

Reconsidering Cancer Through a Systemic Metabolic Perspective: A Holistic Approach to Tumor Metabolism and Clinical Evidence

 **Berrin Ustundag**^{1*}

¹Department of Scientific Research Project Office, Van Yuzuncu Yıl University, Van, Türkiye

*Corresponding Author:

Berrin Ustundag

Department of Scientific Research
Project Office, Van Yuzuncu Yıl
University, Van, Türkiye

Email: berrinustundag@yyu.edu.tr

ORCID ID: 0000-0001-5211-7874

DOI: 10.66588/NCMR.3.2.05

Received: 19 April 2026

Accepted: 11 August 2026

Published: 31 August 2026

The author(s) - Available online at
www.neurocellmolres.com.tr

This open-access article is distributed
under the terms of Creative Commons
Attribution-Non Commercial 4.0
International License



© 2026. The copyright of this
article is retained by the author(s).

ABSTRACT

Cancer has traditionally been viewed as a genetic disease driven by accumulated mutations; however, growing evidence indicates that metabolic dysregulation also plays an important role in tumor initiation and progression. This review aims to evaluate the evidence supporting a systemic metabolic perspective of cancer by integrating molecular, cellular, and clinical findings related to tumor metabolism. Key metabolic alterations such as aerobic glycolysis (Warburg effect), mitochondrial dysfunction, altered lipid and amino acid metabolism, and redox imbalance are critically examined in the context of cancer development. In addition, to clarify the bidirectional relationship between genetic and metabolic changes, the interaction between metabolic reprogramming and oncogenic signaling pathways, and clinical evidence supporting metabolic interventions such as metabolic inhibitors and retargeted drugs targeting tumor bioenergy are also discussed. The common conclusion drawn from all these parameters in light of the current findings is that explaining cancer metabolism solely as a consequence of genetic mutations is insufficient; current evidence suggests that metabolic alterations may actively contribute to tumor initiation and progression. Therefore, incorporating systemic metabolic perspectives may facilitate future advances in early diagnosis, therapeutic targeting, and personalized oncology.

Keywords: Cancer metabolism, Warburg effect, Metabolic reprogramming, Mitochondrial dysfunction, Tumor microenvironment, Systems biology.

Cite this article as: Ustundag B. Reconsidering Cancer Through a Systemic Metabolic Perspective: A Holistic Approach to Tumor Metabolism and Clinical Evidence. Neuro-Cell Mol Res. 2026;3(2):76-84. doi:10.66588/NCMR.3.2.05

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide. Recent studies have expanded the traditional genetic paradigm by emphasizing the contribution of systemic metabolic alterations to cancer biology [1,2]. This study presents current evidence for reconsidering cancer not as a disease limited solely to changes in intracellular genetic/epigenetic processes, but as a systemic metabolic disorder that progresses through bidirectional feedback loops encompassing tumor metabolism, the tumor microenvironment, and the tumor macroenvironment (host physiology). In recent years, the emergence of concepts such as the “tumor macroenvironment” and “host metabolic fitness” in the literature, supported by research, has provided a broader framework for examining cancer biology from a systemic metabolic perspective [3,4].

The central concept explored in this review is that cancer metabolism now goes beyond the incomplete interpretation of the Warburg effect accepted by scientific authorities, and achieves tumor adaptation to environmental pressures through multiple fuel networks such as the glucose–lactate axis, lipid and amino acid fuels, mitochondrial flexibility, and redox/one-carbon metabolism [5-7]. The intracellular metabolic reprogramming observed in tumor cells is not only an autonomous feature of cancer but is also in a bidirectional and dynamic interaction with the systemic metabolism of the host organism. Therefore, conditions such as insulin resistance, metabolic syndrome, prediabetes, and type 2 diabetes constitute the biological infrastructure that significantly affects both cancer development risk and the clinical course of the disease [8,9]. This situation is effective not only at the epidemiological level but also at the molecular and cellular levels. The relationship between the development of cancer incidence and the combination of one or more components of metabolic syndrome, such as abdominal obesity, hyperglycemia, dyslipidemia, and hypertension, has been demonstrated by some recent studies [10,11]. Ultimately, it has been reported that rather than the mere presence of metabolic disorders, their clustering and temporal progression may be more determinative of oncological risk. This approach suggests that metabolic impairment may contribute to cancer development and progression in specific biological contexts. In summary, persistent hyperglycemia increases genomic instability through increased production of reactive oxygen species (ROS), accumulation of advanced glycation end products (AGEs), and chronic low-grade inflammation; this creates a “microenvironment” that supports cellular metabolic reprogramming. However, the magnitude of these effects

varies among different tumor types and clinical settings [12,13]. Insights provided by large-scale population analyses indicate that insulin resistance may not only be a metabolic parameter but also a predictive risk marker for multiple cancer types. These studies suggest that HOMA-IR and related metabolic indicators have significance as independent risk factors in various malignancies, including pancreatic, hepatocellular, colorectal, and breast cancer [14,15]. Such data-driven models further support an association between metabolic dysfunction and cancer risk, although the strength of this relationship may vary across cancer types and populations.

From the perspective of molecular mechanisms, inflammation accompanying insulin resistance and obesity renders the tumor microenvironment pro-tumorigenic through adipokine imbalance (increased leptin, decreased adiponectin), chronic NF- κ B activation, macrophage infiltration, and cytokine-mediated signaling [16,17]. In addition, lipotoxicity and mitochondrial dysfunction caused by metabolic syndrome trigger the reorganization of cellular energy production pathways (glycolysis, fatty acid oxidation, glutamine metabolism), thereby enhancing the metabolic flexibility of cancer cells [18,7].

According to the available evidence, cancer metabolism should not be considered solely as the “Warburg effect” or as a cell-autonomous energy shift; rather, it should be addressed within a systemic context in which host metabolic integrity is disrupted. Current data indicate that metabolic syndrome development patterns, glycemic progression models, and the level of insulin resistance are consistently and strongly associated with cancer development [11]. Ultimately, this reveals the potential impact of reinterpreting cancer as a metabolic disease and of metabolic interventions (glycemic control, weight management, improvement of insulin sensitivity) on oncological prevention and prognosis.

Biochemically, the mechanism that concretizes this approach is the inter-organ transport of metabolites and the indirect fueling of tumors by dietary components (for example, fructose increasing tumor growth via liver-mediated lipid intermediates) [19]. The reshaping of pre-metastatic niches by obesity and a high-fat diet through the platelet-endothelium axis facilitating metastasis, or the triggering of lipolysis via gap junctions through tumor–adipocyte contact providing fuel to tumor biology, demonstrate that host metabolism is directly linked to metastasis biology [20,21].

Despite all this information, in some of the clinical outcome evidence that would make the claim that “cancer is a metabolic disease” solely determinative, metabolically

targeted drug trials have not demonstrated the expected benefit; for example, systemic metabolic modulators such as metformin have not improved cancer outcomes in large-scale RCTs [22]. Therefore, rather than characterizing cancer as “purely metabolic” or “purely genetic,” it is a more appropriate approach to generate clinically testable hypotheses through multi-scale, host–tumor shared metabolic phenotypes.

not only for ATP production but also for supplying intermediate metabolites required for nucleotide, amino acid, and lipid biosynthesis [24,5]. Processes such as multi-organ involvement, reprogramming of host physiology, and the dynamic co-evolution of immune-endocrine-metabolic networks with the tumor constitute markers of systemic disease [1,2]. The “hallmarks of systemic disease” approach

Table 1. Milestones in the Evolution of the Metabolic and Systemic Framework of Cancer Metabolism

Period	Conceptual Development	Description
1920s	Warburg Phenomenon (Aerobic glycolysis hypothesis)	Otto Warburg demonstrated that cancer cells prefer glycolysis even in the presence of oxygen and defined aerobic glycolysis as the fundamental metabolic characteristic of tumor metabolism.
2000–2010	Emergence of the concept of metabolic reprogramming	The Warburg effect began to be interpreted not solely as energy inefficiency, but as the reorganization of metabolic fluxes for biosynthesis, redox balance, and rapid proliferation.
2020	Reconsideration of cancer as a metabolic disease	It has been shown that cancer metabolism is not limited to intracellular energy production; it includes large-scale reprogramming of lipid, amino acid, and nucleotide metabolism.
2023–2024	Strengthening of the systemic metabolic disease paradigm	It has begun to be accepted that cancer is not only a metabolic disorder of tumor cells; it is a multi-organ systemic process affecting host metabolism, the immune system, and endocrine regulation.
2024–2025	Tumor–host interaction and metabolic ecology	It has been demonstrated that metabolite exchange between the tumor microenvironment (TME), stromal cells, immune cells, and distant organs plays a critical role in tumor growth and metastasis.
2025	Inter-organ metabolic redistribution	The metabolic fluxes of organs such as the liver, muscle, adipose tissue, and the immune system are reorganized during tumor development; this indicates the formation of a tumor–host metabolic network.
2026 and beyond	Multi-scale metabolomics and systems biology approach	Multi-omics, metabolomics, and network biology approaches in which metabolic networks at the cellular, tumor microenvironment, and host levels are analyzed together are becoming standard in cancer research.

Shift from Genetic Paradigms to the Concept of Systemic Metabolic Disease

Until recent years, modern approaches to interpreting cancer metabolism centred on the Warburg effect (increased glycolysis in the presence of oxygen). However, according to current knowledge provided by increasing studies, the Warburg phenomenon is no longer defined as a singular “energy inefficiency”; rather, it is defined as an adaptive and flexible form of metabolic reprogramming that supports the biosynthetic requirements, redox balance, and macromolecule production of tumor cells [23,6]. For this reason, aerobic glycolysis is now considered an anabolic platform responsible

expands the classical tumor-intrinsic hallmarks framework and indicates that the host organism is reshaped alongside tumor development and that the systemic environment (“soil”) constitutes determinants of tumor biology [1,2]. This perspective reinterprets cancer not merely as clonal cellular proliferation but as a multilayered adaptation process at the organismal level. The metabolic counterpart of this system has been identified with the concepts of the “tumor macroenvironment” and host “metabolic fitness” [4].

Current research has demonstrated that tumors interact metabolically not only with stromal and immune cells in the microenvironment but also with the liver, skeletal muscle,

adipose tissue, the circulating metabolite pool, the inflammatory axis, and neuroendocrine signals within a metabolic network [3,4]. This multidirectional metabolic communication is determinative in the formation of clinical phenotypes such as metastatic spread and systemic inflammation. Thus, cancer metabolism extends beyond intracellular biochemical pathways and evolves into a different perspective as the redistribution of energy and matter flow at the organismal level. Therefore, as a result of these multi-scale conceptual transformations, a methodological shift in cancer research has also become necessary.

To understand cancer metabolism holistically, *in vitro* metabolite concentration measurements alone are no longer sufficient. Methods such as stable isotope tracing techniques, spatial metabolomics approaches, single-cell metabolomic analyses, and multi-scale metabolomics workflows make it possible to resolve cellular metabolic fluxes in the context of tumor tissue and the systemic macroenvironment [7,3]. A comprehensive review published in 2026 systematized metabolomics workflows across three scales—cell, tumor tissue, and systemic macroenvironment—thereby framing this methodological transformation and proposing a semi-standard reference framework for the field [25].

In conclusion, our understanding of cancer metabolism has evolved from genetic mutation-centered, intracellular-focused explanations toward a systemic disease model involving the reorganization of metabolic networks at the organismal level. This transformation is progressing not only conceptually but also in terms of experimental design, data integration, and clinical translation strategies. The timeline below is a conceptual map summarizing the milestones in the literature of the discussion from “metabolic phenotype → systemic metabolic disease.”

The milestones for the 2020–2026 period (**Table 1**) in this timeline are based on the studies of DeBerardinis & Chandel (2020), Swanton et al. (2024), Fowle-Grider et al. (2024), Altea-Manzano et al. (2025), and Rowles & Patti (2026).

Interaction of Multi-Scale Mechanisms: Tumor Metabolism, Microenvironment, and Macroenvironment

In this section, the mechanisms underlying the reinterpretation of “cancer as a systemic metabolic disorder” (intracellular tumor cell reprogramming, microenvironmental metabolic ecology (nutrient competition and metabolite accumulation), and macroenvironmental/inter-organ metabolic networks) are discussed separately.

Intracellular Metabolic Reprogramming in Tumor Cells

It has been reported in several important studies in the literature that cancer cells exhibit the ability to dynamically switch between glucose, glutamine, fatty acids, and one-carbon metabolism (“metabolic plasticity”) [6,7]. At this stage, the organelle “mitochondria,” which enters the field, is considered to play a critical role not only as the center of cellular energy production but also in the multidimensional regulation of current cellular metabolism [18]. In cancer cells, mitochondria function as an important metabolic hub that supports proliferation by providing intermediate metabolites required for lipid, amino acid, and nucleotide biosynthesis through the tricarboxylic acid (TCA) cycle, in addition to ATP production via oxidative phosphorylation [18,5]. In addition, they play an important role in maintaining cellular redox homeostasis and in metabolic signal transduction through the controlled production of reactive oxygen species derived from the electron transport chain and the activity of antioxidant systems. Metabolic plasticity, one of the fundamental features of cancer metabolism, enables tumor cells to dynamically switch between glycolysis and oxidative phosphorylation depending on microenvironmental conditions [6]. However, this situation leads to the compensation of the inhibition of a single metabolic pathway through the use of alternative energy and carbon sources, giving rise to the “metabolic escape” mechanism and limiting the effectiveness of metabolically targeted therapies [7]. In light of such current knowledge, these observations suggest that therapeutic strategies targeting multiple metabolic vulnerabilities may warrant further investigation, although their clinical efficacy remains to be established [18].

Microenvironmental Metabolic Ecology: Nutrient Competition and Metabolite Accumulation

Limited glucose/oxygen, acidosis, and metabolite density in the tumor microenvironment create selective pressures that determine the fate of both tumor and immune. In other words, the TME is a dynamic metabolic ecosystem shaped by the imbalance between the high metabolic demands of rapidly proliferating tumor cells and limited nutrient and oxygen resources. Lactate accumulation and an acidic environment accompanying glucose and oxygen scarcity create strong selective pressures on both tumor and immune cells, thereby reprogramming cellular functions [26]. In particular, it has been demonstrated that lactate produced as a result of intense glycolytic activity of tumor cells is not merely a metabolic byproduct; rather, it plays a critical role in regulating the TME as a signaling molecule that modulates intercellular metabolic

communication, suppresses immune cell function, and affects gene expression through epigenetic mechanisms [26]. As a result, tumor metabolism, in addition to the process of energy production, is “a dynamic that contributes to the formation of the biochemical basis of immune escape by directly affecting immune cell functions,” and it has been reported that the metabolic dynamics in the TME are also closely related to the systemic metabolic state of the host organism, and that this interaction can transform tumor progression and the immune response.

Macroenvironment: Inter-Organ Metabolite Flow and Host–Tumor Feedback Mechanism

According to current research, explaining cancer metabolism solely through tumor cell-specific biochemical reprogramming is insufficient; therefore, it is emphasized that it should be evaluated within the framework of dynamic metabolite exchange established between the tumor and different organs and tissues of the host organism [4,3]. Thus, metabolically active organs such as the liver, adipose tissue, skeletal muscle, and intestine are considered fundamental components of a systemic macroenvironment that can directly influence tumor biology by reshaping circulating nutrient derivatives, lipid intermediates, and signaling metabolites [4]. One of the most striking examples of this topic is a study published in *Nature* in 2024, which reported that dietary fructose, instead of directly feeding tumor cells, reprograms liver metabolism, leading to an increase in certain circulating lipid intermediates, particularly lysophosphatidylcholine (LPC) types, and that this change may indirectly accelerate tumor growth [19]. This result suggests that interorgan metabolic transport may be a regulatory axis of causal importance, not merely an accompanying factor, in cancer development. Similar studies published in recent years have also reported that metabolic interactions occurring between, for example, liver-tumor, adipose tissue-tumor, and gut microbiota-tumor axes may play an active role in tumor cell proliferation, metabolic plasticity, invasive potential, and treatment response [3,4]. Furthermore, this metabolic flow system not only provides nutrient and energy support but also indirectly strengthens host-tumor feedback loops by influencing processes such as inflammation, immunosuppression, and stromal remodeling [2]. Based on all these features, “cancer metabolism” is now reinterpreted not as a field limited solely to the intrinsic metabolic characteristics of the tumor cell, but as a multi-layered supply and regulatory network where host metabolism can function favorably or unfavorably for the tumor. According to this

school of thought, future metabolic therapeutic strategies may therefore consider not only intratumoral pathways but also inter-organ metabolite transport and host–tumor feedback mechanisms.

Adipose Tissue-Tumor Interaction

In adipose-rich organs such as the breast cancer, an “active metabolic and paracrine collaboration” is observed between tumor cells and neighboring fat cells. Recent findings have revealed that direct contact between tumor cells and fat cells stimulates fat cell lipolysis via gap junction-mediated cAMP transfer, thereby increasing lipid influx that fuels tumor growth. For example, one study reported that disruption of the Zeb1 axis in adipocytes reprogrammed the tumor-associated adipose tissue microenvironment and shaped lipid and metabolite flow favorably for tumor progression. Current literature emphasizes that treating this metabolic coupling as a universal model is not an accurate approach, as all these effects can vary significantly depending on the tumor subtype, organ context, and host metabolic status. Consequently, while adipose tissue-tumor interactions offer a strong conceptual framework for explaining conditions such as metastasis and tumor progression, it is considered that clinical interpretations should be made taking context-specific biological differences into account.

From Systemic Metabolic Dysfunction to Cancer: Interpretation of Epidemiological and Clinical Evidence

The aim of this section is to critically evaluate findings obtained from the current literature supporting the claim that “cancer is a metabolic disease” within the framework of epidemiology and clinical data. The main emphasis here is based on evaluating cancer risk together with the “course and pattern of change of metabolic status over time.”

Metabolic Syndrome (MetS) Trajectories and Cancer Risk

In a study published in the journal *Cancer* in 2024, MetS score trajectories were defined using latent class/mixture modelling in 44,115 individuals, and it was reported that the “elevated-increasing” MetS score pattern increased overall cancer risk, particularly the risk of breast, endometrial, kidney, colorectal, and liver cancers. This study also showed that the relationship may be strengthened in the subgroup with high levels of the inflammation marker (CRP), presenting the combination of “metabolic dysfunction + chronic inflammation” as a clinically measurable risk map [11,10].

Modelling Prediabetes → Diabetes → Cancer Transitions

A multistate modelling study published in *The Lancet Diabetes & Endocrinology* in 2026 evaluated the development of diabetes and cancer over nearly 20 years in 328,049 individuals diagnosed with prediabetes in the United Kingdom. As a result, they showed that age strongly determines transition probabilities and that the development of diabetes can create dramatic increases in cancer incidence compared to the prediabetic state. The most striking clinical implication of this study is the idea that cancer-related metabolic processes may begin before the clinical diagnosis of diabetes, thus shifting the prevention window to the prediabetic stage [9].

Scaling Insulin Resistance as A Direct Risk Marker

In a study published in *Nature Communications* in 2026, insulin resistance was estimated using a machine learning-based “AI-IR” metric with nine clinical parameters in UK Biobank data, and significant risk associations were demonstrated between this metric and various cancer types (particularly uterine, kidney, esophageal, pancreatic, colon, and breast cancers). The unique contribution of this study to the discussion of cancer metabolism is that insulin resistance can be captured at the population scale without relying on gold-standard methods that are difficult to apply, such as the clamp test, and that it can provide comparative performance analyses with metabolic syndrome/BMI [15,14].

Current findings indicate that cancer risk can be understood more comprehensively not only through single-time-point metabolic measurements but also through the temporal course and transition dynamics of metabolic impairment. One study reported that individuals following a high and progressively increasing trajectory of metabolic syndrome had increased overall cancer risk as well as the risk of certain specific cancer types, and that this relationship became more pronounced, especially at high CRP levels [11]. Similarly, there are studies indicating that the processes extending from prediabetes to diabetes and cancer development differ significantly depending on age, but that the difference in cancer incidence remains relatively limited according to diabetic status, suggesting that pathological processes may begin much earlier than clinical diagnosis. In parallel, Lee et al. (2026) demonstrated that the artificial intelligence-based estimated insulin resistance indicator developed on UK Biobank data shows strong performance in predicting diabetes and composite cancer incidence and can provide similar or superior discriminative ability compared to traditional indicators such as BMI. All these findings are

consistent with the view that tumor metabolism is embedded within systemic physiology [15,2].

Immuno-Metabolic Networks and the Tumor Microenvironment: Nutrient Competition, Lactate–Acidosis, and Treatment Response

Metabolic conditions may influence not only tumor growth but also the functional capacity of anti-tumor immunity. For this reason, research—especially after 2025—on the effects of systemic metabolic disorders (obesity, sedentary lifestyle, dietary patterns) on immunotherapy responses has accelerated [27].

Lactate, Acidosis, and Immune Suppression

In a comprehensive review published in *Signal Transduction and Targeted Therapy* in 2025, it was stated that lactate shapes the immune landscape in the TME by affecting different cell populations and can contribute to cancer biology in a multilayered manner through epigenetic mechanisms such as lactylation. The critical point here is that lactate accumulation often occurs together with hypoxia and nutrient scarcity and limits the metabolic “fitness” of immune cells; in other words, metabolic ecology becomes a rate-limiting step of the immune response [28,26].

Systemic Metabolism ↔ Tumor–Immune Interaction: Diet, Obesity, Exercise

A review published in *Cell Reports* in 2025 reported that systemic metabolic changes alter tumor–immune interactions through metabolites transported into the tumor, signaling molecules, and immune cell composition, and that factors such as diet, obesity, and exercise function as biologically meaningful “external modulators” within this framework [27,3].

Exercise, Microbiota, Metabolite, and T Cell Axis

A 2025 *Cell* study reported at the preclinical level that exercise can increase CD8 T cell anti-tumor immunity by altering the microbiota and microbiota-derived metabolites and can contribute to the effectiveness of immunotherapy [29]. Such findings present a new research field that associates “metabolic intervention” not only with the calorie/insulin axis but also with broader biochemical networks such as the “microbiota–metabolite axis” [3].

Obesity and Immunotherapy Response

A study published in the *Journal for ImmunoTherapy of Cancer* in 2025 discussed obesity (the observation that in some

patient groups, higher BMI may be associated with better immunotherapy response) using prospective clinical data and circulating cytokine analyses, and presented findings suggesting that obesity may affect immune components in different directions [30]. This literature provides an important critical perspective on interpreting cancer as a “metabolic disease.” Because BMI is a crude indicator that does not fully reflect metabolic fitness and actual metabolic status, some observed paradoxical relationships may often be exaggerated due to “insufficient phenotyping and the effects of confounding factors.” In this context, it is considered that future studies should stratify their analyses according to insulin resistance, body composition, and systemic inflammation markers in order to more accurately assess metabolic risk [15,17].

Therapeutic Potential and Structural Limitations within the Framework of Metabolic Targets and Clinical Applicability

Although cancer metabolism has been at the center of therapeutic research over the past decade, the clinical success rate of metabolically targeted approaches has not yet reached the desired level [7,4]. In the context of the systemic metabolic cancer model, therapeutic strategies generally develop at two levels: pharmacological targeting of tumor cell-specific metabolic nodes and systemic interventions aimed at modulating host metabolism. However, according to current data, metabolic targeting has a more complex biological context compared to genetic targeting. The main reason for this is that tumor metabolism is highly flexible and contextual. Tumor cells can respond to the suppression of a single metabolic pathway by activating alternative fuel pathways and can exhibit metabolic buffering through metabolite exchange established between the tumor microenvironment, stromal cells, immune cells, and host tissues. Therefore, it has been reported that metabolic vulnerabilities observed in cell culture or isolated tumor models often disappear at the organismal level. In other words, metabolic targeting often cannot be explained by the inhibition of a single biochemical reaction because it occurs through the rebalancing of inter-organ metabolic networks.

In clinical studies, there are examples showing that metabolically targeted treatments do not always demonstrate the expected clinical benefit. For example, the combination of the glutaminase inhibitor telaglenastat with cabozantinib in renal cell carcinoma did not demonstrate a significant advantage in progression-free survival or overall survival in randomized clinical trials [31]. Similarly, although the use of

telaglenastat in combination with immune checkpoint inhibitors was found to be safe in early-phase studies, it did not show consistent clinical efficacy across different patient groups. In addition, metformin, one of the most common examples of systemic metabolic modulation, did not significantly increase invasive disease-free survival in a Phase 3 randomized trial conducted in non-diabetic high-risk breast cancer patients [22]. These findings indicate that metabolically targeted approaches may not always provide the anticipated benefit in clinical practice. These results may stem not from the failure of metabolic therapies but from a fundamental issue in clinical research design. Since metabolic dysfunction is not evenly distributed in a heterogeneous population, studies conducted without metabolic phenotyping may fail to fully measure biological effects. Indeed, recent cohort studies report that cancer risk is more strongly associated not only with static metabolic measurements but also with metabolic trajectories and insulin resistance phenotypes. The areas where metabolic targeting has been most successful clinically are tumor subtypes in which metabolic changes are genetically fixed. For example, the Phase 3 INDIGO trial conducted in low-grade gliomas with IDH mutations showed that the IDH inhibitor vorasidenib significantly prolonged progression-free survival [32]. This finding suggests that the conditions in which metabolic therapies may be most effective are specific tumor subgroups in which metabolic changes can be both genetically defined and biochemically validated.

Multi-scale metabolomic approaches and digital biomarkers have an important role in advancing this integration between metabolic medicine and oncology. According to current reviews, metabolomic studies should not be limited to examining metabolic changes in tumor tissue alone but should also include inter-organ metabolite flow and systemic metabolic interactions. In parallel, artificial intelligence-based biomarkers derived from large population data, such as AI-IR scores that estimate insulin resistance, may provide new tools that enable more accurate metabolic stratification of cancer risk and the development of targeted prevention strategies [25,15].

DISCUSSION

Is Cancer a Metabolic Disease?

Recent studies reveal that cancer metabolism is not limited to the energy production strategies of tumor cells alone. Adipose tissue–tumor metabolic interactions, inter-organ metabolite transport, diet-induced pre-metastatic niche formation, and immuno-metabolic reprogramming processes support the view that cancer metabolism is strongly a systemic

ecosystem [2,4,19]. Similarly, large-scale cohort analyses report that demonstrating the relationships between the temporal continuity and trajectories of metabolic disorders and cancer risk is more reliable [11]. However, clinical application data indicate that metabolic therapies have not yet achieved large-scale oncological success; as seen in examples such as metformin and glutaminase inhibitors, metabolic targeting does not always translate into clinical success [22,31]. This suggests that rather than the limited causal role of metabolism in cancer, metabolic interventions are dependent on “context” and “patient subgroups” [7,4].

For this reason, the increasingly widespread consensus in the current literature is that instead of defining cancer as a purely “metabolic disease,” it is a disease “characterized by metabolic reprogramming and evolving through reciprocal interaction with host systemic metabolism” [1,2]. In this context, three main approaches stand out for future research. First, conducting metabolic phenotyping through more precise biomarkers such as body composition, insulin resistance indicators, and metabolomic profiles rather than crude measurements such as body mass index [15,17]. Second, integrating metabolic trajectories, especially early metabolic stages such as prediabetes, into cancer prevention strategies [9]. Third, developing new therapeutic strategies through “immunometabolic combination approaches” that target both metabolite pressure in the tumor microenvironment and the metabolic fitness of T cells [33,34].

In conclusion, progress in the field of cancer metabolism will depend on research frameworks that address metabolism not as a single biochemical pathway but as a multi-scale system established between the tumor, the immune system, and host metabolism [35,36].

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

Disclosure

The authors have reported no conflicts of interest in preparing and publishing this article.

Funding

The authors have no funding to disclose.

Referee Evaluation Process

Externally peer-reviewed

REFERENCES

1. Hanahan D. Hallmarks of cancer: New dimensions. *Cancer Discov.* 2022;12(1):31-46. <https://doi.org/10.1158/2159-8290.CD-21-1059>
2. Swanton C, Bernard E, Abbosh C, André F, Auwerx J, Balmain A, et al. Embracing cancer complexity: Hallmarks of systemic disease. *Cell.* 2024;187(7):1589-1616. <https://doi.org/10.1016/j.cell.2024.02.009>
3. Elia I, Haigis MC. Metabolites and the tumour microenvironment: From cellular mechanisms to systemic metabolism. *Nat Metab.* 2021;3(1):21-32. <https://doi.org/10.1038/s42255-020-00317-z>
4. Altea-Manzano P, Lehuédé C, Sauvat A. Metabolic interplays between the tumour and the host shape the tumour macroenvironment. *Nat Rev Cancer.* 2025;25(4):274-292. <https://doi.org/10.1038/s41568-024-00786-4>
5. DeBerardinis RJ, Chandel NS. We need to talk about the Warburg effect. *Nat Metab.* 2020;2(2):127-129. <https://doi.org/10.1038/s42255-020-0172-2>
6. Pavlova NN, Thompson CB. The emerging hallmarks of cancer metabolism. *Cell Metab.* 2016;23(1):27-47. <https://doi.org/10.1016/j.cmet.2015.12.006>
7. Faubert B, Solmonson A, DeBerardinis RJ. Metabolic reprogramming and cancer progression. *Science.* 2020;368,eaaw5473. <https://doi.org/10.1126/science.aaw5473>
8. Gallagher EJ, LeRoith D. Obesity and diabetes: The increased risk of cancer and cancer-related mortality. *Physiol Rev.* 2020;100(3):1001-1044. <https://doi.org/10.1152/physrev.00030.2019>
9. Pearson-Stuttard J, Papadimitriou N, Markozannes G, Cividini S, Kakourou A, Gill D, et al. Type 2 diabetes and cancer: An umbrella review of observational and Mendelian randomization studies. *Cancer Epidemiol Biomarkers Prev.* 2021;30(6):1218-1228. <https://doi.org/10.1158/1055-9965.EPI-20-1245>
10. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: A systematic review and meta-analysis. *Diabetes Care.* 2012;35(11):2402-2411. <https://doi.org/10.2337/dc12-0336>
11. Deng L, Liu T, Liu CA, et al. The association of metabolic syndrome score trajectory patterns with risk of all cancer types. *Cancer.* 2024;130(12):2150-2159. <https://doi.org/10.1002/cncr.35235>
12. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: How are they linked? *Free Radic Biol Med.* 2010;49(11):1603-1616. <https://doi.org/10.1016/j.freeradbiomed.2010.09.006>
13. Schmitt M, Greten FR. The inflammatory pathogenesis of colorectal cancer. *Nat Rev Immunol.* 2021;21(10):653-667. <https://doi.org/10.1038/s41577-021-00534-x>
14. Orgel E, Mittelman SD. The links between insulin resistance, diabetes, and cancer. *Curr Diab Rep.* 2013;13(2):213-222. <https://doi.org/10.1007/s11892-012-0356-6>
15. Lee CL, Hiraike Y, et al. Machine learning-predicted insulin resistance is a risk factor for 12 types of cancer. *Nat Commun.* 2026;17:68355. <https://doi.org/10.1038/s41467-026-68355-x>
16. Park J, Euhus DM, Scherer PE. Paracrine and endocrine effects of adipose tissue on cancer development and progression. *Endocr Rev.* 2011;32(4):550-570. <https://doi.org/10.1210/er.2010-0030>
17. Iyengar NM, Gucalp A, Dannenberg AJ, Hudis CA. Obesity and cancer mechanisms: Tumor microenvironment and inflammation. *J Clin Oncol.* 2016;34(35):4270-4276. <https://doi.org/10.1200/JCO.2016.67.4283>
18. Martínez-Reyes I, Chandel NS. Mitochondrial TCA cycle metabolites control physiology and disease. *Nat Commun.* 2020;11:102. <https://doi.org/10.1038/s41467-019-13668-3>

19. Fowle-Grider R, Rowles JL, Shen I, et al. Dietary fructose enhances tumour growth indirectly via interorgan lipid transfer. *Nature*. 2024;636(8043):737-744. <https://doi.org/10.1038/s41586-024-08258-3>
20. Nieman KM, Kenny HA, Penicka CV, Ladanyi A, Buell-Gutbrod R, Zillhardt MR, et al. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. *Nat Med*. 2011;17(11):1498-1503. <https://doi.org/10.1038/nm.2492>
21. Dirat B, Bochet L, Dabek M, Daviaud D, Dauvillier S, Majed B, et al. Cancer-associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion. *Cancer Res*. 2011;71(7):2455-2465. <https://doi.org/10.1158/0008-5472.CAN-10-3323>
22. Goodwin PJ, Chen BE, Gelmon KA, Whelan TJ, Ennis M, Lemieux J, et al. Effect of metformin vs placebo on invasive disease-free survival in patients with breast cancer: The MA.32 randomized clinical trial. *JAMA*. 2022;327(20):1963-1973. <https://doi.org/10.1001/jama.2022.6147>
23. Liberti MV, Locasale JW. The Warburg effect: How does it benefit cancer cells? *Trends Biochem Sci*. 2016;41(3):211-218. <https://doi.org/10.1016/j.tibs.2015.12.001>
24. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: The metabolic requirements of cell proliferation. *Science*. 2009;324(5930):1029-1033. <https://doi.org/10.1126/science.1160809>
25. Rowles JL III, Patti GJ. Decoding cancer across scales with metabolomics. *Nat Rev Cancer*. Advance online publication. <https://doi.org/10.1038/s41568-026-00908-0>
26. Colegio OR, Chu NQ, Szabo AL, Chu T, Rhebergen AM, Jairam V, et al. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. *Nature*. 2014;513(7519):559-563. <https://doi.org/10.1038/nature13490>
27. Cote AL, Munger CJ, Ringel AE. Emerging insights into the impact of systemic metabolic changes on tumor-immune interactions. *Cell Rep*. 2025;44(2):115234. <https://doi.org/10.1016/j.celrep.2025.115234>
28. Chen J, Huang Z, Chen Y, Tian H, Chai P, Liang Y, et al. Lactate and lactylation in cancer. *Signal Transduct Target Ther*. 2025;10(1):38. <https://doi.org/10.1038/s41392-024-02082-x>
29. Phelps CM, et al. Exercise-induced microbiota metabolite enhances CD8 T cell antitumor immunity promoting immunotherapy efficacy. *Cell*. 2025;188(20):5680-5700.e28. <https://doi.org/10.1016/j.cell.2025.06.018>
30. Alden SL, Charmsaz S, Li HL, Tsai HL, Danilova L, Munjal K, et al. Pan-tumor analysis to investigate the obesity paradox in immune checkpoint blockade. *J Immunother Cancer*. 2025;13(1):e009734. <https://doi.org/10.1136/jitc-2024-009734>
31. Tannir NM, DiNatale RG, Hammers HJ, Jonasch E, Pili R, Stadler WM, et al. Efficacy and safety of telaglenastat plus cabozantinib vs placebo plus cabozantinib in patients with advanced renal cell carcinoma: The CANTATA randomized clinical trial. *JAMA Oncol*. 2022;8(10):1411-1418. <https://doi.org/10.1001/jamaoncol.2022.3511>
32. Mellinghoff IK, van den Bent M, Blumenthal DT, Touat M, Peters KB, Clarke JL, et al. Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. *N Engl J Med*. 2023;389(7):589-601. <https://doi.org/10.1056/NEJMoa2304194>
33. Buck MD, Sowell RT, Kaech SM, Pearce EL. Metabolic Instruction of Immunity. *Cell*. 2017;169(4):570-586. <https://doi.org/10.1016/j.cell.2017.04.004>
34. Leone RD, Powell JD. Metabolism of immune cells in cancer. *Nat Rev Cancer*. 2020;20(9):516-531. <https://doi.org/10.1038/s41568-020-0273-y>
35. Akay İrem B, Günel MY, Övey İshak S. TRPV1 channel-mediated apoptotic effects of Liquidambar Orientalis Miller balsam on gastric cancer cell line: Liquidambar Orientalis Miller Gum induces apoptosis in gastric cancer cells. *Neuro-Cell Mol Res*. 2024;1(3):82-88. <https://doi.org/10.66588/NCMR.v01i03.4>
36. Aydoğan E, Övey İshak S, Karahan O. Melatonin Reverses Bupivacaine-Induced Cardiotoxicity in Human Cardiomyocytes by Attenuating TRPV1-Mediated Apoptosis, ROS Production, and Mitochondrial Depolarization. *Neuro-Cell Mol Res*. 2026;3(1):13-19. <https://doi.org/10.66588/NCMR.v3i1.2>