefit in preclinical and early translational studies,[145] but durable clinical efficacy likely requires biomarker-guided patient stratification, particularly in IL-6 dominant cachexia subtypes. These findings reinforce the concept that oncogenic programs shape cachexia-inducing secretomes. Consistent with this view, oncogenic KRAS regulates metabolic and inflammatory signaling in PDAC through pathways including IL-6/STAT3.[146,147] Clinically, covalent $KRAS^{G12C}$ inhibitors, such as sotorasib and adagrasib, achieve rapid and durable tumor regression in molecularly defined cancers.[148] This provides framework to test whether suppression of oncogene-driven secretomes can secondarily stabilize host metabolism and attenuate cachexia. In contrast, early trials targeting TNF-α or IL-1 signaling yielded limited benefit in unselected populations, underscoring cachexia heterogeneity.[149,150] Beyond inflammatory cytokines, TGF-β superfamily ligands such as activin and myostatin exert potent anti-anabolic effects on skeletal muscle. Recent work identifying circANAPC7 as a tumor-suppressive circular RNA that restrains PDAC-associated cachexia by dampening tumor-linked TGF-β signaling further highlights tumor-intrinsic regulatory nodes that may be therapeutically exploitable.[151] ActRIIB-based ligand traps robustly increase muscle mass in preclinical models, although translation to meaningful clinical benefit remains challenging.[40,152] Neuroendocrine pathways also represent actionable nodes: the GDF15-GFRAL-RET axis mediates tumor-induced anorexia via hindbrain-restricted signaling, and GDF15 neutralization improves appetite and weight in animal models and early clinical studies.[107,153–156] Tumor-derived PTHrP further promotes adipose browning and thermogenic energy expenditure, suggesting additional opportunities to limit energy wasting.[37]

Cancer treatments can also influence cachexia biology by amplifying tumor-driven catabolic signaling rather than acting as independent processes. Cisplatin induces skeletal muscle atrophy and activates NF-κB signaling even without tumor progression.[157] Mechanistically, it increases expression of the ubiquitin ligases MuRF1 and atrogin-1 while suppressing IGF-1/Akt signaling, pathways central to tumor-induced cachexia.[158,159] In addition, supportive medications frequently administered during chemotherapy, such as dexamethasone, can further enhance these catabolic pathways and exacerbate muscle wasting.[160] Together, these findings suggest that tumor-derived inflammation and treatment-associated stress converge on shared pathways promoting skeletal muscle atrophy.

Immunotherapy may also indirectly improve host metabolic status by reducing tumor-derived inflammation; however, cachexia itself can impair T cell fitness, metabolic flexibility, and responsiveness to immune checkpoint blockade. Tumor-induced IL-6-dependent metabolic reprogramming has been shown to suppress anti-tumor immunity,[161] and multiple clinical studies associate cachexia with inferior responses to PD-1/PD-L1 inhibitors, including in non-small cell lung cancer.[162] Finally, although conventional cytotoxic therapies can transiently exacerbate anorexia and fatigue, effective tumor control in highly secretory malignancies, such as PDAC and small-cell lung cancer, often stabilizes systemic inflammation and treatment tolerance, reinforcing tumor-directed therapy as a foundational pillar of cachexia management.

Looking ahead, these insights support a shift toward precision, tumor-informed cachexia therapy rather than uniform cytokine blockade. Integrating tumor genotype, secretome composition, and host inflammatory and metabolic signatures will be essential for identifying dominant catabolic drivers and matching patients to mechanism-appropriate interventions. Prospective incorporation of cachexia-specific endpoints into oncogene-targeted and immunomodulatory trials will be critical to determine whether suppression of tumor-encoded inflammatory and metabolic programs can meaningfully stabilize host physiology. Ultimately, combining tumor-directed therapies with selective modulation of tumor-derived catabolic signals and neuroendocrine pathways offers a rational framework for transforming cachexia from an untreatable comorbidity into a biologically tractable and clinically actionable syndrome.

Muscle- and adipose-directed therapies

Skeletal muscle wasting represents a principal determinant of functional decline and impaired treatment tolerance in cancer cachexia, and thus numerous strategies have focused on restoring anabolism or suppressing proteolysis. Clinical studies

of anabolic strategies, including androgens, selective androgen receptor modulators, and β2-agonists, often demonstrate increases in lean mass. However, effects on strength, functional capacity, and quality of life have varied, reflecting the confounding influence of persistent inflammation and metabolic stress.[143,163] Direct inhibition of proteolytic pathways, including the UPS and autophagy-lysosome axis, remains largely preclinical and context dependent. Proteasome inhibitors show mixed efficacy across models, while modulation of autophagy yields divergent outcomes depending on disease stage and tissue context.[164] Consistent links between cachexia and impaired oxidative metabolism exist, and therefore mitochondrial-directed strategies, including antioxidants, modulators of mitochondrial biogenesis, and mitochondria-protective peptides, such as SS-31, are being explored to improve energetic capacity and fatigue-related phenotypes.[165] Emerging evidence suggests that NMJ dysfunction and functional denervation may contribute to muscle wasting in cancer cachexia, with implications for therapies focused solely on inhibiting muscle catabolism. Experimental studies show that disruption of motor neuron-muscle signaling can destabilize NMJs and induce denervation before activation of muscle proteolytic pathways, indicating that impaired innervation may precede myofiber atrophy.[83] Consistent with this, transcriptomic analyses of cachectic muscle reveal denervation-associated gene programs, suggesting that atrophy pathways may arise secondary to compromised neuromuscular signaling.[166] However, human data are heterogeneous; structural analyses of muscle biopsies from cancer patients did not detect widespread NMJ degeneration in all cases, indicating context-dependent contributions.[167] Together, these findings suggest that therapies targeting muscle proteolysis alone may be insufficient if underlying neuromuscular dysfunction is not addressed.

In parallel, adipose-focused interventions aim to restrain excessive lipolysis and the hypermetabolic consequences of browning. Genetic or pharmacologic inhibition of key lipases (ATGL/HSL) and blockade of browning drivers such as PTHrP support adipose tissue as a tractable therapeutic lever in cachexia.[37,95] Finally, exercise and prehabilitation represent multisystem interventions.[168] Emerging clinical data, particularly in PDAC, suggest that structured programs may help preserve muscle metrics and functional capacity, especially when initiated early before refractory cachexia develops.[169,170]

Cancer therapies can also directly impair skeletal muscle metabolism. Doxorubicin disrupts mitochondrial energy metabolism, reduces respiratory capacity, and increases oxidative stress in skeletal muscle, indicating mitochondrial dysfunction as a key mechanism of treatment-associated toxicity.[171] Because mitochondrial dysfunction is also a hallmark of cancer cachexia, treatment-related metabolic injury may exacerbate tumor-driven muscle wasting. Chemotherapy can additionally affect adipose tissue; in a preclinical colorectal cancer model, 5-fluorouracil plus irinotecan reduced adipocyte size and downregulated proteins involved in fatty-acid oxidation and energy metabolism, suggesting impaired lipid storage capacity.[172] Since adipose tissue loss often precedes skeletal muscle wasting in cachexia, treatment-induced adipose dysfunction may contribute to systemic energy imbalance.

CNS-targeted therapies

Dysregulated CNS signaling plays a critical role in anorexia, fatigue, and increased energy expenditure in cancer cachexia. Clinically used appetite stimulants, including megestrol acetate, ghrelin receptor agonists (e.g., anamorelin), and cannabinoids, can increase caloric intake in some patients.[173] However, these agents generally confer limited benefit for muscle mass, functional outcomes, or survival, particularly when systemic metabolic stress predominates over simple intake deficits. Recent clinical trials in cancer cachexia increasingly target specific biological pathways while distinguishing among metabolic, functional, and patient-reported endpoints. In the phase III ROMANA trials in advanced non-small cell lung cancer, the ghrelin receptor agonist anamorelin increased body weight and lean mass but did not improve handgrip strength, highlighting discordance between body composition and functional outcomes.[173] More recently, targeting the GDF15-GFRAL anorexia pathway has also shown promise: a phase II trial of the anti-GDF15 antibody ponsegromab improved body weight, appetite, cachexia symptoms, and physical activity, with body weight change at 12 weeks as the primary endpoint.[154] Ongoing trials, including NCT06989437 in metastatic pancreatic cancer, are further evaluating ponsegromab using integrated metabolic, functional, and patient-reported outcomes. A recent landmark preclinical study further identifies the vagal brain-liver axis as a novel neuro-metabolic regulator of cachexia.[174] Tumor-induced inflammation disrupts vagal tone and brain-liver communication, leading to hepatic metabolic reprogramming, systemic inflammation, and cachectic phenotypes. Modulation of this pathway, via surgical, chemical, electrical, or non-invasive vagal interventions, attenuates cachexia progression, improves feeding and muscle mass, and extends survival in mouse models, highlighting a new class of CNS-directed, circuit-level therapies. Additional studies implicate hypothalamic and neuroimmune inflammatory circuits, including microglia-mediated responses, in cachexia-associated dysregulation of appetite and energy balance, although clinical translation remains nascent.[103]

Cancer therapies may also influence appetite regulation and central metabolic control. Experimental studies demonstrate that cisplatin induces hypothalamic inflammation and microglial activation, leading to reduced food intake and body weight loss.[175] In addition, doxorubicin has been shown to impair hypothalamic energy metabolism independent of inflammatory cytokine signaling.[176] These findings suggest that treatment-induced anorexia may interact with tumor-derived neuroendocrine signals, such as the GDF15-GFRAL pathway, to worsen negative energy balance during cancer therapy.

Multimodal approaches

Cancer cachexia has a multiorgan biology, and thus integrated multimodal regimens combining nutritional counseling, structured exercise, pharmacologic modulation of inflammation or catabolism, appetite support, and tumor-directed therapy are increasingly prioritized. Multimodal trials in advanced lung and PDAC have demonstrated feasibility and safety of combining nutrition, exercise, and anti-inflammatory interventions during chemotherapy.[177] Programs initiated early, concurrent with first-line systemic therapy, appear to achieve higher adherence and greater preservation of functional trajectories. For example,

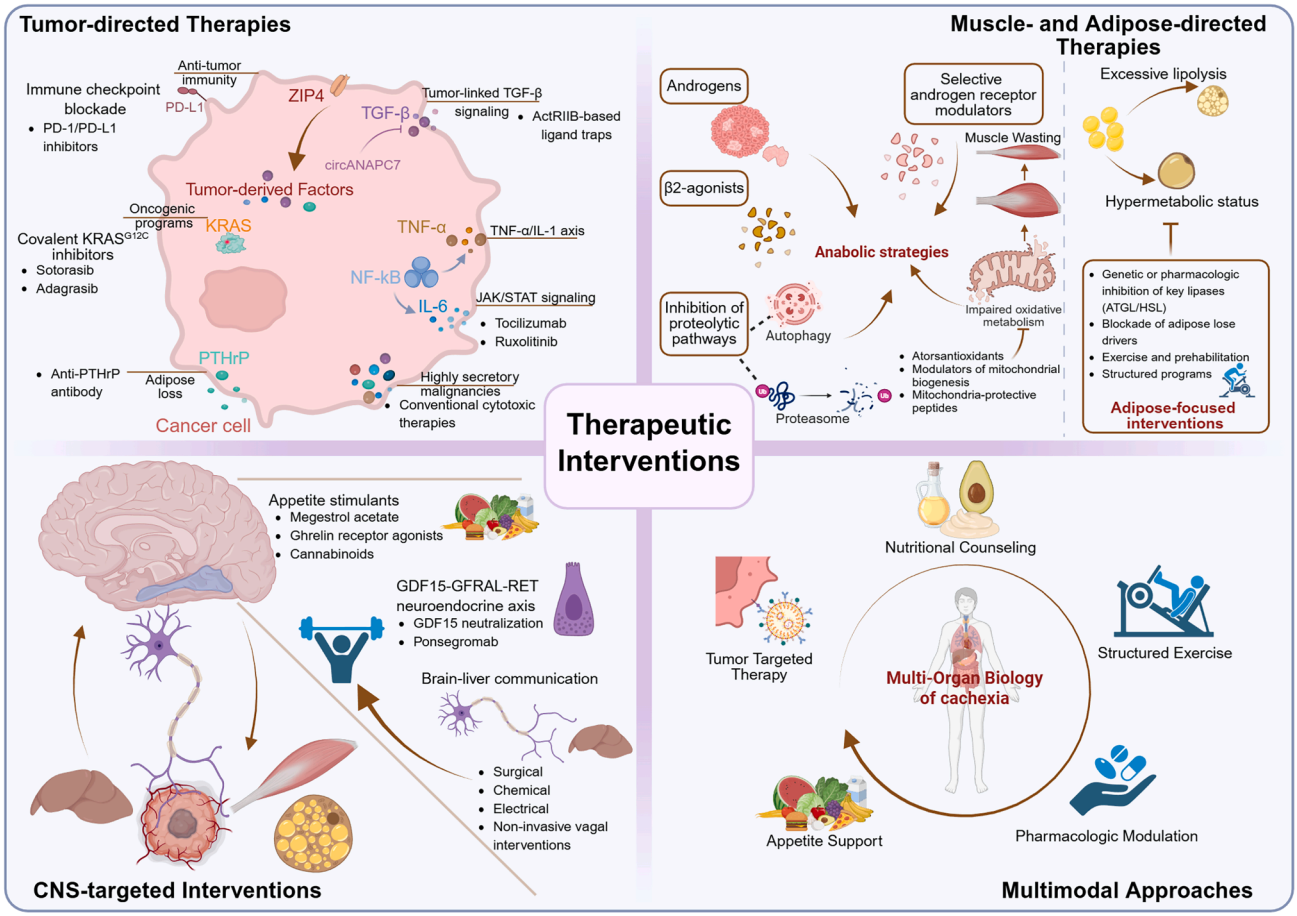

Figure 2. Therapeutic landscape of cancer cachexia: Targeting tumor-host dysregulation across organ systems

This schematic summarizes current and emerging therapeutic strategies for cancer cachexia within a systems framework. Tumor-directed interventions target oncogenic signaling and cachexia-inducing secretomes, including pro-inflammatory cytokines (e.g., IL-6, TNF-α, and IL-1), TGF-β superfamily ligands, GDF15, and metabolic programs that drive systemic inflammation, nutrient competition, and neuroendocrine dysregulation. Host-directed therapies aim to restore metabolic balance by modulating skeletal muscle proteolysis and anabolism, improving mitochondrial function, and restraining adipose lipolysis and hypermetabolism. Central nervous system-directed approaches target anorexia and energy imbalance through modulation of appetite and neuroendocrine circuits, including the GDF15-GFRAL/RET axis and brain-liver signaling pathways. Multimodal strategies integrate tumor control, nutritional support, exercise, and selective pharmacologic interventions to address the multiorgan biology of cachexia. Together, the figure highlights how effective cachexia management will likely require mechanism-guided, multitarget approaches tailored to tumor type, dominant biological drivers, and disease stage rather than isolated single-pathway interventions.

early multimodal intervention in older patients initiating chemotherapy showed excellent compliance and safety, and the randomized Nutrition and Exercise Treatment in Patients with Pancreatic and Non-Small Cell Lung Cancer (NEXTAC) program has emphasized disability-free survival as a clinically meaningful endpoint.[178]

Lessons from prior clinical trials

Many cachexia trials have underperformed due to late-stage enrollment, biologically heterogeneous populations, and heavy reliance on body weight or lean mass as primary endpoints, despite consensus that cachexia is defined by progressive muscle loss leading to functional impairment. Reviews of historical trial designs highlight persistent variability in endpoint selection and emphasize the need to prioritize patient-centered functional outcomes, including composite and longitudinal measures, over weight alone.[179] Equally important, insufficient attention to cancer-type-specific drivers and secretome heterogeneity can result in weak target engagement even when the underlying biology is sound. These limitations underscore the need for biomarker-guided patient selection, molecular subtyping, and standardized imaging and functional endpoints. An additional challenge in cachexia trial design is the interaction between anticancer therapies and cachexia biology. Many trials enroll patients receiving concurrent chemotherapy or corticosteroids without accounting for treatment-induced metabolic effects. Preclinical studies indicate that chemotherapy and supportive medications can activate the same downstream mediators implicated in tumor-driven cachexia, including NF-κB signaling, MuRF1/atrogin-1 activation, and suppression of IGF-1/Akt pathways.[157,159,160] As a result, tumor-derived signals and treatment-associated stress may synergize to accelerate muscle wasting, which may partially explain the limited efficacy of single-pathway interventions in heterogeneous clinical populations.

Emerging frameworks also advocate incorporation of ecologically valid measures of physical activity, including digital and real-world activity metrics,[180] to better capture meaningful clinical benefit (Figure 2).

A SYSTEMS FRAMEWORK: CANCER CACHEXIA AS A TUMOR-DRIVEN COLLAPSE OF SYSTEMIC HOMEOSTASIS

As introduced above, cancer cachexia can be conceptualized through complementary tumor-type-specific and phenotype-oriented frameworks. While tumor heterogeneity shapes the biological context in which cachexia develops, a systems-level perspective provides an integrative model explaining how diverse tumor and host processes converge to drive progressive organismal dysfunction. Accumulating mechanistic and clinical evidence supports a fundamentally different view: cancer cachexia represents a tumor-initiated failure of whole-body homeostatic control that cannot be corrected by nutritional support alone and ultimately results in progressive functional decline.[11,101] This systems-level framework integrates observations across skeletal muscle, adipose tissue, liver, immune compartments, neuroendocrine circuits, and tumor metabolism. Together, these components form the host macroenvironment (MAE), a network of peripheral metabolic organs and regulatory systems that sense, integrate, and respond to tumor-derived stress signals. From this perspective, the heterogeneity, progression, and therapeutic resistance of cachexia reflect coordinated disruption of organism-level regulatory networks rather than independent organ-specific pathologies. Once persistently engaged by tumor-derived signals, these networks transition from adaptive responses to maladaptive programs that sustain systemic catabolism.

Tumor-driven stress reprogramming of host homeostasis

Within this framework, tumors function as chronic systemic stressors that reprogram host physiology through sustained secretion of cytokines, growth factors, metabolites, lipids, and EVs.[21] These signals do not simply perturb individual tissues but instead lock the host into evolutionarily conserved stress-response programs that are adaptive during acute infection or starvation, yet become maladaptive when chronically activated by malignancy.

Host organs respond by engaging emergency metabolic and inflammatory pathways: skeletal muscle activates proteolytic programs to release amino acids,[181] adipose tissue mobilizes lipid stores and may increase energy dissipation,[37] the liver prioritizes APRs and gluconeogenesis, neuroendocrine circuits suppress appetite and reshape autonomic output, and immune compartments adopt a chronically activated inflammatory state. While each response is individually rational in the context of acute stress, their persistent, uncoordinated activation overwhelms compensatory capacity, resulting in systemic energy imbalance and progressive tissue loss.[182] Thus, cachexia reflects not a failure of a single organ, but a breakdown in the integration and resolution of whole-body stress responses driven by continuous tumor signaling.

Self-reinforcing catabolic feedback architecture

A defining feature of cancer cachexia is the emergence of interconnected feedback loops that stabilize and amplify catabolism. Metabolites released from skeletal muscle and adipose tissue fuel hepatic gluconeogenesis and tumor bioenergetics, while inflammatory cytokines reinforce proteolysis, lipolysis, and neuroendocrine appetite suppression. Hepatic APRs further intensify systemic inflammation, and anorexia limits the host's ability to replenish depleted reserves.[181]

Once established, this feedback architecture may generate a self-reinforcing metabolic cascade that becomes increasingly difficult to reverse with late intervention. This framework may help explain why cachexia often progresses despite aggressive nutritional support or inhibition of individual pathways, although multiple mechanisms, including processes not directly targeted by current metabolic or muscle-focused therapies, such as neuromuscular dysfunction, which has been implicated in some preclinical studies, are also likely to contribute.[83,183]

TME-MAE triangular regulation as a determinant of cachexia phenotypes

Although cancer cachexia shares core systemic features, its clinical manifestation varies markedly across cancer types, disease stages, and individual patients. We propose that this heterogeneity is governed by dynamic triangular regulatory architectures linking the tumor, tumor-tumor microenvironment (TME), and MAE. In this framework, cachexia emerges not from isolated organ dysfunction but from context-dependent crosstalk among these three interconnected compartments.

Tumor cells initiate cachexia by deploying oncogene-encoded metabolic and inflammatory programs that reshape both local and systemic physiology. Within the TME, immune cells, stromal populations, and extracellular matrix components interpret and amplify tumor-derived signals, converting them into sustained inflammatory, metabolic, and stress-related outputs. These TME-mediated signals, in turn, engage the MAE, a composite of peripheral organs and regulatory systems including skeletal muscle, adipose tissue, liver, immune compartments, and neural circuits, that execute, integrate, and feedback systemic responses such as tissue catabolism, altered energy expenditure, anorexia, and immune dysfunction. Importantly, MAE components are not passive targets but actively modulate tumor and TME behavior through metabolic feedback, inflammatory tone, neuroendocrine signaling, and resource availability.

Critically, the composition, dominance, and directionality of TME-MAE triangular regulation are not fixed. Instead, they evolve dynamically in response to tumor genotype, tumor burden, host metabolic reserve, systemic inflammation, and therapeutic pressure. As a result, cachexia may manifest as neuroendocrine-dominant, inflammation-dominant, or metabolism-dominant across different cancers and disease stages (Figure 3). This dynamic triangular framework reconciles why identical molecular pathways can be pathogenic in one context yet dispensable in another, and why cachexia exhibits distinct trajectories, organ priorities, and therapeutic vulnerabilities across malignancies.

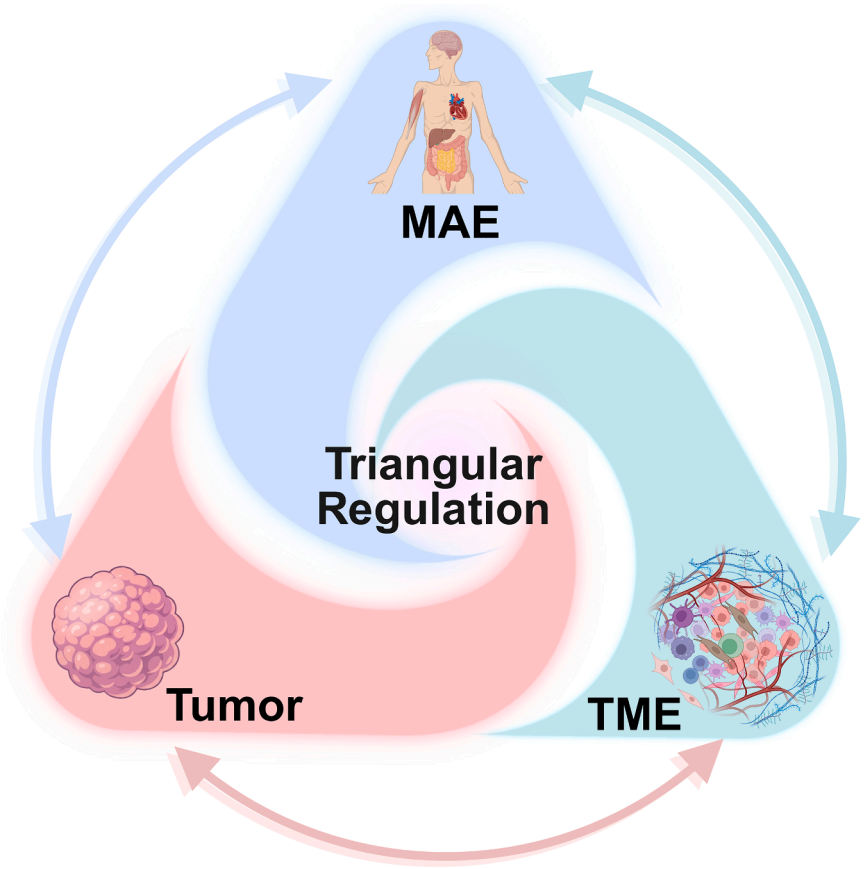

Figure 3. A systems framework for cancer cachexia: Dynamic tumor-host regulatory networks

This schematic depicts cancer cachexia as a tumor-driven collapse of systemic homeostasis arising from dynamic triangular regulation among the tumor-tumor microenvironment (TME), and the host macroenvironment (MAE). Tumor-intrinsic oncogenic programs generate inflammatory, metabolic, and stress signals that are interpreted and amplified within the TME by immune and stromal components. These signals engage the MAE, comprising peripheral metabolic organs and regulatory systems such as skeletal muscle, adipose tissue, liver, immune compartments, and neural circuits, to execute systemic responses including tissue catabolism, altered energy expenditure, anorexia, and immune dysfunction. Reciprocal feedback from the MAE further reshapes tumor and TME behavior, establishing evolving, self-reinforcing regulatory loops. Dynamic reconfiguration of TME-MAE interactions drives cachexia heterogeneity, progression, and resistance to single-pathway interventions.

Implications for precision research and therapy

Viewing cachexia as a tumor-driven collapse of systemic homeostasis has several important implications. First, it underscores the need for tumor-type-specific and stage-aware models, as cachexia is shaped by evolving tumor-host interactions rather than static pathways. Second, it highlights the importance of organ-resolved and systems-level biomarkers, including imaging-derived body composition, inflammatory and hormonal profiles, and functional measures, to define mechanistic subtypes beyond weight loss alone.

From a therapeutic standpoint, this framework explains the limited success of single-node interventions and supports multitarget, timing-sensitive strategies that reduce tumor-derived stress signals, dampen immune amplification, restore anabolic capacity in metabolic tissues, and rebalance neuroendocrine control. Importantly, interventions deployed during early or pre-cachectic stages, before feedback loops become entrenched, are far more likely to reestablish a stable metabolic equilibrium than late-stage approaches.

Together, this systems-level perspective reframes cancer cachexia from an inevitable end-stage complication into a biologically defined and potentially modifiable syndrome. By integrating tumor biology, immunometabolism, neuroendocrine regulation, and host stress responses, this framework provides a foundation for precision stratification and mechanism-guided interventions aimed at preserving function, improving treatment tolerance, and ultimately altering the clinical course of aggressive cancers.

CONCLUSIONS AND FUTURE DIRECTIONS

Cancer cachexia remains one of the most devastating complications of malignancy. However, accumulating evidence now establishes cachexia as a mechanistically defined and biologically tractable syndrome, rather than a passive consequence of advanced disease. International consensus definitions emphasize that cachexia is driven by ongoing skeletal muscle loss, is not fully reversible by nutritional support alone, and culminates in progressive functional impairment.[11] Integration of molecular, physiological, and clinical insights has reframed cachexia as a tumor-driven collapse of systemic homeostasis, characterized by coordinated dysfunction across skeletal muscle, adipose tissue, liver, heart, immune compartments, and the CNS.[50,101,184] At the core of this process, tumors function as systemic signaling hubs, releasing complex secretomes that reprogram host metabolism, inflammatory tone, and neuroendocrine regulation. These tumor-derived cues initiate catabolic programs, while maladaptive host stress responses amplify inflammation, energetic inefficiency, and appetite suppression, generating self-reinforcing loops that accelerate tissue loss and compromise treatment tolerance. This system-level perspective explains both the marked heterogeneity of cachexia across cancer types and the limited efficacy of single-pathway interventions applied to unselected patient populations.

Looking forward, several priorities will shape the next phase of cachexia research. High-resolution characterization of tumor secretomes and tumor-host signaling axes across cancer types will be essential to identify upstream drivers, enable early risk stratification, and guide mechanism-matched intervention. Equally important is comprehensive mapping of multiorgan

metabolic and inflammatory circuits, recognizing cachexia as a form of cancer-associated multiorgan failure rather than isolated muscle wasting. Together, these efforts will support biological subtyping of cachexia based on dominant drivers, such as inflammatory amplification, neuroendocrine anorexia, or metabolic collapse, thereby enabling precision therapeutic strategies.

Clinical translation will require a fundamental shift in trial design. Reliance on body weight alone has repeatedly failed to capture meaningful biological or clinical benefit. Instead, multidimensional endpoints incorporating physical function, imaging-derived body composition, circulating biomarkers, and patient-reported outcomes, including symptom burden and quality of life, are needed to reflect true disease modification.[115] Combination strategies integrating tumor-directed, host-directed, and CNS-directed therapies are likely to be most effective, particularly when deployed early, before irreversible tissue loss and entrenched feedback loops develop.

By conceptualizing cancer cachexia as a tumor-driven failure of systemic homeostasis, the field moves beyond a purely reactive framework toward prevention, stratification, and mechanism-guided therapy. Cachexia is not an inevitable endpoint of cancer progression but a modifiable syndrome with identifiable biological drivers. Continued integration of cancer biology, metabolism, immunology, and clinical science offers an encouraging path toward improving treatment tolerance, functional outcomes, and quality of life for patients with aggressive malignancies.

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AUTHOR CONTRIBUTIONS

Study conception and design, Y.Z. and M.L.; visualization, Y.Z., R.D.N., T.J.,Y.-P.L., D.C.G., and M.L.; resources, Y.Z., R.D.N., T.J., Y.-P.L., D.C.G., and M.L.; funding acquisition, M.L.; writing – original drafts, Y.Z. and M.L.; writing – review and editing, Y.Z., R.D.N., T.J., Y.-P.L., D.C.G., and M.L.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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