Hypothesis

Homeostatic Deception via Dissociated Catabolic Ketosis

Cristofer L Johnson *

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Homeostatic Deception via Dissociated Catabolic Ketosis

Cristofer L Johnson

Independent Researcher; Patient-Author, USA; edivebuddy@gmail.com

Abstract

After decades of in vivo isotope tracing, human solid tumors have not been shown to derive the majority of their carbon from circulating glucose. Despite this, glucose uptake by tumors continues to be widely interpreted as evidence of glucose dependence for growth. In contrast, clinical evidence indicates that glucose and glutamine are consumed primarily as regulatory and biosynthetic substrates rather than as dominant carbon sources, with tumor biomass supplied largely by lactate, glutamine, and host-derived amino acids and lipids. Their high-rate consumption depletes local availability for immune effectors as a consequence of normal proliferative cell biology rather than as a targeted competitive mechanism. Cachexia is commonly described as a secondary complication of advanced cancer, yet this metabolic behavior results in a tumor-benefiting systemic metabolic state that favors malignant persistence at the expense of host tissues. High rates of glucose and glutamine consumption are associated with systemic metabolic effects that include immune substrate depletion and signaling pathways that promote host catabolism. Dietary deprivation strategies often fail in solid tumors not because tumor growth depends directly on dietary glucose availability, but because restriction accelerates host metabolic collapse without materially limiting the substrates tumors can access. Central to this argument is a newly proposed construct: homeostatic deception via dissociated catabolic ketosis, a tumor-associated metabolic state in which physiological ketogenesis is genuinely present but decoupled from its normal protein-sparing function. Circulating ketones contribute to this dysfunction: central energy-sensing circuits interpret the ketotic state as adaptive fasting and generate a response appropriate to that interpretation, while GDF-15 and inflammatory signaling drive progressive wasting through independent pathways. As tumor burden increases those signals amplify, deepening the catabolic program rather than resolving it. The resulting catabolic loop supplies tumors with substrates released from host tissues while the host's regulatory systems register a state that resembles metabolic adaptation rather than pathological catabolism. The component mechanisms described here are individually established in the literature; the novelty of this manuscript is the proposal that in aggregate they constitute a syndrome-level state, dissociated catabolic ketosis, that explains why cachexia persists despite preserved or elevated ketone signaling. Cachexia persists as long as the tumor driver remains active and reverses primarily when tumor burden and inflammatory signaling are controlled. *A documented case of metastatic NSCLC with longitudinal clinical and photographic records is presented as the generative observation that motivated this framework.* (Johnson CL, 2026, https://doi.org/10.5281/zenodo.18974929). The tumor does not mimic ketosis or any other metabolic state. It simply executes the normal stress-response programs of a severely compromised cell. The systemic result happens to resemble ketosis to the host's energy-sensing apparatus; that resemblance is the mechanism of harm. This manuscript integrates metabolic tracing, immunometabolism, and clinical observation to propose a mechanistic hypothesis in which cachexia is the primary clinical manifestation of a tumor-benefiting syndrome driven by homeostatic deception via dissociated catabolic ketosis. The framework proposes multiple targets for companion therapeutic intervention and offers a mechanistic account of the oft-observed failure of diet-based strategies.

Keywords: Cachexia; dissociated catabolic ketosis; CNS Energy Sensing; homeostatic deception; GDF-15; GFRAL; tumor metabolism; cancer metabolism

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1. Introduction

Cancer cachexia affects a majority of patients with advanced solid tumors and is strongly associated with mortality independent of tumor burden [1,2]. Historically, cachexia has been viewed as an end-stage metabolic "exhaustion" or a passive consequence of malignancy, implying the tumor acts as a metabolic parasite outcompeting the host for nutrients [2]. However, the metabolic consequences of tumor growth (hypoxia, inflammation, and cellular stress) persistently activate normal host crisis-response programs that were never designed to run without resolution.

Several clinical observations support this shift away from a simple nutritional deficiency model:

- Cachexia frequently develops prior to intensive therapy [1]
- It progresses despite adequate or forced caloric intake [2]
- Nutritional supplementation alone rarely reverses it [1]
- Reversal is most consistently observed after effective tumor control [1,2]

The framework proposed here, homeostatic deception via dissociated catabolic **ketosis**, offers a mechanistic explanation for how this program may operate and why interventions targeting dietary substrate may fail to interrupt it. Recognizing cachexia as a tumor-associated state rather than a passive consequence suggests a shift from nutritional support alone toward strategies that disrupt tumor-driven metabolic signaling.

The foundational frameworks for understanding cancer cachexia are well established. Fearon et al. defined the clinical and diagnostic criteria that remain in use today, characterizing cachexia as a multifactorial syndrome driven by negative energy balance and systemic inflammation [1]. Baracos et al. provided a comprehensive account of the parallel molecular mechanisms that sustain the cachectic state, including cytokine signaling, muscle proteolysis, and hepatic reprogramming [2]. The identification of GDF-15/GFRAL as a dedicated brainstem axis for somatic distress signaling established the central nervous system as an active participant in the cachectic phenotype rather than a passive recipient of peripheral signals [35]. These contributions form the evidential foundation on which the present framework is built. What they do not collectively explain is why cachexia persists despite preserved or elevated ketone signaling, and why nutritional interventions fail even when caloric delivery is adequate. The framework proposed here addresses that specific gap by proposing that the components identified in prior work together constitute a syndrome-level state, dissociated catabolic ketosis, in which CNS ketone sensing sustains a fasting-adaptive interpretation of the metabolic environment while tumor-driven catabolism runs unrestrained through independent pathways.

Homeostatic deception via dissociated catabolic ketosis is here framed as the syndrome, of which cachexia is the primary clinical manifestation. No single component explains the full picture, but the components together produce a unified mechanistic account of the observed biology. The component mechanisms described here are individually established in the literature; the novelty of this manuscript is the proposal that in aggregate they constitute a syndrome-level state that explains why cachexia persists despite preserved or elevated ketone signaling. This framework was motivated by direct observation of the author's own case of metastatic NSCLC, documented in a separate case report [3].

2. Glucose Is Not the Predominant Source of Tumor Carbon In Vivo

Many still assume solid tumors grow primarily by burning glucose for energy and biomass. This assumption persists despite extensive in vivo evidence indicating that glucose is not the dominant contributor to tumor carbon. Stable isotope tracing using ^{13}C glucose in living patients consistently demonstrates incorporation of glucose carbon into tumor metabolites, yet quantitative analyses reveal that glucose accounts for only a minority of tumor biomass and TCA cycle fueling [4].

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Across solid tumors, the majority of carbon and building blocks are supplied by lactate, glutamine, and especially host-derived amino acids and lipids. In non-small cell lung cancer, lactate predominates over glucose as a TCA fuel in vivo [4]. Tumors exhibit marked metabolic heterogeneity across regions, drawing on multiple circulating nutrients rather than a single dominant fuel source [5,6]. In human glioblastoma, less than 50 percent of the acetyl-CoA pool derives from blood-borne glucose [7], and independent tracing work confirms that even where glucose flux is active it is directed toward amino acid synthesis rather than bulk carbon supply [8], two independent lines of evidence converging on the same conclusion. Protein scavenging, lipid uptake, and intracellular recycling pathways are extensively utilized, with lipids and amino acids frequently derived from host tissue stores rather than diet [2,9,10].

If glucose is not the primary source of tumor carbon, then dietary glucose restriction cannot selectively starve the tumor. Restriction targets the wrong variable and has not produced consistent clinical benefit in established cachexia.

Instead, glucose and glutamine function primarily as regulatory substrates. They act as metabolic control signals that reprogram host physiology, suppress immune function, and initiate the catabolic release of the substrates tumors actually depend on. In this framework, glucose is less fuel than signal, a switch that activates oncogenic pathways such as HIF-1α and mTOR, sustains glycolytic flux, and reshapes both local and systemic metabolism [10-12,13] (see Figure 1: Fuel vs. Signaling Diagram).

The Warburg Effect is therefore not simply an inefficient ATP-producing pathway. It represents a regulatory metabolic configuration that reshapes the metabolic environment of both tumor and host. By fermenting glucose to lactate, tumors generate a lactate-rich microenvironment that suppresses immune surveillance, promotes angiogenesis, and induces metabolic stress in surrounding and distant tissues [4,11,12]. Lactate and related metabolic signals extend beyond the local tumor microenvironment and can influence systemic physiology. These signals propagate through inflammatory and endocrine pathways, contributing to insulin resistance and activating catabolic programs that mobilize amino acids and lipids from skeletal muscle and adipose tissue. What appears to be an inefficiency in ATP production is in fact a regulatory metabolic program in which metabolic flux reshapes host physiology in ways that expand the circulating pool of substrates available to the tumor.

The non-specificity of aerobic glycolysis is consistent with this interpretation. The Warburg Effect is not a cancer-specific metabolic invention; it is a conserved stress-response program observed in any rapidly dividing or metabolically stressed cell, including activated T cells, macrophages, healing wounds, and inflammatory lesions [41]. High FDG uptake on PET imaging does not equate to malignancy for precisely this reason: activated inflammatory cells at sites of infection, granulomatous disease, or tissue injury display markedly increased glycolytic rates and can produce high standardized uptake values without any malignant histology [42]. What distinguishes solid tumors is not that stressed cells ferment glucose, but that the tumor constitutively maintains the signaling state that drives that program without resolution. A healing wound generates the same metabolic signature transiently and then resolves. The tumor never resolves. This non-specificity therefore reinforces rather than undermines the regulatory signaling model: aerobic glycolysis is normal stress biology, and cancer's contribution is the chronic, unresolvable driver that keeps it running.

The clinical implication is not simply one of supply. Dietary restriction strategies may transiently slow primary tumor growth while simultaneously accelerating the catabolic signaling state the tumor has already established, deepening host wasting and ultimately expanding the circulating pool of host-derived substrates available for tumor proliferation. The net outcome favors the tumor. Targeting glucose as bulk fuel misses its true role. The relevant variable is metabolic signaling, not caloric deprivation.

Recognizing that glucose is not the dominant source of tumor carbon reframes the entire metabolic problem. The central question is no longer how tumors extract calories from the diet, but

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how they use specific substrates to regulate host metabolism and immune function. Glucose and glutamine exert their influence less through bulk contribution and more through signaling roles that reshape systemic physiology [14,15]. Understanding this distinction is essential before any dietary or metabolic intervention can be meaningfully evaluated.

The distinction between the traditional bulk-fuel model and the regulatory signaling model proposed here is summarized schematically in Figure 1.

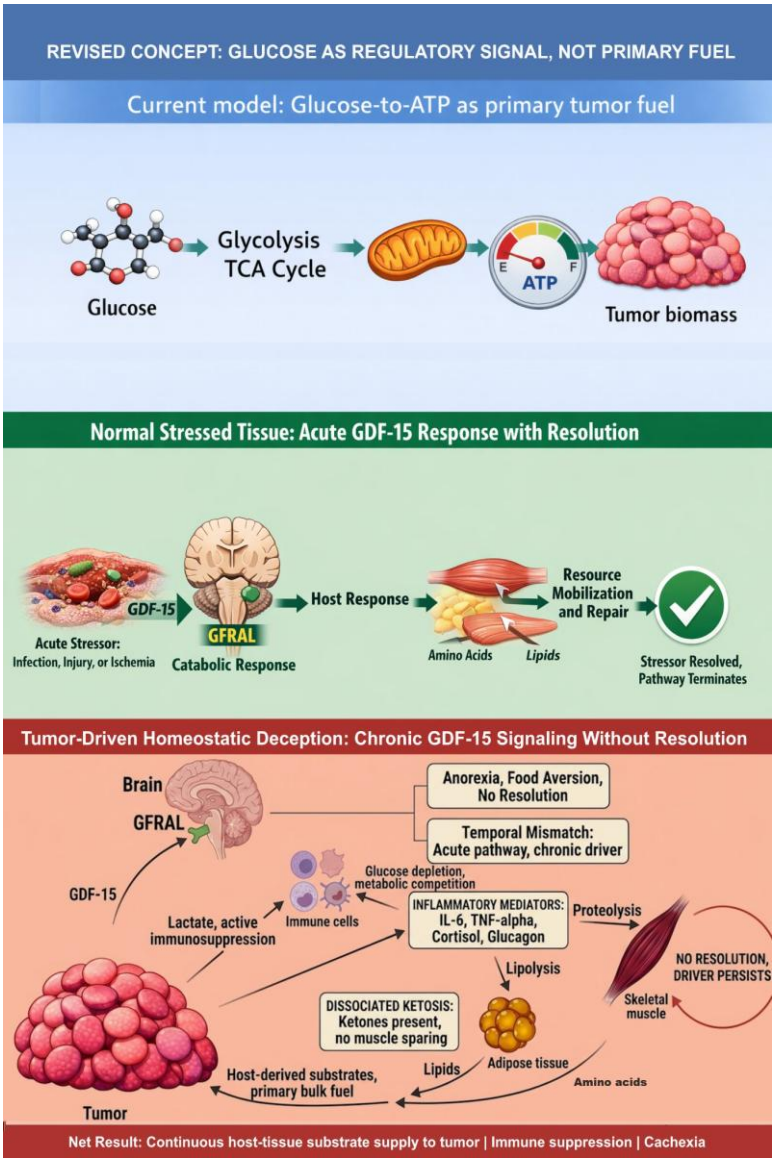

Figure 1. Revised concept: glucose as regulatory signal, not primary tumor fuel. Top panel: Current model treats glucose as primary tumor fuel; restriction is expected to limit growth. Middle panel: Acute stress triggers GDF-15/GFRAL signaling, causing temporary anorexia and catabolism that resolves when the stressor clears. Bottom panel: Tumors maintain this signal chronically. Catabolism continues, host tissue is broken down, and substrates supply the tumor. Ketones are present but muscle is not preserved. .

3. Glucose and Glutamine as Regulatory, Not Bulk, Substrates

The distinction between bulk fuel and regulatory substrate is central to this analysis. Glucose uptake by solid tumors has been widely interpreted as evidence of metabolic dependence on dietary glucose, yet quantitative in vivo carbon tracing consistently demonstrates that glucose accounts for a minority of tumor biomass carbon in every human solid tumor examined by in vivo isotope tracing to date, with the strongest evidence in NSCLC, glioblastoma, and pancreatic adenocarcinoma [4,5,7].

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This analysis proposes that glucose and glutamine function primarily as regulatory signaling substrates rather than dominant carbon sources, with their significance lying in what they signal, suppress, and mobilize rather than in their direct contribution to tumor mass.

3.1. Glucose

In vivo, glucose functions in solid tumors primarily as a regulatory signaling substrate rather than a bulk carbon source. It serves as a flux hub enabling branching biosynthesis through glycolytic intermediates, and as a redox regulator through the pentose phosphate pathway. More consequentially, glycolytic flux sustains the activation of mTOR, MYC, and HIF-1α, oncogenic pathways that drive proliferation, angiogenesis, and metabolic reprogramming at a systems level [16]. Glucose also functions as a high-flux consumed substrate: glycolysis at tumor rates depletes local glucose to concentrations insufficient for T-cell activation and cytotoxic function [11,17], an immune consequence of normal proliferative metabolism rather than a targeted competitive mechanism. The result is that glucose consumption shapes the tumor microenvironment and systemic immune landscape far beyond any direct contribution to tumor mass.

3.2. Glutamine

Glutamine exerts comparable regulatory influence through distinct mechanisms. It supports TCA anaplerosis and nucleotide synthesis, providing carbon and nitrogen for biosynthetic demands [16], and regulates redox buffering through glutathione synthesis, protecting tumor cells from oxidative stress. Glutamine availability also modulates extracellular acidity and downstream signaling within the tumor microenvironment. Critically, high-rate glutamine consumption by tumor cells depletes the substrate that immune cells require for activation, proliferation, and cytotoxic activity, a consequence of normal biosynthetic demand that impairs the antitumor immune response [18,19,20].

The systemic consequences of this depletion extend beyond the local tumor microenvironment. In vivo, host-produced glutamine, synthesized primarily in skeletal muscle and lung, represents the dominant available source rather than endogenous tumor cell synthesis, consistent with the catabolic mobilization of host lean tissue that characterizes the established disease state. The rate and severity of cachexia likely reflect tumor biology and signaling output rather than burden alone [21,22]. Glucose and glutamine are not incidental substrates; their consumption is the initiating event. High-flux uptake establishes the immune-depleting microenvironment, activates oncogenic signaling cascades, and triggers the host stress responses that drive cachexia. By the time cachexia is established the regulatory consequences of that consumption are already self-sustaining. Restriction strategies may hasten this process rather than reverse it, worsening the host's metabolic position while the tumor adapts to alternative substrates.

4. Cytokine-Driven Metabolic Signaling

A central feature of cancer cachexia is persistent systemic inflammation driven by tumor-derived and host-derived cytokines. Among these mediators, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are consistently implicated as major regulators of the cachectic phenotype. These cytokines act not only as inflammatory signals but also as metabolic regulators that reshape whole-body energy handling [2,23].

IL-6 signaling promotes hepatic acute-phase responses, alters insulin signaling, and contributes to increased hepatic glucose output. Elevated IL-6 levels have been strongly associated with muscle wasting, systemic inflammation, and poor clinical outcomes in cancer patients. At the same time, TNF-α contributes to insulin resistance, promotes lipolysis in adipose tissue, and accelerates proteolysis within skeletal muscle. Together these cytokines disrupt normal anabolic signaling and favor persistent catabolism [2,23,24].

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Importantly, these inflammatory signals interact with endocrine stress pathways. Elevated glucagon, cortisol, and catecholamine signaling frequently accompany cachexia, amplifying insulin resistance and reinforcing a systemic metabolic state that resembles fasting despite ongoing nutrient availability. The combined effect of inflammatory cytokines and counter-regulatory hormones produces a coordinated metabolic shift that mobilizes host energy reserves [2].

It directs specific organs into characteristic metabolic programs. Skeletal muscle becomes a primary source of amino acids through accelerated proteolysis, adipose tissue releases fatty acids and glycerol through lipolysis, and the liver responds by activating pathways normally associated with fasting metabolism. These coordinated responses establish the systemic conditions that drive progressive tissue loss and metabolic instability in cancer cachexia [1,2].

The molecular effectors described above, including cytokine-driven proteolysis, UPS-mediated muscle protein degradation, activin and myostatin signaling, and lipolytic programs in adipose tissue, are well-characterized components of the cachexia literature [1,2,25]. This account does not replace these mechanisms. It proposes an upstream explanation for why they are chronically activated. Tumor-maintained stress signaling, operating through pathways including GDF-15/GFRAL and sustained inflammatory cytokine output, continuously drives the host into the crisis-response state in which these effectors operate. The established molecular mechanisms are the execution layer. The homeostatic deception framework describes the persistent signal that keeps them running.

In a pooled comparison of serum GDF-15 signal magnitude and cachexia prevalence across solid tumor types, combining GDF-15 measurements from Wang et al. 2014 (n=1,712, single-cohort ELISA, nine tumor types measured against the same healthy control group) [26] with cachexia prevalence rates drawn from the best available per-tumor-type published sources with explicit patient populations using consistent diagnostic criteria [27,28,29], presenting a heuristic pattern as an exploratory cross-study comparison (Table 2). This comparison is not a statistically tested association; the GDF-15 and cachexia prevalence data derive from different cohorts, time periods, and diagnostic frameworks, and should be interpreted accordingly. Seven tumor types with clean per-tumor prevalence data are included; gastric and ovarian carcinoma appear in the GDF-15 dataset but are excluded from the prevalence comparison because no single-cohort prevalence estimate using consistent diagnostic criteria with an explicit n was available to the author. Tumor types with the highest serum GDF-15 elevation tend to carry higher cachexia rates, consistent with the proposed framework. Two tumor types represent partial exceptions requiring direct acknowledgment: breast carcinoma shows a GDF-15 signal statistically indistinguishable from healthy controls ($p=0.856$) yet carries a 34% cachexia prevalence, consistent with cachexia arising predominantly through IL-6 and TNF-α-driven peripheral catabolism rather than GDF-15/GFRAL-mediated central signaling, a dissociation that illustrates the framework's distinction between these two convergent but mechanistically independent pathways. Prostate adenocarcinoma shows one of the higher GDF-15 signals in the dataset yet carries only 29% cachexia prevalence; androgen signaling may partially offset GDF-15-driven catabolism through sustained anabolic drive on skeletal muscle, and the ≥5% weight loss threshold may be harder to meet in a population that typically presents with higher baseline body mass; both factors that could suppress recorded cachexia prevalence independently of the underlying inflammatory biology [30]. Both exceptions share a common feature: hormonal anabolic signaling (estrogenic in breast, androgenic in prostate) may partially offset inflammatory catabolism at the level of body weight, such that weight-based diagnosis may underestimate true cachexia prevalence in hormonally active tumor types [2]. Weight loss remains the universal clinical standard because it requires no technology and is available at every clinical encounter; serial laboratory markers and skeletal muscle quantification from routine staging CT add characterization that weight alone cannot provide but cannot substitute for its frequency and accessibility. Both limitations in hormonally active tumor types are noted here as an area warranting prospective body composition study. Individual variation within each tumor type is expected given the continuous

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nature of the underlying biology. Table 2 is presented as exploratory. The detailed sources underlying each data point in Table 2 are provided in Supplementary Table S1.

Table 2. Pooled Analysis: Serum GDF-15 Signal Magnitude and Cachexia Prevalence by Solid Tumor Type.

Tumor Type	Mean Serum GDF-15 (pg/mL ± SD)	p vs Controls	Cachexia Prevalence
Healthy controls	416.8 ± 286.9	Reference	—
Pancreatic adenocarcinoma	1,731.0 ± 1,181.0	<0.001	62.5% [29]
Colorectal adenocarcinoma	1,371.0 ± 818.7	<0.001	51% [27]
Non-small-cell lung carcinoma	1,258.0 ± 587.3	<0.001	55% [27]
Prostate adenocarcinoma	1,167.0 ± 804.9	<0.001	29% [27]
Esophageal squamous cell carcinoma	1,018.0 ± 618.7	<0.001	48% [28]
Breast carcinoma	426.5 ± 264.0	NS (p=0.856)	34% [27]
Thyroid carcinoma	336.4 ± 172.2	NS (p=0.132)	— b

GDF-15 values: Wang et al. BMC Cancer 2014 [26], single-cohort ELISA, n=1,712 total study population, n=30 per tumor type in cross-tumor comparison cohort, same healthy control group (n=500). Cachexia prevalence: per-tumor-type best available published sources with explicit n, as cited; see Supplementary Table S1 for full source details. a Gastric and ovarian carcinoma GDF-15 values are from [26] but are excluded from the prevalence column: no single-cohort prevalence estimate using consistent diagnostic criteria with an explicit n was available. b Thyroid carcinoma cachexia prevalence excluded: available estimates are substantially confounded by multikinase inhibitor (MKI) toxicity-driven weight loss (nausea, diarrhea, anorexia) rather than tumor-driven wasting; no clean single-cohort estimate using consistent Fearon-equivalent criteria with explicit n was identified. NS = not significant vs healthy controls.

5. Hepatic Metabolic Response

Tumor-driven insulin resistance, inflammatory cytokine signaling, and counter-regulatory hormone excess do not merely resemble starvation systemically. They specifically reprogram the liver into a chronic fasting-response state.

In this state, hepatic gluconeogenesis and ketogenesis are activated in parallel, but they are not equivalent processes. Gluconeogenesis is the liver's production of glucose, largely from alanine, lactate, glycerol, and other host-derived precursors. Ketogenesis, in contrast, is the production of ketone bodies from fatty-acid-derived acetyl-CoA. The first sustains circulating glucose at the expense of substrate extraction from host tissues, while the second provides an alternative oxidative fuel and a signal typically associated with successful fasting adaptation.

Under normal physiological fasting, these pathways operate within a coordinated protective program. Ketogenesis rises as adipose-derived fatty acids become the primary fuel source, while skeletal muscle proteolysis is progressively suppressed in order to preserve lean mass. Circulating ketones signal to the brain that energy availability is adequate and that lean mass is being preserved, dampening counter-regulatory stress responses.

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In cancer cachexia, however, inflammatory signaling and stress hormone dominance prevent this program from remaining protein-sparing. Muscle proteolysis and adipose lipolysis continue despite the presence of circulating ketones. The liver therefore continuously converts products of tissue breakdown into glucose and ketone bodies, linking peripheral tissue wasting directly to systemic fuel redistribution.

The result is a pathologic hepatic response in which the liver converts the products of muscle proteolysis and adipose lipolysis into circulating fuels that sustain both host metabolism and tumor persistence. This is not simply starvation physiology. It is starvation physiology held open under malignant signaling [2,23,24]. IL-6-driven acute-phase signaling, combined with insulin resistance and counter-regulatory hormones such as glucagon and cortisol, can prevent normal termination of the fasting-response program. Under these conditions the liver can remain biased toward gluconeogenesis and ketogenesis even when nutrients are present, creating a persistent catabolic state rather than a transient adaptive fast.

Systemic autophagy in skeletal muscle and liver contributes to amino-acid liberation during cancer cachexia. Tumor-derived IL-6 has been shown to directly accelerate autophagic flux in muscle cells via trans-signaling through the soluble IL-6 receptor, independently of nutritional status [31], with autophagy-inducing activity confirmed in serum from cachectic lung and gastrointestinal cancer patients and directly correlated with weight loss [45]. Because this autophagic drive is cytokine-mediated rather than substrate-mediated, it persists even when caloric intake is restored or supplemented. The oncologic signaling environment continues to instruct tissue catabolism regardless of nutrient availability. Nutritional support may attenuate the rate of wasting, but it cannot extinguish the upstream inflammatory signal. Through this mechanism, tumor-driven IL-6 signaling sustains catabolic recycling in distant tissues, increasing the circulating availability of amino acids such as glutamine, which can then be scavenged by tumor cells through mechanisms including macropinocytosis [32].

Dissociated catabolic ketosis describes this pathological state in which ketones are produced, as in normal fasting, but the protective protein-sparing response is overridden by tumor-driven inflammation (see Table 1). The syndrome may be operationally recognized by a characteristic pattern: progressive lean mass loss on serial CT or DEXA in the presence of active tumor burden, with one or more of the following associated features: elevated serum beta-hydroxybutyrate, elevated GDF-15, or elevated inflammatory markers such as IL-6 or CRP. No single marker is required; the defining feature is unrestrained catabolism in the absence of the protein-sparing response that characterizes voluntary fasting. This distinguishes dissociated catabolic ketosis from starvation ketosis, where protein-sparing is preserved, and from diabetic ketoacidosis, which is driven by insulin deficiency in a distinct clinical context. Circulating ketones contribute to this dysfunction: central energy-sensing circuits interpret the ketotic state as adaptive fasting and generate a response appropriate to that interpretation, while GDF-15 and inflammatory signaling drive progressive wasting through independent pathways. The system is not failing to respond; it is responding to what it detects, in a context where that response is pathological. The net biochemical consequence is a profoundly negative nitrogen balance: protein catabolism exceeds synthesis at the whole-body level regardless of intake [1,2], in direct contrast to the neutral or positive nitrogen balance maintained during protective ketosis.

The defining features that distinguish protective ketosis from dissociated catabolic ketosis are summarized in Table 1.

Table 1. *Protective Ketosis vs. Dissociated Catabolic Ketosis.*

Feature	Protective Ketosis (Voluntary Fasting)	Dissociated Catabolic Ketosis (Tumor-Driven)
Trigger	Caloric deprivation	Tumor-driven inflammation and stress

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Ketone production	Present	Present
Muscle proteolysis	Suppressed	Active and unrestrained
Primary fuel source	Adipose tissue	Host muscle and fat tissue
Inflammation signaling	Low	High (IL-6, TNF-α)
Hormonal environment	Low cortisol, adaptive glucagon	Elevated cortisol and glucagon
Brain interpretation of state	Adaptive fasting	Adaptive fasting
Homeostatic alarm response	Appropriately dampened	Pathologically silenced
Host tissue outcome	Lean mass preserved	Progressive tissue loss
Nitrogen balance	Neutral to positive; lean mass preserved	Profoundly negative; protein loss exceeds synthesis regardless of intake
Net biological effect	Host protection	Tumor nourishment

This signaling environment produces a state the brain experiences as adaptive fasting while simultaneously extracting the amino acids and lipid substrates released by that state. Unrestrained muscle proteolysis releases alanine, glutamine, and branched-chain amino acids into circulation, which the tumor scavenges, exploiting the same physiological program the host uses to survive a fast [32].

The liver becomes a central metabolic effector of this deception, not merely a passive victim, because it is the organ that converts tumor-induced inflammatory and hormonal signals into sustained gluconeogenic and ketogenic output [2,24].

This program evolved for short-term fasting but is now driven continuously by persistent stress signaling rather than caloric deprivation. The resolution signal that would normally terminate the program never arrives. Instead, hepatic metabolism remains locked in a prolonged fasting-response state, contributing to the metabolic dysregulation characteristic of advanced cachexia.

An important clinical implication follows. Ketosis in cancer patients is often interpreted as evidence of metabolic adaptation rather than recognized as the surface manifestation of active tissue destruction. The metabolic state that therapeutic fasting or ketogenic diets attempt to induce is therefore the same state the tumor has already established. Deepening this metabolic state is unlikely to deprive tumors of nutrients and may instead accelerate the delivery of host-derived substrates that fuel tumor growth and progression [33].

6. Central Nervous System Signaling and the Basis of Homeostatic Deception

The anorexia of cancer cachexia is not a failure of appetite regulation. It is appetite regulation working correctly, responding to a legitimate stress signal through an intact and functional pathway.

6.1. GDF-15, Somatic Distress Signaling, and the Brainstem Threat-Response Pathway

Growth differentiation factor 15 (GDF-15) is a stress-responsive cytokine produced by tissues under conditions of severe metabolic stress, inflammation, hypoxia, and cellular injury. In normal physiology it functions as a signal of somatic distress, communicating the severity of a peripheral crisis to the central nervous system [34]. Its receptor, GFRAL, is expressed exclusively in the area postrema and nucleus tractus solitarius of the brainstem, structures that evolved to detect circulating danger signals and generate protective aversive and behavioral responses [35].

When GDF-15 reaches GFRAL it activates the GFRAL-RET signaling complex, suppressing orexigenic NPY neurons, activating anorexigenic POMC neurons, and stimulating glucocorticoid release through HPA axis activation [35]. The result is anorexia, food aversion, and initiation of a peripheral hypercatabolic state. This is the response the brainstem is designed to produce when

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somatic distress signaling is elevated: stop intake, mobilize resources, redirect physiology toward managing the crisis.

Circulating GDF-15 is elevated in cancer patients and correlates with weight loss, reduced lean body mass, and mortality [36]. The tumor, as metabolically stressed, hypoxic, and rapidly proliferating tissue, generates GDF-15 as any severely stressed tissue would, through the same stress-response pathways active in severe infection, ischemia, or major tissue injury. The signal is real. The brainstem responds correctly. The problem is that it never resolves. Total parenteral nutrition, which eliminates all barriers to caloric delivery, does not reverse cachexia, an observation consistent with tumor-driven GDF-15 signaling maintaining the cachectic state rather than nutritional inadequacy alone.

6.2. The Temporal Mismatch: Acute Biology, Chronic Driver

The GDF-15-GFRAL pathway involves a crisis that can normally resolve. Infection clears. Wounds heal. Ischemia either causes death or recovers. In each case the somatic distress signal eventually falls, the brainstem aversion response terminates, and the host recovers. The anorexia and catabolism that redirected resources toward the crisis were temporary.

The tumor does not resolve. It maintains the somatic distress signal continuously, and the host's entirely appropriate response to that signal runs without interruption. What in any other context would be a brief protective catabolism becomes a sustained and progressive one. The host's resource-mobilization response, anorexia, proteolysis, lipolysis, gluconeogenesis, continues not because the system is failing but because the signal driving it never stops.

This is the homeostatic deception. The central nervous system is not confused or blind. It is receiving an accurate signal and responding exactly as its biology dictates. The signal means crisis. Crisis means mobilize. The system has no mechanism to distinguish between a crisis that will resolve and one that will not, because that distinction was never required before. Every component of this response is normal. The only distinguishing element is the oncologic driver, which does not resolve.

6.3. Peripheral Catabolism as a Parallel and Converging Process

The brainstem aversion pathway accounts for the anorexia. Simultaneously, the tumor-associated inflammatory environment, elevated IL-6, TNF-α, cortisol, and glucagon, drives muscle proteolysis and adipose lipolysis through peripheral mechanisms that operate independently of central appetite signaling [2,23,24]. The GFRAL-RET pathway additionally recruits the peripheral sympathetic nervous system, promoting lipolysis in adipose tissue through a mechanism that further amplifies tissue mobilization independent of food intake [35].

The result is a state in which the CNS suppresses intake while peripheral catabolism simultaneously accelerates the mobilization of host tissue, both functioning through normal biological pathways, and both converging to supply a continuous nutrient stream to the tumor from host reserves.

The host is not failing to respond. It is responding to a signal its biology was built for, in a context where that response actively undermines the immune defenses that would otherwise contain the source of the signal.

This mechanism is not specific to a particular tumor type. GDF-15 secretion by metabolically stressed tissue is normal biology; a solid tumor that failed to generate it would be the anomaly. The pathway therefore applies across solid tumors broadly, with variation in the degree of GDF-15 output, reflecting tumor metabolic state, mutation profile, and burden, rather than in whether the pathway is active. GDF-15/GFRAL is presented here as a major candidate upstream signal; the framework does not require GDF-15 to be the dominant driver in all tumor types or all patients, and the breast and prostate anomalies noted in Table 2 illustrate that other signaling axes are likely operative in some populations. Parallel cachectic pathways including myostatin and activin signaling, hypothalamic inflammation, and tumor-derived proteolytic factors operate independently and may predominate in specific tumor types or patient populations.

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6.4. CNS Ketone Sensing as an Established Physiological Mechanism

The role of circulating ketones as active signals to central energy-sensing circuits is not inferential. Hypothalamic ketone body sensing is a documented physiological mechanism: direct cerebral exposure to beta-hydroxybutyrate stimulates food intake through upregulation of the orexigenic neuropeptides NPY and AgRP and activation of AMPK, responses that are driven by ketones detected by the brain independently of peripheral blood levels [43]. At the receptor level, BHB binds HCAR2 and FFAR3, G-protein-coupled receptors that reduce lipolysis and suppress sympathetic tone in direct response to circulating ketone availability [44]. These are active feedback mechanisms through which the brain registers the ketotic state as adaptive and attenuates counter-regulatory alarm accordingly.

This is the normal and correct response to fasting ketosis. The problem in dissociated catabolic ketosis is not that this mechanism is absent or malfunctioning. It is that the mechanism operates as designed while an independent catabolic program, driven by GDF-15/GFRAL signaling and inflammatory cytokines, simultaneously dismantles host tissue through pathways the ketone-sensing circuit cannot detect or override. The brain reads the ketone signal accurately. The signal means adaptation is underway. Alarm is appropriately attenuated. What the circuit cannot distinguish is whether the ketosis it is registering reflects successful fasting adaptation or the surface output of a tumor-driven catabolic loop that will not resolve. That distinction was never required in the evolutionary context for which this system was built.

The deception is therefore mechanistically grounded, not metaphorical. Ketone sensing suppresses alarm through documented receptor pathways. GDF-15 drives catabolism through the independently documented GFRAL axis. Both run simultaneously, and the resolution signal that would terminate the catabolic program under normal fasting never arrives because the tumor driver does not resolve.

7. Cachexia as a Systemic State Benefiting Tumor Growth

Once established, cachexia does not represent systemic failure or nutritional inadequacy. It represents a tumor-favorable metabolic state sustained by malignant signaling [1,2]. The cachectic state creates conditions favorable to continued tumor survival and proliferation, in a metabolic environment conducive to malignant growth at the expense of host preservation.

Cachexia benefits the tumor in several ways:

• Continuous nutrient supply independent of dietary intake.

Unrestrained muscle proteolysis releases amino acids such as glutamine, alanine, and branched-chain amino acids, while adipose breakdown liberates fatty acids and glycerol. These substrates enter circulation and are scavenged by the tumor, ensuring reliable nutrient availability even during caloric deprivation.

• Immune suppression through metabolic depletion.

High-flux tumor glycolysis actively reshapes the metabolic environment into an immune "nutrient desert," metabolically disabling effector cells rather than merely outcompeting them for resources [17,18]. By the time effector cells infiltrate the site, the tumor has already depleted the local fuel supplies of glucose and glutamine required for T-cell proliferation, cytokine production, and sustained cytotoxic activity.

• Hepatic reprogramming that favors tumor persistence.

Sustained gluconeogenesis and ketogenesis, driven by inflammatory cytokines and stress hormones, disrupt normal hepatic metabolism. This alters drug handling, worsens systemic inflammation, and narrows the therapeutic window for cytotoxic and immune-based treatments [2].

• Reduced treatment tolerance and efficacy.

Cachectic patients exhibit decreased tolerance to chemotherapy and immunotherapy, increased toxicity, and poorer overall outcomes, independent of tumor burden [2]. The same metabolic state that nourishes the tumor undermines host resilience to treatment.

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• Self-reinforcing inflammatory signaling.

Elevated IL-6, TNF-α, and related cytokines perpetuate insulin resistance, proteolysis, and lipolysis, maintaining dissociated catabolic ketosis and preventing resolution of the hepatic fasting program [23,24]. As tumor burden increases, GDF-15 output and inflammatory signaling amplify in proportion, deepening the catabolic program rather than resolving it. The loop does not reach equilibrium; it accelerates, which accounts for the progressive and ultimately refractory character of advanced cachexia.

At this stage, tumor supply is driven primarily by host-derived substrates, not diet. Tumor nutrient supply occurs upstream of dietary absorption, drawing increasingly on substrates released from host tissues rather than directly from dietary intake. Calories consumed by the patient do not meaningfully interrupt tumor access to nutrients once cachexia is established.

Inflammatory catabolic signaling within cachexia impairs the metabolic capacity required for effective immune responses: immune checkpoint inhibitors depend on metabolically competent T cells, yet the same cytokine milieu driving tissue wasting: elevated IL-6, TNF-α, and cortisol degrade that competence [17].

Consistent with this interpretation, host-directed signaling modifiers may influence treatment outcomes without exerting direct antitumor effects. A retrospective analysis from MD Anderson Cancer Center reported improved outcomes in patients receiving immune checkpoint inhibitors who were concurrently taking H1 histamine antagonists [37]. H1 signaling amplifies cytokine release, promotes anorexia, worsens insulin resistance, and accelerates host catabolism. Attenuation of this signaling may therefore partially disrupt the tumor-associated metabolic environment, expanding the functional window in which PD-1 blockade can operate. This observation aligns with the homeostatic deception framework, in which modifying host signaling can influence tumor behavior indirectly by weakening the metabolic conditions the tumor requires. More directly, GDF-15 inhibition with ponsegromab, a humanized monoclonal antibody blocking the GDF-15/GFRAL axis described in Section 6, produced significant weight gain, improved appetite, and reduced cachexia symptoms in a Phase 2 randomized trial in patients with cancer cachexia and elevated GDF-15 levels, with registration-enabling Phase 3 trials now underway [38].

Cachexia is not merely a consequence of advanced cancer. The cachectic state creates conditions favorable to continued tumor survival and proliferation. This may also help explain the difficulty of controlling metastases in metabolically sensitive organs such as the liver and brain.

8. Why Starvation and Restriction Strategies May Fail

Dietary restriction fails in cachectic states not because tumors depend directly on dietary glucose, but because host counter-regulatory responses amplify the same catabolic physiology already established by tumor-associated signaling. The following mechanisms illustrate how this occurs:

- The host adapts by increasing catabolism, supplying the tumor from tissue stores rather than diet.
- Immune cells lose metabolic function before tumor cells [11,17].
- Activated immune effector cells depend heavily on glycolytic metabolism and lose functional capacity under conditions of glucose deprivation, whereas tumor cells generally retain greater metabolic flexibility.
- Tumors are metabolically stress-tolerant and can switch between fuel sources.
- Host tissue becomes the dominant nutrient source in the cachectic state.
- Ketogenic and caloric restriction protocols may deepen the dissociated catabolic ketosis the tumor has already established. In IL-6-high tumor models (which include lung, pancreatic, and colorectal cancers), experimental evidence demonstrates that ketogenic interventions accelerate cachexia onset and shorten survival despite slowing tumor growth [33]. The mechanism involves NADPH competition between tumor ferroptosis and systemic corticosterone biosynthesis: the same redox demand that kills tumor cells through lipid peroxidation simultaneously impairs

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glucocorticoid production, removing a critical brake on cachexia progression. The concern raised here is therefore not that ketogenic strategies are universally harmful, but that in the presence of active IL-6-driven cachexia they may amplify the catabolic physiology already present rather than interrupt it.

- Cellular scavenging adaptations, including macropinocytosis and autophagy-mediated recycling, allow tumor cells to consume extracellular proteins and cellular debris released during host tissue catabolism [32].

The mechanism of homeostatic deception is central to understanding this failure. Because the brain interprets the ketotic state as adaptive, normal hunger and stress signals that would otherwise drive counter-regulation are blunted. Restriction strategies therefore do not create selective tumor starvation; they amplify the tumor-associated catabolic program, advancing the host toward the very nutrient-release state the malignancy has established, while the host's own regulatory systems remain unalarmed.

This failure is not simply one of supply. When glucose is restricted, tumor cells do not starve; they adapt. Wu et al. in multiple orthotopic murine tumor models observed that glucose restriction suppressed primary tumor growth while simultaneously increasing metastatic spread to the lung through tumor-derived exosomal TRAIL signaling that depletes NK cells [39]. Tumor burden increased and disease spread while the primary lesion temporarily slowed. Independently, Ferrer et al. observed that ketogenic intervention delayed tumor growth while accelerating cachexia onset and shortening overall survival in IL-6-driven cancer models [33]. This finding may establish proof-of-concept in preclinical models; clinical extrapolation awaits human data. The cachectic host, already being dismantled to supply the tumor from host tissue reserves, cannot survive the additional cost.

9. Reversibility of Cachexia

Cachexia reversal is observed primarily when:

- Tumor burden is reduced
- Inflammatory cytokines decline
- Stress hormone dominance resolves

This suggests cachexia is maintained by persistent tumor-associated metabolic signaling. When reversal occurs, it reflects loss or suppression of that signaling state. The inflammatory and hormonal signals that maintain dissociated catabolic ketosis are no longer present; resolution follows tumor control, not nutritional correction. Once the driver is suppressed, the hepatic fasting-response program can terminate as inflammatory cytokine dominance declines and normal metabolic regulation reasserts itself. In physiologic terms, this transition likely reflects a shift from IL-6 and TNF-α-driven signaling back toward restored insulin sensitivity and balanced metabolic control. Ketogenesis normalizes, proteolysis slows, and tissue recovery begins. The Fearon et al. staging framework specifically defines refractory cachexia by the presence of active catabolism associated with advanced tumor burden, supporting the interpretation that irreversibility reflects driver persistence rather than biological impossibility [1]. Where recovery does not follow tumor control, the more likely explanation is cumulative host tissue depletion: muscle, hepatic, and immune reserve exhausted beyond the threshold required for rebuilding. In the most severely depleted patients, nutritional reintroduction itself carries risk: refeeding syndrome, a potentially fatal electrolyte cascade triggered when nutrition is reintroduced after prolonged starvation, is a recognized hazard in advanced cancer cachexia [40].

10. Clinical Implications

10.1. During Active Treatment

By the time cachexia is clinically apparent, the underlying syndrome is already established. Intervention targeting cachexia alone is behind the biology driving it.

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- Caloric adequacy outweighs macronutrient composition as a clinical priority. Weight maintenance and treatment tolerance are primary goals. Restriction during treatment risks accelerating the dissociated catabolic ketosis the tumor maintains.
- Interventions that induce or mimic ketotic states, including therapeutic fasting and strict ketogenic protocols, may risk deepening the cachectic state: the host interprets the ketotic signal as adaptive while the tumor accelerates extraction of host-derived substrates [33]. This caution is not a categorical rejection of ketogenic strategies in cancer care. It is a stage and context-dependent warning: deepening a metabolic state the tumor is already exploiting, without simultaneously reducing tumor burden, compounds rather than counters the cachectic program.
- Nutritional support should be framed as preserving host viability for treatment, not as a tumor-targeting strategy.

10.2. Interpretation of Intake

- Increased intake usually reflects improving systemic control. The homeostatic deception is resolving as the tumor driver weakens.
- Forced intake may support host viability but cannot replace tumor control.
- Intake is more often a marker than a driver of recovery [2].

10.3. Clinical Considerations Within the Current Evidence Base

Given the absence of RCT-level evidence (addressed in Section 11), clinical practice must be guided by mechanistic plausibility and the primacy of tumor control. The following principles are consistent with the homeostatic deception framework:

- Prioritize metabolic neutrality. Support host reserves through nutritionally adequate, anti-inflammatory dietary patterns.
- Avoid escalating interventions, including caloric restriction or aggressive ketogenic protocols while tumor burden remains uncontrolled. These may deepen the dissociated catabolic state rather than counter it.
- Treat intake as a biomarker, not a lever. Declining intake in cachectic patients should trigger reassessment of tumor control and systemic inflammation, not escalation of nutritional pressure alone.
- Monitor dissociated ketosis where feasible. Where resources permit, serial beta-hydroxybutyrate alongside lean mass assessment may help detect the dissociated pattern; however, this remains speculative and is only offered as a conceptual extension of the framework.
- Align nutritional counseling with oncological stage. Patients with controlled or responding disease have different nutritional risk profiles than those with active, uncontrolled tumor burden. Stage-appropriate guidance prevents both under-support and iatrogenic acceleration of the cachectic state.
- Consider early detection before clinical weight loss thresholds are met. Inflammatory markers including IL-6 and CRP are routinely available and a rising trend in the context of active tumor burden may signal the onset of the catabolic program before significant lean mass loss is apparent. Lean mass quantification from routine staging CT, imaging already being performed, provides body composition data that weight alone cannot capture and requires no additional testing. Intervention targeting the upstream driver before the catabolic loop is self-sustaining is more consistent with the framework than waiting for clinical cachexia to declare itself.

11. Ethical Limits and Evidence Inference

Causal inference in cancer cachexia research follows the framework established by Bradford Hill for domains where randomized controlled trials are ethically prohibited or practically impossible. Several Bradford Hill considerations are partially supported by the available evidence. Temporality: cachexia precedes nutritional decline and reverses with tumor control, not with nutritional

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intervention, consistent with the proposed causal sequence. Plausibility: the GDF-15/GFRAL brainstem pathway, inflammatory cytokine signaling, and hepatic metabolic reprogramming provide a mechanistically coherent account of how the cachectic state is driven. Coherence: metabolic tracing, immunometabolism, clinical observation, and the reversal pattern converge without contradiction across independent lines of evidence. Direct causal testing remains incomplete; the framework provides mechanistic plausibility and temporal consistency, not causal proof. These considerations are offered in the tradition of causal reasoning applied in smoking epidemiology, famine physiology, and other domains where deliberate human exposure trials cannot be conducted.

The specific ethical constraint here is narrow. Randomized trials deliberately restricting intake in cachectic cancer patients are unethical and will not be conducted. This does not preclude prospective observational research. A longitudinal cohort study following patients from diagnosis through all disease stages, measuring GDF-15, serum beta-hydroxybutyrate, lean mass by quantitative CT, inflammatory markers, and intake simultaneously, would be both ethical and scientifically powerful. Such a study would test the framework's primary predictions across the full disease course in a single design. The testable predictions in Section 14 constitute precisely that research agenda.

Inference therefore rests on:

- Temporal patterns (cachexia precedes restriction; reversal follows tumor control)
- Mechanistic consistency across metabolic tracing, immunometabolism, and cachexia physiology
- Reversibility with tumor control as a natural experiment
- Failure of nutritional counterfactuals to reverse established cachexia

12. Limitations

This framework addresses tumor-driven cachexia specifically. Treatment-associated wasting shares the same downstream catabolic mechanisms but arises from a distinct upstream cause, iatrogenic tissue injury from toxicity rather than persistent tumor stress signaling. The primary intervention target differs accordingly, and the framework does not address treatment-toxicity-driven wasting as a separate entity.

The framework is inferential, integrating mechanisms established across independent human data streams into a proposed syndrome-level account rather than reporting primary experimental findings. The Bradford Hill criteria are partially satisfied, with temporality, plausibility, and coherence supported by human observational and clinical data, but direct prospective causal testing in longitudinal cohorts remains incomplete.

13. Conclusions

Solid tumors generate the same metabolic stress signals as any severely compromised tissue, driving normal host crisis-response programs that mobilize substrates for tissue repair. Tumor cells, proliferating rapidly and without restraint, consume those substrates faster than host tissues can recover. High-rate glucose and glutamine consumption depletes immune effectors, while the resulting inflammatory and hormonal signaling drives cachexia, a catabolic state that releases further substrates, amplifies the stress signal, and perpetuates the cycle for as long as tumor burden remains uncontrolled.

Central to this process is *homeostatic deception via dissociated catabolic ketosis*: a state of physiological ketogenesis in which central energy-sensing circuits interpret the ketotic state as adaptive fasting, while muscle proteolysis and lipolysis run unrestrained, supplying the tumor from host tissues. The liver, running a short-term fasting program without resolution, degrades over time as the driver remains active. Cachexia represents a tumor-favorable metabolic environment, not an incidental complication. Effective reversal requires elimination or suppression of the tumor driver, with nutrition serving a supportive, not curative, role.

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What Warburg identified were early metabolic markers at the tumor level that appear to be only part of a broader systemic syndrome, one in which normal stress-response physiology operates across multiple axes simultaneously without resolution.

This systemic interdependence may help explain why in vitro models consistently fail to reproduce the metabolic behavior of solid tumors. When tumors are removed from the host, the stress-response context that drives immune, hepatic, and whole-body metabolic changes is lost, leaving only isolated metabolic fragments to study [6].

The syndrome can be characterized by five interrelated components:

- Dissociated catabolic ketosis
- Persistent stress signaling without resolution
- Immune metabolic depletion
- Progressive hepatic degradation
- Skeletal muscle catabolism as the primary substrate source

By the time cachexia is clinically apparent, the underlying syndrome is already established. What is recorded as the cause of death in advanced solid tumor patients may underrepresent cachexia as a primary contributor, with organ failure events representing the terminal manifestation of the catabolic syndrome described here rather than causes independent of it [1,2]. Intervention targeting cachexia alone is behind the biology driving it. When viewed within this syndrome, cachexia is not merely a complication of cancer but part of a metabolic state that creates a nutrient-rich environment favorable to tumor growth.

14. Testable Predictions

The homeostatic deception framework generates the following testable predictions:

- Ketone levels in cachectic patients will not correlate with muscle mass preservation, distinguishing dissociated catabolic ketosis from healthy fasting ketosis, where ketosis and muscle sparing co-occur. The primary empirical test is concurrent measurement of serum beta-hydroxybutyrate (threshold >0.8–1.2 mmol/L) and quantitative CT lean mass across serial timepoints in the same patients.
- Appetite signal blunting in cachectic patients will dissociate from ketone levels, consistent with GDF-15/GFRAL-driven aversion rather than ketone-mediated satiety; elevated BOHB will co-occur with anorexia rather than predicting appetite preservation.
- Cachexia severity correlates more strongly with inflammatory signaling (IL-6, TNF-α) than with caloric intake
- Immune metabolic depletion (T-cell and NK-cell dysfunction within the tumor microenvironment, assessable from diagnostic or staging biopsy tissue) precedes volumetric tumor expansion
- Glutamine flux from host tissues predicts progression better than dietary glucose intake
- Early preservation of host metabolism via anti-inflammatory or anti-catabolic strategies, rather than dietary restriction, will improve treatment tolerance and outcomes

In vitro substrate manipulation in tumor cell cultures would provide a direct test of the regulatory versus bulk fuel thesis. A bidirectional substrate matrix, graded glucose reduction to zero while holding lactate, amino acid, and lipid substrates constant, and the inverse, removing host-derived substrates while maintaining normal glucose, would test whether tumor growth depends on glucose as bulk carbon or on host-derived substrates. A cachexia-mimicking condition replicating the substrate profile that cachexia delivers to the tumor, elevated amino acids, fatty acids, and lactate with low glucose, would test whether the cachectic substrate environment is actively favorable to tumor proliferation. This experiment requires no animal model or human subjects and is accessible to any cancer metabolism laboratory. Murine IL-6-high tumor implant models would extend validation to the complete cachectic signaling loop, allowing simultaneous measurement of ketones, lean mass, inflammatory markers, and tumor substrate access, with GDF-15/GFRAL neutralization as a direct interventional test. Large animal models, particularly porcine, would provide the strongest

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translational validation given their closer approximation to human whole-body metabolic physiology, body composition, and HPA axis response, and are large enough to support CT-based lean mass quantification using clinical-grade segmentation tools.

A longitudinal dataset identifying cachectic patients with progressive lean mass loss in the absence of elevated GDF-15, inflammatory signaling, or hormonal dysregulation, and with starvation excluded as a confound, would challenge the central claims of this framework.

Retrospective review of staging CT imaging and laboratory records in patients with established cachexia would test whether lean mass loss, elevated inflammatory markers, and declining albumin were present before death in those whose immediate cause of death was recorded as organ failure rather than cachexia. Such a study requires no new data collection, is ethically straightforward, and would directly address whether cachexia is systematically undercoded as a contributor to cancer mortality. If confirmed in this population, the question extends naturally to the wider advanced solid tumor patient base.

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Informed Consent Statement: The patient described in this report is the author of the manuscript and provided informed consent for publication of all clinical data, laboratory values, imaging studies, and photographs included in this report. All materials were derived from the author's own medical records obtained during routine clinical care.:

Data Availability Statement: All imaging measurements were derived from routine clinical CT studies using 3D Slicer and the TotalSegmentator segmentation framework. Quantitative data generated during the analysis are included within the manuscript tables. Additional details regarding segmentation methodology or derived measurements are available from the author upon reasonable request.

References

1. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489-495. doi:10.1016/S1470-2045(10)70218-7
2. Baracos VE, Martin L, Korc M, Guttridge DC, Bhullar AS, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Primers. 2018;4:17105. doi:10.1038/nrdp.2017.105
3. Johnson CL. Systemic Physiologic Changes During Treatment of Metastatic NSCLC: Documented by Quantitative CT Volumetry, Serial Clinical Photography, and Longitudinal Laboratory Biomarkers. Zenodo. 2026. https://doi.org/10.5281/zenodo.18974929
4. Faubert B, Li KY, Cai L, Hensley CT, Kim J, Zacharias LG, et al. Lactate metabolism in human lung tumors. Cell. 2017;171(2):358-371.e9. doi:10.1016/j.cell.2017.09.019
5. Hensley CT, Faubert B, Yuan Q, Lev-Cohain N, Jin E, Kim J, et al. Metabolic heterogeneity in human lung tumors. Cell. 2016;164(4):681-694. doi:10.1016/j.cell.2015.12.034
6. Dragic H, Chaveroux C, Cosset E, Manie SN. Modelling cancer metabolism in vitro: current improvements and future challenges. FEBS J. 2024;291(3):402-411. doi:10.1111/febs.16704
7. Maher EA, Marin-Valencia I, Bachoo RM, Mashimo T, Raisanen J, Hatanpaa KJ, et al. Metabolism of [U-13C]glucose in human brain tumors in vivo. NMR Biomed. 2012;25(11):1234-1244. doi:10.1002/nbm.2794
8. Scott AJ, Mittal A, Meghdadi B, et al. Rewiring of cortical glucose metabolism fuels human brain cancer growth. Nature. 2025;646:413-422. doi:10.1038/s41586-025-09460-7
9. Rubin H. Cancer cachexia: its correlations and causes. Proc Natl Acad Sci USA. 2003;100(9):5384-5389. doi:10.1073/pnas.0931287100

 doi:10.20944/preprints202603.1218.v3

10. Bathe OF. Tumor metabolism as a factor affecting diversity in cancer cachexia. Am J Physiol Cell Physiol. 2025;328(5):C908-C920. doi:10.1152/ajpcell.00677.2024
11. Reinfeld BI, Madden MZ, Wolf MM, Chytil A, Bader JE, Patterson AR, et al. Cell-programmed nutrient partitioning in the tumour microenvironment. Nature. 2021;593:282-288. doi:10.1038/s41586-021-03442-1
12. Tufail M, Jiang CH, Li N. Altered metabolism in cancer: insights into energy pathways and therapeutic targets. Mol Cancer. 2024;23(1):203. doi:10.1186/s12943-024-02119-3
13. Cordani M, Michetti F, Zarrabi A, Zarepour A, Rumio C, Strippoli R, Marcucci F. The role of glycolysis in tumorigenesis: From biological aspects to therapeutic opportunities. Neoplasia. 2024;58:101076. doi:10.1016/j.neo.2024.101076
14. Clay R, Li K, Jin L. Metabolic signaling in the tumor microenvironment. Cancers (Basel). 2025;17(1):155. doi:10.3390/cancers17010155
15. Chapman NM, Boothby MR, Chi H, et al. Metabolic rewiring and communication in cancer immunity. Cell Chem Biol. 2024;31(5):862–883. doi:10.1016/j.chembiol.2024.02.001
16. DeBerardinis RJ, Chandel NS. Fundamentals of cancer metabolism. Sci Adv. 2016;2(5):e1600200. doi:10.1126/sciadv.1600200
17. Chang CH, Qiu J, O'Sullivan D, Buck MD, Noguchi T, Curtis JD, et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression. Cell. 2015;162(6):1229-1241. doi:10.1016/j.cell.2015.08.016
18. Leone RD, Zhao L, Englert JM, Sun IM, Oh MH, Sun IH, et al. Glutamine blockade induces divergent metabolic programs to overcome tumor immune evasion. Science. 2019;366(6468):1013-1021. doi:10.1126/science.aav2588
19. Edwards DN, Ngwa VM, Raybuck AL, et al. Selective glutamine metabolism inhibition in tumor cells improves antitumor T lymphocyte activity in triple-negative breast cancer. J Clin Invest. 2021;131(4):e140100. doi:10.1172/JCI140100
20. Byun JK, Park M, Lee S, Jeon JH, Lee J, Choi YK. A glutamine tug-of-war between cancer and immune cells: recent advances in understanding and clinical applications. J Exp Clin Cancer Res. 2024;43:98. doi:10.1186/s13046-024-03013-2
21. Petruzzelli M, Wagner EF. Mechanisms of metabolic dysfunction in cancer-associated cachexia. Genes Dev. 2016;30(5):489–501. doi:10.1101/gad.276733.115
22. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol. 2013;10(2):90–99. doi:10.1038/nrclinonc.2012.209
23. Wang G, Biswas AK, Ma W, Kandpal M, Coker C, Grandgenett PM, et al. Metastatic cancers promote cachexia through ZIP14 upregulation in skeletal muscle. Nat Med. 2018;24(6):770-781. doi:10.1038/s41591-018-0054-2
24. Koh K, Scott R, Cespedes Feliciano EM, Janowitz T, Goncalves MD, White EP, Laird BJA, Haase K, Jamal-Hanjani M. Cancer-associated cachexia: bridging clinical findings with mechanistic insights in human studies. Cancer Discov. 2025;15(8):1543-1568. doi:10.1158/2159-8290.CD-25-0293
25. Liu X, Lu J, Cao J, et al. Cancer-associated cachexia: skeletal muscle loss and its molecular mechanisms. J Hematol Oncol. 2023;16:62. doi:10.1186/s13045-023-01458-z
26. Wang X, Li Y, Tian H, Qi J, Li M, Fu C, et al. Macrophage inhibitory cytokine 1 (MIC-1/GDF15) as a novel diagnostic serum biomarker in pancreatic ductal adenocarcinoma. BMC Cancer. 2014;14:578. doi:10.1186/1471-2407-14-578
27. Roeland E, Cater N, Bonomi P, et al. Incidence of cachexia and health resource use in patients with breast, colorectal, lung, pancreatic, and prostate cancers. Presented at: ESMO Congress 2024; Abstract 1822P. Optum Market Clarity database, n=27,679.
28. Dijksterhuis WPM, Latenstein AEJ, van Kleef JJ, Verhoeven RHA, de Vries JHM, Slingerland M, et al. Cachexia and dietetic interventions in patients with esophagogastric cancer: a multicenter cohort study. J Natl Compr Canc Netw. 2021;19(2):144-152. doi:10.6004/jnccn.2020.7615
29. Permuth JB, Dezsi KB, Judge SM, Beato F, Vyas S, Ali KN, et al. Leveraging real-world data to predict cancer cachexia stage, quality of life, and survival in a racially and ethnically diverse multi-institutional

 doi:10.20944/preprints202603.1218.v3

cohort of treatment-naive patients with pancreatic ductal adenocarcinoma. Front Oncol. 2024;14:1362244. doi:10.3389/fonc.2024.1362244

30. Lambert CP. Anti-cachexia therapy should target metabolism, inflammatory cytokines, and androgens in hormone-independent cancers. J Cachexia Sarcopenia Muscle. 2021;12(5):1352-1353. doi:10.1002/jcsm.12762
31. Pettersen K, Andersen S, Degen S, Tadini V, Grosjean J, Hatakeyama S, Tesfahun AN, Moestue S, Kim J, Nonstad U, et al. Cancer cachexia associates with a systemic autophagy-inducing activity mimicked by cancer cell-derived IL-6 trans-signaling. Sci Rep. 2017;7:2046. doi:10.1038/s41598-017-02088-2
32. Kamphorst JJ, Nofal M, Commisso C, Hackett SR, Lu W, Grabocka E, et al. Metabolic scavenging by cancer cells: when the going gets tough, the tough keep eating. Trends Endocrinol Metab. 2015;26(12):667–677. doi:10.1016/j.tem.2015.09.007
33. Ferrer M, Mourikis N, Davidson EE, et al. Ketogenic diet promotes tumor ferroptosis but induces relative corticosterone deficiency that accelerates cachexia. Cell Metab. 2023;35(7):1147-1162.e7. doi:10.1016/j.cmet.2023.05.008
34. Lockhart SM, Saudek V, O'Rahilly S. GDF15: a hormone conveying somatic distress to the brain. Endocr Rev. 2020;41(4):bnaa007. doi:10.1210/endrev/bnaa007
35. Mullican SE, Lin-Schmidt X, Chin CN, et al. GFRAL is the receptor for GDF15 and the ligand promotes weight loss in mice and nonhuman primates. Nat Med. 2017;23(10):1150–1157. doi:10.1038/nm.4392
36. Lerner L, Hayes TG, Tao N, et al. Plasma growth differentiation factor 15 is associated with weight loss and mortality in cancer patients. J Cachexia Sarcopenia Muscle. 2015;6(4):317–324. doi:10.1002/jcsm.12033
37. Li H, Xiao Y, Li Q, et al. The allergy mediator histamine confers resistance to immunotherapy in cancer patients via activation of the macrophage histamine receptor H1. Cancer Cell. 2022;40(1):36-52. doi:10.1016/j.ccell.2021.11.002
38. Groarke JD, Crawford J, Collins SM, et al. Ponsegromab for the treatment of cancer cachexia. N Engl J Med. 2024;391(24):2291-2303. doi:10.1056/NEJMoa2409515
39. Wu CY, Huang CX, Lao XM, et al. Glucose restriction shapes pre-metastatic innate immune landscapes in the lung through exosomal TRAIL. Cell. 2025;188(20):5701-5716.e19. doi:10.1016/j.cell.2025.06.027
40. Palesty JA, Dudrick SJ. Cachexia, malnutrition, the refeeding syndrome, and lessons from Goldilocks. Surg Clin North Am. 2011;91(3):653-673. doi:10.1016/j.suc.2011.02.007
41. O'Neill LA, Kishton RJ, Rathmell J. The importance of reprogramming metabolism in macrophages and lymphocytes in host defence and immunity. Bioessays. 2016;38(9):863-873. doi:10.1002/bies.201600107
42. Ahn MI, Gleeson TG, Lim CH, Kwon OJ, Ahn YC, Han J, et al. False positive and false negative FDG-PET scans in various thoracic diseases. Korean J Radiol. 2006;7(1):57-69. doi:10.3348/kjr.2006.7.1.57
43. Carneiro L, Geller S, Fioramonti X, et al. Evidence for hypothalamic ketone body sensing: impact on food intake and peripheral metabolic responses in mice. Am J Physiol Endocrinol Metab. 2016;310(2):E103-115. doi:10.1152/ajpendo.00282.2015
44. Newman JC, Verdin E. Ketone bodies as signaling metabolites. Trends Endocrinol Metab. 2014;25(1):42-52. doi:10.1016/j.tem.2013.09.002
45. Pettersen K, Andersen S, Degen S, et al. Cancer cachexia associates with a systemic autophagy-inducing activity