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The inflammatory-metabolic axis in cancer cachexia; a narrative review on recent concepts

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Abstract

Cancer cachexia defined by progressive loss of skeletal muscle with or without fat depletion, affects many cancer patients and significantly impairs quality of life, treatment tolerance, and survival. Recent findings have elucidated the central role of the inflammatory-metabolic axis as a bidirectional crosstalk between systemic inflammation and profound metabolic derangements in cancer cachexia pathogenesis. Several studies detected that, tumor-derived factors and host immune responses trigger chronic elevation of pro-inflammatory cytokines, which activate key signaling pathways that disrupt metabolic homeostasis. This inflammatory milieu induces hypermetabolism, insulin resistance, and aberrant substrate utilization, while simultaneously stimulating muscle proteolysis by ubiquitin-proteasome and autophagy-lysosome systems and promoting adipose tissue lipolysis through browning of white fat. Recent concepts highlight the contribution of tumor exosomes carrying microRNAs and proteins that reprogram host metabolism, organ crosstalk involving liver acute-phase response and gut microbiome alterations, and the role of specific immune cell populations in sustaining inflammation. Meanwhile, metabolic dysfunction itself can amplify inflammation, creating a self-perpetuating cycle that accelerates wasting. These insights challenge the historical view of cachexia as merely a consequence of reduced food intake, positioning it as an active, tumor-driven process. Current therapeutic strategies targeting single cytokines have shown limited efficacy, emphasizing on the need for multimodal approaches that concurrently modulate inflammatory drivers and restore metabolic balance. Therefore, the dynamic interplay within this axis offers promising modalities for early detection biomarkers and mechanism-based interventions to mitigate this devastating syndrome.

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Introduction

Cancer cachexia is a multifactorial syndrome characterized by ongoing loss of skeletal muscle mass, with or without fat loss that cannot be fully reversed by conventional nutrition, leading to functional impairment and poor outcomes. This condition arises from a sustained imbalance between catabolic and anabolic signaling, in which systemic inflammation and metabolic remodeling are tightly interwoven rather than independent processes (1). The inflammatory–metabolic axis denotes this bidirectional crosstalk; inflammatory mediators from tumor and host reshape metabolic pathways in multiple organs, while metabolic stress and organ dysfunction, in turn, amplify inflammatory signaling (2). Recognizing this axis is clinically important, since it explains why cachexia may progress despite adequate caloric intake and why simple body weight monitoring is an insufficient surrogate of disease biology (3). This narrative review considers current findings of the molecular architecture of the inflammatory-metabolic axis in cancer cachexia, and evaluates promising biomarker strategies for patient stratification, and also explores precision medicine opportunities emerging from recent clinical breakthroughs.

Search strategy

For this narrative review, we performed a literature search across multiple databases,

Key point

Cancer cachexia characterized by progressive, involuntary loss of skeletal muscle mass with or without depletion of adipose tissue that cannot be fully reversed by conventional nutritional support. This condition affecting many cancer patients depending on tumor type and stage too. Cancer cachexia also contributes to cancer-related deaths, diminishes treatment tolerance, impairs quality of life, and accelerates functional decline. Historically mischaracterized as simple starvation or anorexia, since Cancer cachexia is a complex systemic disorder driven by dynamic crosstalk between the tumor and host tissues.

including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase. The search strategy employed a variety of relevant keywords, such as: 'cancer cachexia', 'parathyroid hormone-related protein', 'adipocytes', 'inflammation', and 'cytokines'.

Inflammatory-metabolic axis

This axis represents the bidirectional relationship between chronic inflammation, which composed of tumor-derived factors and host immune responses, across with a profound metabolic reprogramming affecting skeletal muscle, adipose tissue, liver, and other organs (2). Rather than viewing inflammation and metabolism as separate phenomena, recent studies positions them as inseparable components of a unified pathophysiological network wherein inflammatory mediators directly reprogram cellular metabolism, while metabolic byproducts and tissue damage further amplify inflammatory signaling. This conceptual framework has transformative implications for biomarker development and therapeutic targeting (2,4).

Focus on the inflammatory architecture of cachexia

Chronic systemic inflammation constitutes the cornerstone of cachexia pathogenesis. Tumors secrete a constellation of pro-inflammatory cytokines and exosome-mediated signals that activate host immune cells, particularly macrophages and T lymphocytes to generate a self-perpetuating inflammatory milieu (5). Among circulating mediators, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interferon-gamma (IFN-γ) have been most consistently implicated (6).

Prior studies detected that, IL-6 has a central orchestrator with dual roles. It directly activates skeletal muscle catabolism through JAK/STAT3 signaling while simultaneously driving hepatic acute-phase protein production that further depletes amino acid reserves (7). Elevated serum IL-6 correlates strongly with weight loss velocity, functional impairment, and reduced survival across multiple tumor types including pancreatic, lung, and gastrointestinal malignancies (8). Mechanistically, IL-6 binding to its receptor complex triggers JAK-mediated phosphorylation of signal transducer and activator of transcription 3 (STAT3), which translocates into the nucleus and upregulates key atrophy-related genes including *Atrogin-1* (MAFbx) and *MuRF1*—E3 ubiquitin ligases that tag contractile proteins for proteasomal degradation (9).

Meanwhile, TNF-α contributes to cachexia through multiple pathways: it activates nuclear factor-kappa B (NF-κB) signaling that suppresses myogenic differentiation and promotes muscle proteolysis; induces insulin resistance in skeletal muscle and adipose tissue; stimulates hepatic gluconeogenesis; and directly suppresses appetite via hypothalamic signaling (10). Though, early anti-TNF strategies showed limited efficacy, likely due to pathway redundancy; nevertheless, TNF-α remains a critical component of the inflammatory network, particularly in synergy with IL-6. Beyond classical cytokines, the TGF-β superfamily has emerged as a dominant driver of muscle wasting (2). Additionally, activin A, myostatin, and growth differentiation factor 15 (GDF-15) signal through activin receptor type IIB (ACVR2B) and downstream SMAD2/3 transcription factors to potently inhibit muscle protein synthesis while activating ubiquitin-proteasome and autophagy-lysosome degradation systems (11). Tumor cells and stromal components overexpress these ligands, creating a paracrine/endocrine assault on skeletal muscle homeostasis. Notably, GDF-15 has gained prominence not only as a mechanistic driver but also as a clinically actionable biomarker and therapeutic target, as discussed below (12). Then, the inflammatory cascade extends beyond cytokine secretion to reprogram host metabolism (13).

Metabolic reprogramming across tissues

Skeletal muscle catabolism represents the hallmark of cachexia. Two primary proteolytic systems mediate muscle protein breakdown: (1) the ubiquitin-proteasome system (UPS), responsible for degrading the majority of contractile proteins, and (2) the autophagy-lysosome pathway, which clears damaged organelles and protein aggregates (14). Inflammatory cytokines, particularly by STAT3 and NF-κB upregulate the E3 ubiquitin ligases *Atrogin-1* and *MuRF1*, which polyubiquitinate myofibrillar proteins targeting them for 26S proteasome degradation (15). Concurrently, autophagy is dysregulated; while, basal autophagy is protective, excessive or impaired autophagic flux contributes to muscle loss (16). In addition, STAT3 activation suppresses protein synthesis by inhibiting mTORC1 signaling and promoting expression of REDD1, an mTOR inhibitor (17). The net result is a profound negative protein balance unresponsive to increased amino acid availability (18). Likewise, adipose tissue wasting occurs through accelerated lipolysis and browning of white adipose tissue (WAT). In the next step, IL-6 and other cytokines activate hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL), liberating free fatty acids that undergo β-oxidation, that often uncoupled

from ATP production, generating futile thermogenesis (19). Simultaneously, tumor-derived factors including parathyroid hormone-related protein (PTHrP) and zinc-α2-glycoprotein induce expression of uncoupling protein 1 (UCP1) in white adipocytes, transforming them into energy-dissipating beige/brown adipocytes. This adipose remodeling contributes significantly to hyper-metabolism and occurs early in cachexia progression, sometimes preceding measurable muscle loss making it a potential window for early intervention (20). Accordingly, hepatic metabolic dysfunction completes the triad of tissue alterations. The liver shifts toward a catabolic phenotype characterized by increased gluconeogenesis by consuming amino acids from muscle breakdown, acute-phase protein synthesis, which diverting amino acids from anabolic processes, and reduced synthesis of albumin and other transport proteins (21). Tumor-induced vagal nerve dysfunction has recently been implicated in disrupting the brain-liver axis, depleting hepatocyte nuclear factor 4α and impairing lipid metabolism, further contributing to the cachexia phenotype. This hepatic reprogramming creates a metabolic sink that perpetuates muscle proteolysis to supply gluconeogenic precursors (22).

Notably, these tissue-specific alterations are not isolated events but interconnected components of systemic metabolic dysregulation. For instance, adipose-derived free fatty acids can impair insulin signaling in muscle, while muscle-derived amino acids fuel hepatic gluconeogenesis. This systems-level understanding underscores why effective therapies must address the network rather than individual nodes (23).

Assort look at the gut–microbiota–immune axis

The gut–microbiota–immune axis has been found as another important component of cachexia's inflammatory-metabolic circuitry. Dysbiosis in cancer can reshape microbial tryptophan metabolism, shifting the balance among indole, kynurenine, and serotonin pathways and thereby altering host immune tone and intestinal barrier function (24). Microbial and host-derived tryptophan metabolites signal through receptors such as aryl hydrocarbon receptor and others, influencing systemic inflammation, insulin sensitivity, and even central appetite regulation (2). In cachexia, altered tryptophan handling may thus couple gut barrier impairment and endotoxemia to heightened systemic cytokine production and metabolic reprogramming in liver and muscle. This positions the microbiota not merely as an epiphenomenon of advanced disease but as a potential modulator of the inflammatory-metabolic axis, with microbiome-directed interventions like prebiotics, probiotics or dietary modulation being explored as adjunctive strategies (24, 25).

Focus on neuroimmune and autonomic dysregulation

Neuroimmune and autonomic dysregulation provide another layer of integration between inflammation and metabolism in cachexia (26). Sympathetic nervous system activity is often elevated in preclinical models and in patients with cancer cachexia, promoting lipolysis and adipose tissue browning while increasing cardiac and brown adipose thermogenic output (26). Recent transcriptomic analyses of sympathetic ganglia in pancreatic cancer–associated cachexia reveal immune cell infiltration and inflammatory gene signatures, linking local immune activation to altered autonomic control of metabolic organs (27). Clinically, beta-adrenergic blockade has shown promise in attenuating weight loss in some cachectic patients, suggesting that targeting sympathetic over-activity might partially reset the hyper-metabolic state (28). At the central level, inflammatory signals interact with hypothalamic nuclei, modifying neuropeptide expression and rewarding aspects of feeding, thereby compounding anorexia and further enforcing the negative energy balance (29). Taken together, these observations highlight an immune–nerve axis where inflammation and autonomic outputs co-drive metabolic wasting (30).

Molecular mediators bridging inflammation and metabolism

Recent studies have identified specific molecular mediators that function as linchpins connecting inflammatory signaling to metabolic reprogramming (31). Foremost among these is GDF-15, a divergent TGF-β superfamily member secreted by tumor cells in response to cellular stress like hypoxia, chemotherapy or oncogene activation (11). Recent investigation demonstrated that, GDF-15 binds to the receptor GFRAL expressed exclusively in the hindbrain area postrema and nucleus tractus solitarius, activating aversive/anorectic pathways that suppress appetite and induce nausea (32). Beyond central effects, GDF-15 also contributes to peripheral metabolic alterations including insulin resistance and altered substrate utilization. Serum GDF-15 levels correlate strongly with cachexia severity across tumor types and predict poor survival independent of tumor burden (33).

The therapeutic relevance of GDF-15 was decisively demonstrated in the phase II trial of ponsegromab, as a monoclonal antibody neutralizing GDF-15. In this randomized, double-blind, 12-week study involving patients with advanced cancer and cachexia, receiving ponsegromab demonstrated statistically significant improvements (34). These results, which representing the first demonstration of clinically meaningful reversal of cachexia manifestations in a randomized trial validate GDF-15 as both a mechanistic driver and actionable target (12). Parallel developments target the activin/myostatin pathway. In this regard, bimagrumab as an anti-ACVR2B antibody and other ligand traps have shown promise in preclinical models and early-phase trials by blocking signaling through ACVR2B, thereby inhibiting SMAD2/3

activation and preserving muscle mass (35). Combination strategies targeting multiple nodes; since GDF-15 plus activin inhibition represent a rational approach given pathway redundancy (36).

The concept of self-reinforcing loop

Conceptually, the inflammatory-metabolic axis in cancer cachexia can be viewed as a self-reinforcing loop. Tumour-derived factors initiate host immune activation and metabolic reprogramming, which in turn alters the systemic environment in ways that may further support tumour growth while undermining host tissue integrity (2). As adipose and muscle tissues waste, substrate fluxes and endocrine signals change, feeding back to immune, hepatic, neural, and microbial compartments, thereby solidifying a new, maladaptive homeostatic set point (2). The challenge for future research is to disentangle which nodes in this network are most amenable to intervention in individual patients, at what stage of disease, and in what combinations (37). Metabolomics and immunophenotyping, combined with clinical markers of inflammation and body composition, may eventually allow stratification into mechanistic cachexia "endotypes" that can guide targeted therapy (37). For clinicians and researchers alike, the emerging picture underscores that treating cancer cachexia will require early recognition and coordinated manipulation of both inflammatory and metabolic pathways, rather than late attempts to reverse established tissue loss (38). Therefore, it seems that, cancer cachexia is an archetypal immunometabolic syndrome in which chronic inflammation, acute phase activation, adipose and muscle remodelling, hepatic and autonomic dysregulation, microbiota-derived signals, and tumour metabolism form an integrated axis driving progressive wasting (10).

Biomarker strategies for patient stratification

The heterogeneity of cancer cachexia varying in onset, progression rate, dominant tissue involvement (muscle versus fat), and underlying molecular drivers, which necessitates biomarker-guided patient stratification for precision medicine approaches (39). Current approaches span multiple analytical dimensions; i) Circulating protein biomarkers remain the most clinically accessible. In fact, GDF-15 has detected as the leading candidate, with levels >1500 pg/mL identifying patients most likely to respond to the GDF-15–targeted therapy (40). Likewise, IL-6 identifies patients with prominent inflammatory drivers who might benefit from JAK/STAT inhibition (41). Composite scores incorporating multiple cytokines like IL-6, TNF-α and CRP, plus nutritional markers such as albumin and prealbumin improve prognostic accuracy over single analytes (2). A recent study also implicates ACVR2B polymorphisms (e.g., rs2268757) and adiponectin levels as potential genetic/metabolic biomarkers for gastrointestinal cancer cachexia (42). Furthermore, body composition imaging provides critical phenotypic stratification beyond simple weight measurements. Preliminary studies detected that, CT-based quantification of skeletal muscle index at the L3 vertebral level identifies sarcopenia; while, temporal changes quantify muscle loss rate (43). Accordingly, adipose tissue compartmentalization (subcutaneous versus visceral) and evidence of browning by specialized MRI techniques may identify patients with predominant adipose wasting who could benefit from lipolysis inhibitors (44). Moreover, dual-energy X-ray absorptiometry and bioelectrical impedance analysis offer more accessible alternatives for serial monitoring in clinical practice (45). Recent investigation showed, metabolomic profiling can reveal the cachexia-associated signatures including elevated branched-chain amino acid catabolites across with altered lipid species and perturbed TCA cycle intermediates (46). Transcriptomic analysis of peripheral blood mononuclear cells identifies inflammatory gene expression signatures predictive of cachexia progression (33). Integration of genomic (germline polymorphisms in cytokine/ACVR2B genes), proteomic (cytokine panels), metabolomic, and imaging data through machine learning algorithms promises to generate robust predictive models for individualized risk assessment and treatment selection (47).

Conclusion

Cancer cachexia is an inevitable consequence of advanced malignancy; however, it is a treatable syndrome driven by a definable inflammatory-metabolic axis. The complex crosstalk among tumor-derived factors, host inflammatory responses, and multi-organ metabolic reprogramming creates both complexity and opportunity, difficulty in the form of redundant pathways requiring multi-target approaches, since opportunity through the identification of actionable points like GDF-15 and ACVR2B signaling. The recent success of ponsegromab validates the precision medicine paradigm: selecting patients based on biomarker profiles (elevated GDF-15) to receive mechanism-targeted therapy yields clinically meaningful improvements in weight, muscle mass, and function. Moving forward, the field must harbor stratification; while not all cachexia is identical, and not all patients will respond to the same intervention. Integration of circulating biomarkers, body composition phenotyping, and emerging multi-omics signatures will enable matching patients to optimal treatments. Combination approaches targeting complementary pathways, initiated early in the cachexia origin, hold promise for transforming this devastating syndrome from a terminal complication into a manageable comorbidity.

Authors' contribution

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Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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