Hypothesis

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Homeostatic Deception via Dissociated Catabolic Ketosis: A Proposed Mechanistic Framework for Tumor-Driven Metabolic Hijacking in Solid Tumors

Cristofer L Johnson *

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Homeostatic Deception via Dissociated Catabolic Ketosis: A Proposed Mechanistic Framework for Tumor-Driven Metabolic Mimicry in Solid Tumors

Cristofer L Johnson

Independent Researcher; Patient-Author; 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, mounting clinical and metabolic evidence indicates that glucose and glutamine are consumed primarily as regulatory and competitive substrates rather than as dominant carbon sources, with tumor biomass supplied largely by lactate, glutamine, and host-derived amino acids and lipids. Cachexia is commonly described as a secondary complication of advanced cancer, yet this metabolic behavior suggests it may function as a tumor-maintained 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 competition and signaling pathways that promote host catabolism. Dietary deprivation strategies therefore 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 satisfy central energy-sensing mechanisms, silencing counter-regulatory alarms while unrestrained muscle proteolysis and lipolysis proceed. The resulting catabolic loop supplies tumors with substrates released from host tissues while the host's regulatory systems interpret the state as normal adaptive fasting. 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 an observation consistent with the framework described here.* (Johnson CL, 2026, https://doi.org/10.5281/zenodo.18974929). This manuscript integrates metabolic tracing, immunometabolism, and clinical observation to propose a mechanistic hypothesis reframing cachexia as a tumor-maintained state. The framework identifies multiple targets for companion therapeutic intervention and explains the failure of diet-based strategies.

Keywords: cachexia; metabolic mimicry; dissociated ketosis; CNS energy sensing; homeostatic deception; tumor 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, emerging evidence suggests a tumor-maintained systemic reprogramming that favors malignant survival at the expense of host integrity [1].

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While metabolic focus often remains on the Warburg Effect as a means for tumors to generate energy, this often overlooks the systemic consequences of such a shift. This shift illustrates why starvation-based strategies are often counterproductive. The Warburg effect may represent a metabolic strategy to shift the host into a catabolic state that fuels tumor expansion.

Several clinical observations support this shift toward a tumor-maintained model rather than a simple nutritional deficiency:

- 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.

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 [3].

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 [3]. Tumors exhibit marked metabolic heterogeneity across regions, drawing on multiple circulating nutrients rather than a single dominant fuel source [4,5]. In human glioblastoma, less than 50 percent of the acetyl-CoA pool derives from blood-borne glucose, though recent tracing shows glucose can be rewired for amino acid synthesis in some GBM models, contributing indirectly to biomass without dominating bulk fueling [6,7]. 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 [2,8,9].

This distinction has important implications for how dietary interventions are interpreted. 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 repeatedly fails in practice.

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] (see Figure 1: Fuel vs. Signaling Diagram).

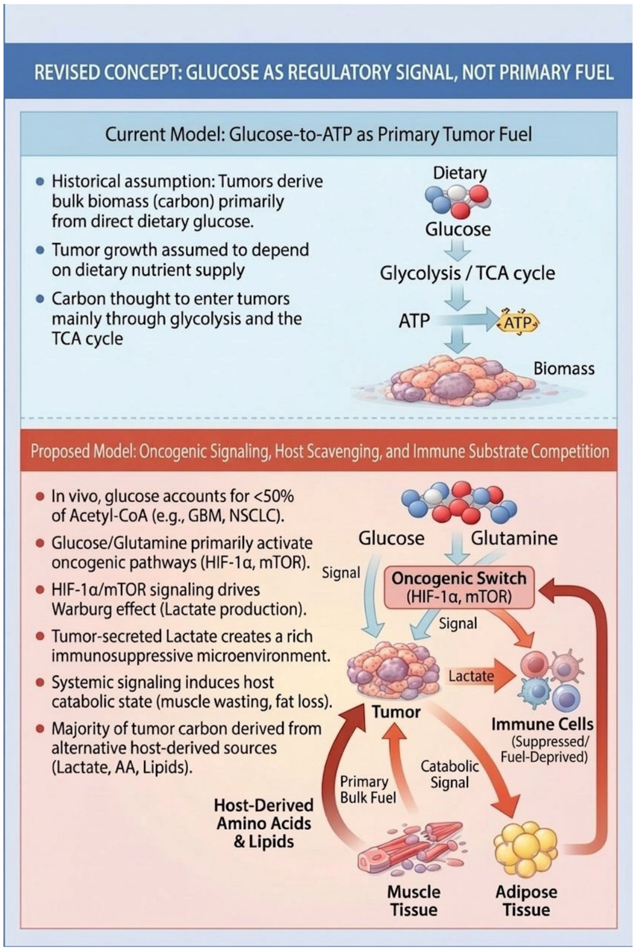
The Warburg Effect is therefore not simply an inefficient ATP-producing pathway. It may instead represent a regulatory metabolic configuration that reshapes the metabolic environment of both tumor and host. By preferentially fermenting glucose to lactate, tumors generate a lactate-rich microenvironment that suppresses immune surveillance, promotes angiogenesis, and induces metabolic stress in surrounding and distant tissues [3,13,14]. 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 may therefore reflect a regulatory metabolic program in which metabolic flux reshapes host physiology in ways that expand the circulating pool of substrates available to the tumor.

Clinical observations align with this interpretation. Cachexia frequently develops despite caloric adequacy and progresses independently of intake, indicating that tumor-driven signaling, not nutrient competition, is the dominant force [2,15]. As host tissues break down, alternative substrates are released into circulation, supplying tumors with a continuous nutrient stream independent of diet. The consequence of this metabolic signaling environment is that nutrient supply becomes increasingly derived from host tissue mobilization rather than directly from dietary intake.

The clinical consequence is straightforward. Dietary restriction strategies do not slow tumor progression because they do not deprive tumors of their primary nutrient sources. Instead, they deepen the same catabolic signaling state the tumor has already established, accelerating host wasting while leaving tumor supply intact. 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 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 [16,17]. 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.


REVISED CONCEPT: GLUCOSE AS REGULATORY SIGNAL, NOT PRIMARY FUEL

Current Model: Glucose-to-ATP as Primary Tumor Fuel

- Historical assumption: Tumors derive bulk biomass (carbon) primarily from direct dietary glucose.
- Tumor growth assumed to depend on dietary nutrient supply
- Carbon thought to enter tumors mainly through glycolysis and the TCA cycle

Proposed Model: Oncogenic Signaling, Host Scavenging, and Immune Substrate Competition

- In vivo, glucose accounts for <50% of Acetyl-CoA (e.g., GBM, NSCLC).
- Glucose/Glutamine primarily activate oncogenic pathways (HIF-1α, mTOR).
- HIF-1α/mTOR signaling drives Warburg effect (Lactate production).
- Tumor-secreted Lactate creates a rich immunosuppressive microenvironment.
- Systemic signaling induces host catabolic state (muscle wasting, fat loss).
- Majority of tumor carbon derived from alternative host-derived sources (Lactate, AA, Lipids).

Figure 1. Fuel versus Signaling Roles of Glucose and Glutamine in Solid Tumors. Left panel illustrates the traditional "bulk fuel" model, in which glucose and glutamine are assumed to contribute directly and predominantly to tumor biomass and TCA cycle energy production. Right panel illustrates the regulatory signaling model supported by in vivo metabolic tracing, in which these substrates exert disproportionate influence through activation of oncogenic pathways, immune suppression, and host catabolic programs, while the majority of tumor carbon is supplied by lactate, amino acids, and lipids derived from host tissues. This distinction explains why dietary restriction of glucose fails to selectively starve tumors and instead amplifies tumor-driven metabolic reprogramming.

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

3.1. Glucose

In vivo, glucose functions primarily as:

- A flux hub enabling branching biosynthesis
- A redox regulator via the pentose phosphate pathway
- A signaling substrate sustaining mTOR, MYC, and HIF pathways [11]
- A competitive substrate depriving immune effector cells [10,13]

3.2. Glutamine

Glutamine emerges as the dominant amino acid shaping tumor microenvironments:

- Supports TCA anaplerosis and nucleotide synthesis [11]
- Regulates redox buffering via glutathione synthesis
- Modulates extracellular acidity and signaling
- Depletes immune cells that require glutamine for activation [18,19]
- Creates a tug-of-war between tumor and immune cells for glutamine availability [20]

Critically, many tumors rely on host-produced glutamine, synthesized primarily in muscle and lung, rather than endogenous synthesis, though local stromal sources including cancer-associated fibroblasts can also contribute conditionally.

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 [2,21].

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 [2,21,22].

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.

This inflammatory-endocrine signaling environment does not simply produce generalized metabolic stress. Instead, 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.

5. Hepatic Metabolic Response

Tumor-driven insulin resistance, inflammatory cytokine signaling, and counter-regulatory hormone excess do not merely mimic 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.

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 [2,21,22]. IL-6–driven acute-phase signaling, combined with insulin resistance and counter-regulatory hormones such as glucagon and cortisol, may 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 [23]. Inflammatory cytokines and stress-hormone signaling associated with tumor burden, including IL-6 and TNF-α, are known to activate proteolytic and autophagic pathways in host tissues [2,21,22]. Through this inflammatory-endocrine environment, the tumor may indirectly sustain catabolic recycling in distant tissues, increasing the circulating availability of amino acids such as glutamine. These substrates can then be scavenged by tumor cells through mechanisms including macropinocytosis and related nutrient-uptake pathways.

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). Muscle breakdown proceeds unchecked while the brain interprets circulating ketones as evidence that metabolic adaptation is proceeding normally. The host is being dismantled while its central monitoring systems report that conditions are under control.

Functional nutrient deprivation in normal tissues normally triggers a hepatic fasting response. Ketogenesis rises under the combined influence of cortisol, glucagon, and inflammatory cytokines. In the tumor-driven state, however, ketone production becomes a false metabolic sufficiency signal rather than a marker of metabolic safety.

In healthy voluntary fasting, ketogenesis is part of an integrated adaptive program. Fat stores are preferentially mobilized, ketones substitute for glucose in the brain, and skeletal muscle proteolysis is actively suppressed. The presence of circulating ketones signals that energy requirements are being met while lean tissue is preserved.

In the tumor-driven state, physiological ketogenesis is genuinely present but decoupled from this protective program. Muscle proteolysis proceeds concurrently rather than being suppressed because inflammatory and hormonal drivers, including IL-6, TNF-α, cortisol, and glucagon, override normal protein-sparing mechanisms. The metabolic signals present resemble those of adaptive fasting, and central regulatory responses remain correspondingly unalarmed. Feedback loops that would otherwise signal metabolic danger are silenced because the ketone signal appears appropriate [11].

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
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
Net biological effect	Host protection	Tumor nourishment

This signaling environment produces a physiologic state that is interpreted as normal yet becomes clinically devastating. It induces a physiological state that 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. These substrates are scavenged by the tumor, mimicking the host's adaptive fasting physiology.

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 [2,22].

This program evolved for short-term fasting but is now driven continuously by tumor-maintained 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.

This framework explains an important clinical observation. 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 [24].

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6. Central Nervous System Energy Sensing and the Basis of Homeostatic Deception

The proposed homeostatic deception arises from the interaction of three central energy-sensing pathways that regulate systemic metabolic perception: hypothalamic ketone sensing, adipose-derived leptin signaling, and intracellular AMPK energy detection. The following mechanisms are presented as a conceptual framework integrating established fasting physiology with observations from cancer cachexia. Direct experimental confirmation of these pathways in human cachexia remains limited, and the model is therefore offered as a mechanistic hypothesis rather than a demonstrated pathway.

6.1. Hypothalamic Ketone Sensing (Primary Signal)

Hypothalamic neurons do not monitor tissue integrity or muscle mass; rather, they detect fuel availability through intracellular energy status [11,17]. Ketone bodies, particularly β-hydroxybutyrate, are efficiently oxidized by neurons and maintain ATP production when glucose availability fluctuates [11].

During physiological fasting this mechanism is protective. Rising ketone concentrations supply oxidative fuel to hypothalamic neurons, preserving ATP levels and suppressing AMPK activation [11]. This signals that the organism has successfully transitioned to fat-derived energy and allows the central nervous system to dampen stress responses associated with acute energy shortage.

In dissociated catabolic ketosis the same ketone signal remains present. Hypothalamic neurons are likely to continue receiving adequate oxidative fuel and may maintain intracellular ATP levels. From the perspective of central energy sensing, the metabolic environment therefore resembles adaptive fasting rather than pathological starvation. The central regulatory system receives no signal indicating metabolic danger. The CNS is not failing to compensate; it is responding appropriately to a fuel signal that normally indicates metabolic sufficiency.

This mechanism forms the first layer of the proposed homeostatic deception. Ketones satisfy hypothalamic energy sensing while peripheral catabolic signaling proceeds unchecked.

6.2. Leptin Signaling (Adipose Status Signal)

Leptin provides the hypothalamus with information about adipose energy stores. Under normal fasting conditions declining leptin levels contribute to adaptive responses that conserve energy and shift metabolism toward fat utilization.

Cancer cachexia disrupts this signaling axis. Accelerated lipolysis reduces adipose mass and lowers circulating leptin, yet inflammatory cytokines and stress hormones alter hypothalamic responsiveness to leptin signaling. Elevated IL-6, TNF-α, cortisol, and sympathetic activation are known to modify leptin sensitivity and appetite signaling within hypothalamic circuits [2,21].

The result is a distorted adipose feedback signal rather than a clean starvation alarm. Ketone availability simultaneously indicates adequate oxidative fuel, further dampening central energy-stress pathways. The hypothalamus therefore interprets the metabolic state as compatible with adaptive fasting even while adipose stores and skeletal muscle are being progressively depleted.

6.3. AMPK Energy Sensing (Intracellular Alarm System)

AMP-activated protein kinase functions as a cellular energy sensor that activates when ATP levels fall and AMP rises [11]. In hypothalamic neurons AMPK activation normally signals energy deficiency and promotes hunger, sympathetic activation, and metabolic counter-regulation.

Ketone oxidation may suppress this alarm mechanism. Because beta-hydroxybutyrate can be efficiently oxidized by neurons, intracellular ATP levels may remain sufficient to prevent activation of hypothalamic AMPK pathways. In the context of cancer cachexia, this mechanism is proposed as a potential explanation for how central energy sensing could remain satisfied while peripheral catabolism continues. [11,17].

Consequently, the central nervous system does not activate a strong counter-regulatory response despite ongoing peripheral tissue loss. Peripheral cytokine signaling and stress hormones drive muscle proteolysis and adipose lipolysis, while central energy-sensing circuits remain in a suppressed state consistent with successful fasting adaptation.

6.4. How These Three Signals Produce the "Deception"

"Homeostatic deception" refers to a mismatch between central energy-sensing signals and the host's true structural energy reserves. When combined, the three sensing pathways create a coherent explanation for the dissociation between central perception and peripheral metabolic reality:

- Ketone sensing signals adequate oxidative fuel.
- Leptin signaling becomes distorted by inflammation and lipolysis.
- AMPK activation remains suppressed because neuronal ATP is preserved.

The hypothalamus therefore interprets the systemic metabolic state as adaptive fasting rather than metabolic failure. Meanwhile inflammatory and endocrine signals maintain a powerful peripheral catabolic program that mobilizes amino acids and lipids from host tissues. The central regulatory system remains reassured while the host's structural reserves are progressively consumed.

7. Cachexia as a Systemic State Benefiting Tumor Growth

Once established, cachexia does not represent systemic failure or nutritional inadequacy. It represents a stable, tumor-favorable metabolic state actively maintained by malignant signaling [1,2]. In this state, the tumor has successfully integrated itself into host metabolism, redirecting physiological regulation to serve malignant growth rather than host preservation.

Cachexia confers multiple direct advantages to the tumor:

- 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 competition.
  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 [10,18]. 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.
- 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 [21,22].

At this stage, dietary intake becomes biologically irrelevant to tumor supply. 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.

In this context, cachexia can be interpreted as a form of tumor-host metabolic integration rather than a secondary complication. It represents a tumor-maintained metabolic state in which host tissues become a sustained substrate source for tumor metabolism. This state is reinforced by persistent inflammatory signaling, including cytokines such as IL-6 and TNF-α, that drive systemic catabolism and reshape immune metabolism. Immune checkpoint inhibitors depend on metabolically competent T cells, yet inflammatory catabolic signaling within cachexia can impair the metabolic capacity required for effective immune responses.

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 [25]. H1 signaling amplifies cytokine release, promotes anorexia, worsens insulin resistance, and accelerates host catabolism. Attenuation of this signaling may therefore partially disrupt the tumor-maintained 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.

Histamine signaling has been linked to increased cytokine production, including IL-6. Attenuation of H1 pathways may dampen inflammatory signaling within the cachectic metabolic environment, potentially improving the conditions under which immune checkpoint blockade operates rather than exerting a direct antitumor effect.

Cachexia is not merely a consequence of advanced cancer. It is something tumors actively create, exploit, and maintain. 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 [10,13].
- 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, particularly in the presence of active tumor-driven inflammation and uncontrolled tumor burden. Evidence for ketogenic interventions in cancer remains mixed, with some studies suggesting potential benefit in specific tumor contexts or treatment settings. However, experimental evidence indicates that ketogenic interventions can accelerate cachexia under certain conditions [24]. The concern raised here is therefore not that ketogenic strategies are universally harmful, but that in the presence of active cachexia they may amplify the same catabolic physiology already present in cachexia.
- Cellular scavenging adaptations, including macropinocytosis and autophagy-mediated recycling, allow tumor cells to consume extracellular proteins and cellular debris released during host tissue catabolism [23].

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.

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 tumor can no longer sustain the inflammatory and hormonal signals that maintain dissociated catabolic ketosis, not because nutrition alone corrected it. 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].

10. Clinical Implications

10.1. During Active Treatment

- 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, risk deepening homeostatic deception: the host interprets the state as adaptive while the tumor accelerates tissue extraction [24]. 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. What Clinicians Can Do Now

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.

11. Ethical Limits and Evidence Inference

Randomized trials deliberately restricting intake in cachectic cancer patients are unethical. Therefore, inference must rely 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

This places cachexia research alongside other domains where causality is inferred without RCTs, including famine physiology, smoking epidemiology, and long-term nutritional intervention studies, where temporal sequence, mechanistic plausibility, and dose-response relationships carry evidential weight in the absence of controlled deprivation trials.

12. Conclusions

Solid tumors exploit glucose and glutamine not primarily to build mass, but to restructure host metabolism, suppress immunity, and induce a cachectic state that ensures continuous nutrient supply independent of diet. Central to this process is *homeostatic deception* via *dissociated catabolic ketosis*: the tumor establishes a state of physiological ketogenesis in which the brain is satisfied by ketone availability 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. Starvation strategies fail because they deepen this state rather than reversing it. Effective reversal requires elimination or suppression of the tumor driver, with nutrition serving a supportive, not curative, role.

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 the tumor restructures host physiology across multiple axes simultaneously.

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 regulatory control they exert over immune, hepatic, and whole-body metabolism is lost, leaving only isolated metabolic fragments to study [5].

The syndrome can be characterized by five interrelated components:

- Dissociated catabolic ketosis
- Homeostatic deception of the CNS

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- Immune metabolic failure
- Progressive hepatic degradation
- Host tissue extraction as the primary fuel supply

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.

13. Testable Predictions

The homeostatic deception framework generates the following testable predictions:

- Cachexia severity correlates more strongly with inflammatory signaling (IL-6, TNF-α) than with caloric intake
- Immune metabolic failure (T-cell and NK-cell dysfunction) precedes volumetric tumor expansion
- Glutamine flux from host tissues predicts progression better than dietary glucose intake
- 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
- Appetite signal blunting in cachectic patients will correlate with ketone levels, consistent with the homeostatic deception hypothesis
- Early preservation of host metabolism via anti-inflammatory or anti-catabolic strategies, rather than dietary restriction, will improve treatment tolerance and outcomes

14. Observational Case Consistent with the Proposed Framework

The mechanistic framework described in this manuscript originated from direct clinical observation during the treatment course of a patient with metastatic non-small cell lung cancer (NSCLC). The following summary is presented as an observational case consistent with the proposed framework rather than as proof of the mechanism. A detailed case report including full imaging datasets, longitudinal biomarker data, and the complete photographic record is available separately [26].

The patient initially presented on July 22, 2020 and was diagnosed in August 2020 with metastatic NSCLC involving cervical lymph nodes, brain metastases, and a small hepatic lesion. Prior to effective systemic treatment, the patient experienced severe anorexia and rapid metabolic deterioration consistent with cancer-associated cachexia. Body weight declined from a pre-treatment baseline of 184.2 lbs (83.7 kg) to a nadir of 155.1 lbs (70.5 kg), representing a loss of approximately 29 lbs (13.2 kg). Concurrent laboratory data demonstrated severe hypoalbuminemia, with serum albumin declining from 4.0 g/dL to a nadir of 2.2 g/dL during the period of peak tumor burden.

Because of rapid clinical progression, the patient required ICU admission on September 3, 2020 and received emergency carboplatin and paclitaxel. Craniotomy for a dominant intracranial metastasis was performed on September 4, 2020. Definitifve chemoimmunotherapy with pembrolizumab, carboplatin, and pemetrexed was initiated on September 28, 2020, followed by stereotactic radiosurgery in October 2020. Within weeks of treatment initiation, a rapid clinical response was observed, including involution of a fungating cervical metastatic lesion documented through serial clinical photography. Over the subsequent months, host physiologic markers demonstrated progressive recovery, with body weight returning to 183.0 lbs by March 2021, approaching the pre-decline baseline.

Host physiologic indicators of recovery accompanied tumor response. Skeletal muscle volumes increased approximately 1% above baseline measurements, indicating active rebuilding of lean tissue. A transient 85.9% increase in splenic volume was observed shortly after initiation of PD-1 blockade, consistent with reactive immune activation, followed by normalization during continued treatment. Serum albumin returned to the normal range by November 2020 and remained stable thereafter.

Taken together, the weight trajectory, biochemical markers, quantitative imaging findings (3D Slicer/TotalSegmentator), and photographic tumor regression form a convergent observational dataset documenting both the catabolic collapse preceding treatment and the systemic physiologic recovery that followed tumor control. These observations are consistent with the framework proposed in this manuscript, in which tumor-maintained metabolic signaling drives the cachectic state and reversal occurs primarily when the tumor driver is suppressed.

Ethics and 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.

Conflicts of Interest Statement: The author declares no financial or commercial conflicts of interest related to this work. The author is the patient described in the accompanying case report and therefore has a direct personal interest in the clinical outcome described, including personal survival. The author received patient assistance support from the Merck Patient Assistance Program for pembrolizumab (Keytruda) and from Amgen for bevacizumab-awwb (Mvasi) during routine clinical treatment. These assistance programs had no role in the analysis, interpretation, or preparation of this manuscript.

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