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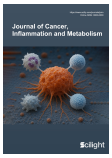

Review

Is Cancer an Evolutionary Adaptation to Metabolic Stress? A Re-Examination of the Fundamental Findings of Warburg, Goldblatt and Cameron

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Abstract: Cancer has traditionally been considered to be a result of genetic mutations, but Otto Warburg's pioneering research, and subsequent studies by Goldblatt and Cameron have suggested that metabolic dysfunction and environmental stress play important roles in tumor development. Warburg proposed that cancer cells demonstrate respiratory dysfunction even under normal oxygen concentrations, and rely excessively on glycolysis. This phenomenon is now known as the "Warburg effect". Additionally, Goldblatt and Cameron demonstrated that repeated hypoxic stress on its own can induce the malignant transformation of normal cells. In this review, we integrate these historical insights with recent advances in modern molecular oncology to emphasize the central role of metabolic reprogramming in cancer initiation, and its therapeutic implications.

Keywords: alkalization therapy; tumor microenvironment; tumor acidity; tumor metabolism

1. Introduction: Cell Metabolism and the Origins of Cancer

Cancer is one of the most complex and multifactorial diseases in human biology. For decades, the onset and progression of cancer were primarily attributed to the accumulation of genetic mutations [1,2]. This genome-centric perspective has driven the development of precision medicine and targeted therapies. Within this integrative view, metabolic reprogramming arises predominantly because of oncogenic/genomic alterations and tissue context: oncogenic signaling and transcriptional programs re-configure metabolic pathways to sustain malignant growth, while the tumor microenvironment further sculpts these states [3,4].

Otto Warburg proposed in the 1920s that the fundamental cause of cancer lies in abnormalities in cellular respiration. He observed that cancer cells ferment glucose into lactic acid, even in the presence of sufficient oxygen; a process he termed "aerobic glycolysis" [3,5,6]. Warburg interpreted this metabolic characteristic as evidence of mitochondrial damage and respiratory dysfunction. Although his interpretation has since been challenged, the observation itself remains a cornerstone of cancer metabolism.

Thirty years since Warburg's proposal, Goldblatt and Cameron provided experimental evidence supporting the role of environmental stress (particularly intermittent hypoxia) in inducing malignancy [7]. By exposing normal rat heart muscle cells to cycles of prolonged hypoxia, they successfully converted the cells into malignant cells showing metabolic stress and being capable of forming tumors, in the absence of any mutagenic factors that could drive the malignant transformation process.

The purpose of this review is to integrate these two foundational perspectives, namely, genetic mutations and metabolic stress, and to evaluate them in consideration of recent advances in molecular oncology. We propose a framework for cancer biology that integrates metabolic, environmental, and genetic dimensions, and presents a

new paradigm that views cancer as an evolutionary adaptation to chronic metabolic stress. This paradigm shift has the potential to profoundly impact future cancer prevention, diagnosis, and treatment methods.

2. Warburg's Hypothesis: Aerobic Glycolysis and Respiratory Deficiency as the Driving Force of Cancer

2.1. Experimental Observations

In the early 20th century, Otto Warburg conducted a series of experiments using tumor cells and normal cells cultured in vitro [6,8]. He found that tumor cells demonstrate extremely high rates of glucose uptake, even under conditions of sufficient oxygen supply, and convert glucose into lactic acid. This behavior contrasted sharply with normal cells, which oxidize glucose into carbon dioxide and water in the presence of oxygen. To quantify this metabolic change, Warburg used a special device called the "Warburg manometer", to measure oxygen consumption and lactate production in tissue samples, which consistently showed that cancer cells tend to suppress mitochondrial respiration and favor glycolysis, even under aerobic conditions. This phenomenon is now known as the Warburg effect, and is recognized as a specific characteristic of most cancers.

2.2. Warburg Effect vs. Pasteur Effect

The Pasteur effect is observed in normal cells, in which glycolysis is inhibited in the presence of oxygen. In the presence of oxygen, cells prioritize oxidative phosphorylation for higher ATP production efficiency. Warburg's discovery contradicted this established theory, showing that cancer cells maintain high glycolysis rates regardless of oxygen availability. From this observation, he concluded that cancer cells have a fundamental defect in respiration.

Subsequent studies have demonstrated that most cancer cells retain functional mitochondria and the ability to perform oxidative phosphorylation [9–12], but the Warburg effect remains a defining feature of tumor metabolism. It is now understood that this metabolic reorganization confers multiple advantages to cancer cells [13–15]. Specifically, it supports rapid biomass synthesis, maintenance of redox balance, and adaptation to fluctuations in oxygen concentration in the tumor microenvironment (TME).

2.3. Modern Re-Evaluation of the Warburg Effect

Modern research using the latest molecular biology techniques and metabolic flux analysis has provided a more detailed understanding of the Warburg effect. Aerobic glycolysis in cancer cells is often driven by tumor gene signaling pathways rather than being a result of irreversible mitochondrial dysfunction [13].

For example, activation of the PI3K-AKT-mTOR signaling pathway with minimal dependence on extrinsic stimulation by growth factors [16], and the overexpression of transcription factors, such as MYC or HIF-1α promotes the expression of glycolysis-associated genes [17,18]. Furthermore, mitochondrial respiration is not necessarily absent in cancer cells; rather, glycolysis and oxidative phosphorylation may coexist depending on nutrient availability and microenvironmental conditions [19]. This dual capability confers tumor cells with metabolic flexibility and resilience, enabling them to survive under various stress conditions.

Although the Warburg hypothesis is partially inaccurate in its original explanation of the mechanism of tumorigenesis, it continues to exert a profound influence on cancer cell biology. Warburg's central claim, i.e., that cancer cells are metabolically unique, and that this characteristic is essential for tumor formation, remains a cornerstone of cancer biology today.

3. Research of Goldblatt and Cameron: Hypoxia as a Causal Factor of Malignant Transformation

3.1. Experimental Design

In 1953, Harry Goldblatt and Gladys Cameron reported groundbreaking research in which they induced malignant transformation in vitro using intermittent anaerobic conditions [7]. Specifically, fibroblast cultures derived from rat heart muscle tissue were exposed to a cycle of hypoxia and reoxygenation over several months. This cancer model is characterized by the use of metabolic stress as the sole mutagenic stimulus, without the use of any chemical carcinogens. Following prolonged intermittent hypoxia, the fibroblasts demonstrated morphological and behavioral changes that were consistent with malignant transformation. These included the loss of contact inhibition, changes in cell shape, enhanced proliferative capacity, and most importantly, the ability to form tumors upon transplantation into syngeneic hosts. Control cells cultured under normal oxygen conditions did not demonstrate such changes.

This study provides compelling experimental evidence that chronic metabolic stress, particularly repeated oxygen deprivation itself is a carcinogenesis-promoting factor This supports the possibility that environmental factors affecting cellular metabolism play a fundamental role in the initiation of the carcinogenic process.

3.2. Relevance to Modern Cancer Biology

Goldblatt and Cameron's research anticipated the modern understanding of TME. In the TME, hypoxic regions and nutrient fluctuations are now known to drive metabolic reorganization and aggressive phenotypes [13,14]. Findings from Goldblatt and Cameron's research emphasize the dynamic interplay between exogenous environmental stresses and intrinsic cellular adaptations, providing a model for nongenotoxic cancer initiation.

In the broader context of systems biology, this research highlights the possibility that abnormalities in metabolic homeostasis disrupt regulatory feedback loops of metabolic pathways and push cells toward malignancy. This provides important insights into understanding the pathomechanisms of cancer in association with tissue-level architecture, vascularization, and limitations of oxygen and substrate diffusion.

4. Unifying Hypothesis: Cancer Is a Evolutionary Metabolic Response

The seemingly unrelated yet complementary findings of Warburg, and Goldblatt and Cameron led to a shared conclusion, namely, cancer is essentially a failure of cells to adapt to metabolic stress. Rather than being driven solely by genetic mutations, persistent environmental stresses, such as hypoxia, acidification, and nutrient fluctuations may select cells capable of surviving under extreme conditions and trigger their malignant transformation [3,20].

From an evolutionary perspective, the TME functions as a dynamic arena for cell selection. As vascular insufficiency progresses and oxygen and nutrient gradients become pronounced, only cells that adopt a glycolytic phenotype and develop increased metabolic plasticity proliferate and dominate the tissue niche. In this context, aerobic glycolysis and metabolic flexibility are not defects but adaptive responses that enhance survival and reproductive fitness [21].

This model shifts the paradigm from viewing cancer as a mere center of mutations to a having ecological and metabolic dimensions. It emphasizes that characteristics of the TME, i.e., local oxygen concentration, pH balance, epithelial-mesenchymal interactions, immune cell infiltration, etc., are important factors affecting cancer initiation, progression, and treatment resistance. Furthermore, this hypothesis provides a conceptual framework for identifying new therapies that target not only the cancer genome but also the metabolic and microenvironmental conditions that underpin tumor development.

4.1. Evolutionary Pressure and Clonal Selection

The metabolic landscape of tumors is highly heterogeneous, and cancer cells are exposed to dynamic environmental pressures. Cells in hypoxic or nutrient-deprived regions are subjected to strong selective pressures that favor clones with glycolytic phenotypes, anti-apoptotic signals, and oxidative stress resistance, leading not only to the emergence of highly aggressive cancer cell populations but also resistance to standard therapies [13,14,22]. In addition, metabolic stress induces epigenetic reprogramming: hypoxia drives hypermethylation of tumor-suppressor gene promoters by impairing TET-mediated DNA demethylation, while lactate generated under acidic, glycolytic conditions installs histone lactylation that rewires gene expression [23,24].

4.2. Specific Features of Cancer Malignancy as a Metabolic Adaptation

Incorporating metabolic adaptation into the specific classical features of cancer reinforces its central role in carcinogenesis. Cancer cells not only undergo unlimited proliferation but also reprogram their metabolic networks to support growth under stress.

These adaptations include the following:

- Increased glycolysis and lactate production [19,25]
- Upregulation of glutamine transporters [26–28]
- Preserved mitochondrial oxidative phosphorylation (OXPHOS) [29,30]
- Resistance to reactive oxygen species (ROS)-induced apoptosis [19]
- Acidosis tolerance and extracellular matrix remodeling [31]

This metabolic reprogramming primarily supports energy-intensive biomass synthesis required for cell growth and proliferation.

4.3. Systems Biology Perspective: Cancer as a Dissipative Structure

From the perspective of nonequilibrium thermodynamics, as proposed by Ilya Prigogine [32], cancer can be understood as a "dissipative structure". Specifically, it is a self-organizing system far from the thermodynamic equilibrium that maintains internal order by releasing entropy to the surrounding environment. This model aligns with the findings of Warburg and Goldblatt and Cameron and conceptualizes cancer as having both stable and dynamic characteristics within a landscape characterized by biological complexity and environmental stress.

From this perspective, tumor formation is not merely a breakdown of normal regulation, but an emergent phenomenon arising from chronic disturbances in metabolic and ecological homeostasis. Therapeutic interventions must extend beyond genetic modification, and methods to modify the energetic and environmental factors underlying malignant stability require future investigation.

5. Molecular Pathways Driving the Warburg Effect

Warburg initially attributed aerobic glycolysis to irreversible mitochondrial damage, but modern cancer biology has demonstrated a sophisticated regulatory network by which cancer cells actively reprogram their metabolism. This metabolic reprogramming integrates oncogenes, tumor suppressors, and environmental signals to regulate nutrient availability, oxygen concentration, and intracellular stress signals.

5.1. A Key Regulator of Hypoxic Adaptation

Hypoxia-inducible factor 1 (HIF-1) is a transcription factor that is stabilized under hypoxic conditions [33]. Under normal oxygen conditions, HIF-1α is rapidly degraded via prolyl hydroxylase-mediated ubiquitination. However, under hypoxic conditions, HIF-1 induces pyruvate dehydrogenase kinase 1 (PDK1) to phosphorylate and inhibit PDH, diverting pyruvate away from mitochondrial oxidation and actively repressing respiration [34]. In addition, HIF-1 increases the expression of several glycolytic enzymes (e.g., hexokinase II, phosphofructokinase, and lactate dehydrogenase A), glucose transporters glucose transporter-1 (GLUT1) and GLUT3 [33,35]. Therefore, cancer cells remain dependent on glycolysis and suppress oxidative phosphorylation even in the presence of oxygen [34].

5.2. myc and PI3K-AKT-mTOR Signaling

The proto-oncogene *myc* is frequently amplified in cancer cells, and regulates glycolysis, glutaminolysis, and mitochondrial biogenesis [36–38]. MYC-driven cells demonstrate extremely high rates of nutrient uptake and macromolecular biosynthesis. Additionally, the PI3K-AKT-mTOR pathway, which is often activated by receptor tyrosine kinases, regulates cell growth and energy utilization [39]. The activation of PI3K-AKT promotes glucose uptake and utilization, whereas mechanistic target of rapamycin complex 1 (mTORC1) promotes protein and lipid synthesis, and inhibits autophagy [39]. Furthermore, an alkaline shift in intracellular pH (pHi)—which can arise as cells adapt to an acidic tumor microenvironment—acutely increases mTORC2 catalytic activity and activates AMPK to promote survival under growth-factor limitation, and elevates PI3K activity to drive both mTORC1 and mTORC2 signaling even in serum-free conditions [40,41] (Figure 1).

These pathways converge to support anabolic growth and biomass production, which are hallmarks of proliferating cancer cells.

5.3. Tumor Suppressors: p53 and AMPK

The tumor suppressor gene *p53* regulates metabolism by promoting oxidative phosphorylation and inhibiting glycolysis [42]. p53 activates genes essential for mitochondrial function, such as synthesis of cytochrome c oxidase 2 (SCO2), a key regulator required for assembly and activity of cytochrome c oxidase (complex IV) and thus for efficient mitochondrial respiration. Additionally, p53 induces TP53-induced glycolysis and apoptosis regulator (TIGAR), which inhibits glycolysis through reducing the level of fructose-2,6-bisphosphate (Figure 1).

AMP-activated protein kinase (AMPK) is a cellular energy stress sensor that, under nutrient-limited conditions decreases anabolic pathways and induces a catabolic program including autophagy [43] (Figure 2). A previous study showed that AMPK negatively regulates aerobic glycolysis in cancer cells [44]; notably, it is activated in hypoxic environment *in vivo*, thereby coupling energy stress in the acidic TME to catabolic programs [45]. Notably, AMPK is activated in authentic hypoxic tumor regions *in vivo*, coupling energy stress in the TME to catabolic programs that antagonize anabolic growth. In terms of the tumor immune microenvironment (TIME), the AMPK-mediated inflammatory response facilitates the recruitment of immune cells to the TIME, therefore

impeding tumorigenesis, cancer progression, and metastasis [46]. AMPK, which connects cell energy homeostasis, tumor bioenergetics, and anti-tumor immunity, is expected to play a crucial role in cancer treatment in the future.

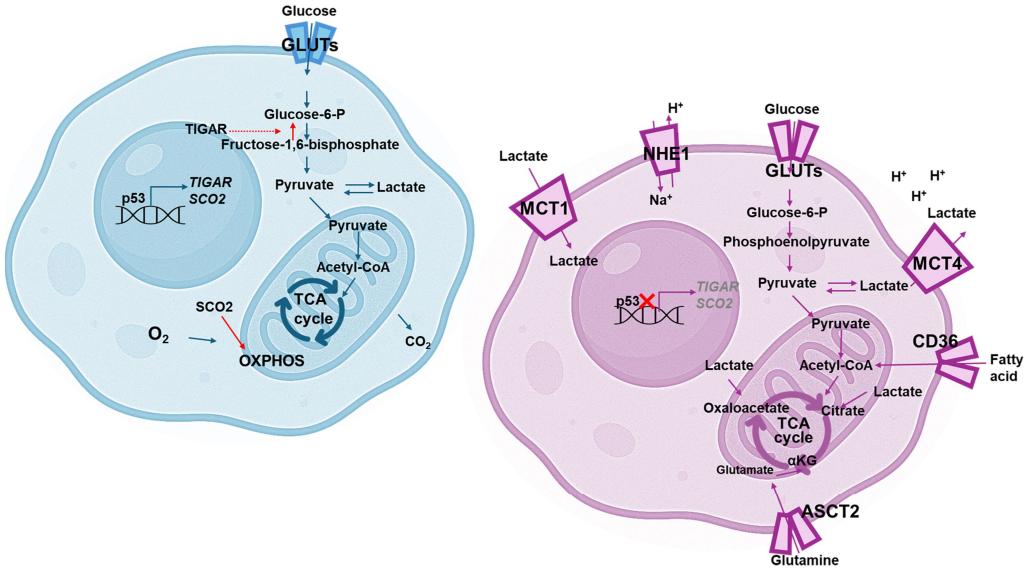

Figure 1. Metabolism orchestration in normal cells and rewired metabolism in a cancer cell. Left; Under physiologic conditions, p53 transcriptionally supports mitochondrial respiration by inducing SCO2 (synthesis of cytochrome c oxidase 2), which promotes activity of complex IV and OXPHOS. p53 also induces TIGAR, lowering fructose-2,6-bisphosphate, dampening PFK-1 activity and glycolytic flux, thereby channeling glucose-6-phosphate toward redox-supportive pathways while maintaining balanced TCA cycle oxidation of pyruvate to acetyl-CoA and CO_2. Right; Tumor cells adopt a glycolytic, anaplerotic, and export-oriented metabolic program even under normoxic conditions. GLUTs drive high glucose uptake; pyruvate is preferentially reduced to lactate and exported via MCT4, while MCT1 can import extracellular lactate. Activated NHE1 induce acidified extracelluar pH . Enhanced uptake of glutamine (ASCT2) fuels the TCA cycle (α-ketoglutarate) and biosynthesis; fatty-acid uptake via CD36 followed by β-oxidation supplies acetyl-CoA to the TCA cycle. In many cancers, p53 is inactivated, reducing SCO2/TIGAR programs and favoring glycolysis over mitochondrial oxidation. Abbreviations: ASCT2, alanine/serine/cysteine transporter 2 (SLC1A5); GLUT, glucose transporter; MCT1/4, monocarboxylate transporters 1/4; NHE1, Na^+/H^+ exchanger 1; OXPHOS, oxidative phosphorylation; PFK-1, phosphofructokinase-1; SCO2, synthesis of cytochrome c oxidase 2; TIGAR, TP53-induced glycolysis and apoptosis regulator; TCA, tricarboxylic acid; αKG, α-ketoglutarate.

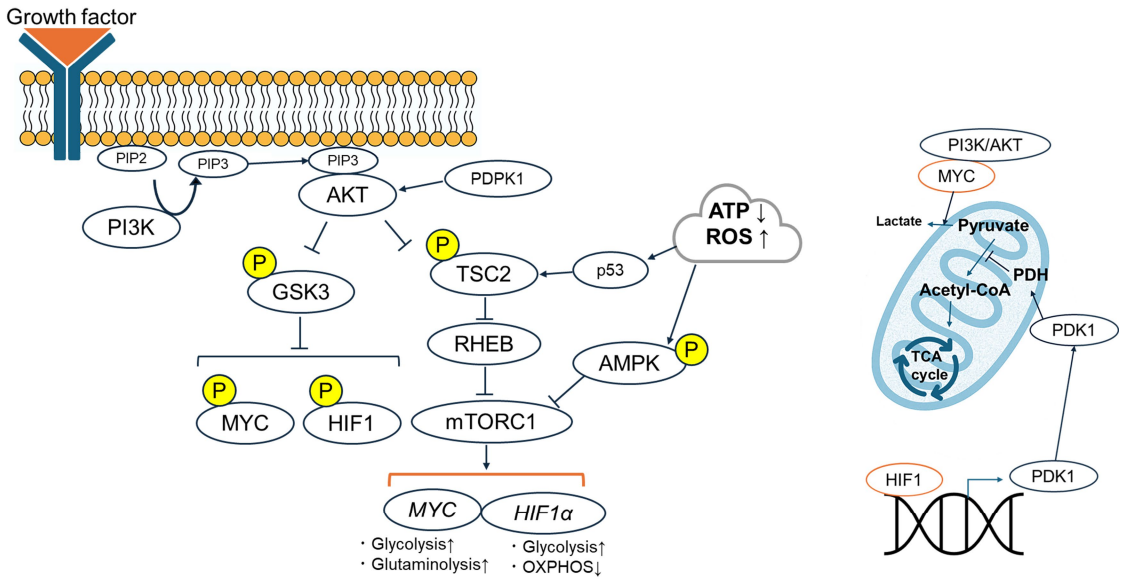

Figure 2. Tumor Metabolic Rewiring: Roles of RTK–PI3K–AKT–mTOR, AMPK, MYC, and HIF-1. RTK signaling activates PI3K–AKT–mTOR, increasing glucose uptake and anabolic synthesis while suppressing

autophagy. Elevated ROS or nutrient starvation activate AMPK, which inhibits mTORC1 and promotes catabolic programs (including autophagy). MYC amplifies glycolysis and glutaminolysis in cancer cells. Under hypoxia, HIF-1 reinforces glycolysis by inducing PDK1, which inhibits PDH, diverts pyruvate from the TCA cycle, and represses OXPHOS. Abbreviations: AKT; AMPK; GLUT; HIF-1; HK2; LDHA; mTORC1/2; MCT4; MYC; PDK1; PDH; PFK; PI3K; RTK; TCA; OXPHOS.

5.4. Oncometabolites and Epigenetic Regulation

Mutations in metabolic enzymes, such as isocitrate dehydrogenase 1 and 2 succinate dehydrogenase, and fumarase lead to the accumulation of "oncometabolites", such as 2-hydroxyglutarate, succinate, and fumarate, respectively [47,48].

Of note, fumarate inhibits the activity of 2-oxoglutarate/Fe^{2+}-dependent dioxygenases by acting as a competitive inhibitor of α-ketoglutarate (α-KG) [48]. Consequently, the hydroxylation of histone and DNA 5-methylcytosine, which is catalyzed by dioxygenases, is suppressed, leading to increased histone and DNA methylation.

5.5. Redox Balance and Antioxidant Systems

Increased metabolic activity leads to an increase in ROS, which causes DNA damage and cellular ageing. To counteract this, cancer cells activate antioxidant pathways, such as glutathione synthesis, nicotinamide adenine dinucleotide phosphate (NADPH) production via the pentose phosphate pathway, and the expression of the thioredoxin system [49]. Under nutrient stress, cancer cells also activate the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2), which rewires metabolism toward NADPH generation, thereby maintaining redox balance and promoting therapy resistance [50].

Maintaining redox balance is essential for the survival of rapidly proliferating cancer cells. Disruption of this balance, resulting in abnormalities, such as the inhibition of glutathione metabolism, is a promising therapeutic target that is currently under investigation.

These molecular pathways demonstrate how cancer cells complexly rewire their metabolic machinery to maintain growth, resist cell death, and adapt to hostile microenvironments. This knowledge opens new frontiers in oncology by paving the way for therapies targeting cancer metabolism.

6. Therapeutic Implications in Metabolic Models

The metabolic reorganization of cancer cells offers numerous therapeutic targets beyond those of traditional mutation-focused methods. Targeting pathways involved in glycolysis, redox balance, and biosynthesis enables the development of novel treatments that take advantage of metabolic weakness of cancers.

6.1. Glycolysis Inhibitors

Several inhibitors targeting key enzymes involved in glycolysis (i.e., hexokinase 2, lactate dehydrogenase, pyruvate kinase M2, etc.) are currently in the preclinical or early clinical evaluation stages [51–56]. These compounds aim to inhibit the energy supply to cancer cells, as well as the biosynthetic intermediates that are essential for their proliferation.

However, monotherapy has challenges owing to the metabolic plasticity of cancer cells. Tumors may compensate under conditions of monotherapy, by increasing oxidative phosphorylation or using alternative fuels, such as glutamine and fatty acids [48]. Therefore, combination therapy might be necessary to achieve sustained anti-cancer effects.

6.2. Targeting Hypoxia and HIF-1α Signaling

Agents for the inhibition of HIF-1α signaling include small molecule inhibitors, antisense oligonucleotides, and chemicals that enhance the activity of prolyl hydroxylase to destabilize HIF-1α [57–60]. Reducing HIF-1 activity has been shown to inhibit angiogenesis, glycolysis, and stem cell-like behavior in hypoxic tumor cells [60] (Figure 2).

6.3. Metformin and AMPK Activation

Metformin is a widely used antidiabetic drug that activates AMPK and inhibits mitochondrial complex I (Figure 2). It demonstrates antiproliferative effects in some cancers, and may enhance sensitivity to

chemotherapeutic agents [61]. Owing to its excellent safety profile, it is gaining attention as a candidate drug for repurposing in oncology, particularly for metabolism-driven cancers.

6.4. Targeting Redox Homeostasis

Therapeutic molecules that inhibit glutathione synthesis, thioredoxin reductase, and NADPH production are being explored [62]. These molecules aim to induce lethal oxidative stress in cancer cells while preserving the robust homeostasis mechanisms of normal tissues. For example, the "synthetic lethality approach", which combines redox-targeting drugs with DNA damage therapy, may enhance tumor selectivity and efficacy.

6.5. Diet, Fasting, and Metabolic Restriction

Dietary interventions, such as calorie restriction, ketogenic diets, and intermittent fasting have been proposed to exploit the metabolic inflexibility of cancer [63]. These strategies may reduce systemic glucose and insulin levels, regulate insulin-like growth factor 1 **(**IGF-1) signaling, and induce metabolic stress in tumors. Although clinical data remain preliminary, these approaches demonstrate potential as adjuvants to standard therapies by creating conditions that are unfavorable to cancer metabolism.

7. Conclusions and Future Prospects

Reconceptualizing cancer, from a disease caused solely by genetic mutations to a disease of metabolic adaptation has profound implications for oncology. The foundational research of Warburg, Goldblatt and Cameron demonstrated that bioenergetic dysfunction and environmental stress promote tumor initiation independently of mutagenic factors.

These early discoveries have long been ignored or misunderstood, but are now being supported by new evidence from systems biology, metabolic flux analysis, and TME research. In the modern context, these insights are converging with advances in systems biology, molecular genetics, and tumor ecology to support a unified theory of cancer evolution.

This new theory views malignant mutations not as linear genetic errors but as emergent properties of cells adapting to chronic metabolic instability, environmental pressures, and intercellular competition. Within this framework, cancer arises as a form of cellular adaptability, i.e., a maladaptive survival strategy that exploits metabolic flexibility to gain clonal advantage.

This broad perspective compels a re-evaluation of treatment goals. Rather than simply destroying cancer cells with cytotoxic agents, treatments that regulate the conditions promoting malignant selection are needed. Strategies aimed at normalizing the TME, stabilizing cellular energy metabolism, or preventing the formation of hypoxic niches may reverse the evolutionary trajectory of precancerous tissues toward homeostasis.

Furthermore, this new theory reaffirms the importance of early metabolic intervention and preventive approaches. Public health measures targeting systemic inflammation, insulin resistance, and dietary imbalances may significantly influence cancer incidence, by altering the metabolic landscape before malignant adaptation occurs.

Future cancer treatments should therefore integrate metabolic, genetic, and ecological perspectives. Approaches targeting the metabolic basis supporting tumor growth may act as promising complements to existing therapies. Furthermore, interventions aimed at restoring or stabilizing the metabolic environment, including dietary, pharmacological, and lifestyle strategies, may help prevent cancer progression and recurrence.

Ultimately, adopting this integrative treatment model could lead to the development of more effective, less toxic, and personalized cancer therapies that are better suited to the complex and adaptive nature of cancer. Understanding cancer as a dynamic and systemic process rather than a localized molecular abnormality opens new possibilities for cancer intervention, prevention, and cure.

Author Contributions

S.K.: conceptualization, methodology, data curation, formal analysis, visualization, writing—original draft preparation; H.W.: supervision, resources, validation, writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used *ChatGPT (OpenAI)* to assist in language editing and refinement of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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