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Review Article

Metabolic Memory in Cancer Cells: Unraveling the Long-Term Epigenetic Footprint of Transient Stressors - A Narrative Review

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Abstract

Cancer cells demonstrate remarkable metabolic plasticity, allowing them to adapt and endure under harsh conditions such as nutrient deprivation, hypoxia, and chemotherapy. This plasticity is not merely short-term; it can create a cellular memory that persists. Notably, exposure to stressful conditions can trigger stable epigenetic changes that preprogram cell behavior, enhancing tumor growth, metastasis, and drug resistance. This review examines the phenomenon of metabolic memory in cancer, aiming to explain how temporary stressors lead to long-term epigenetic adaptations that reshape cellular metabolism and phenotype. Key mechanisms include DNA methylation, histone modifications, and non-coding RNAs, all of which contribute to the reprogramming of metabolic pathways. This concept could hold therapeutic potential. Reversing stress-induced remodeling may be possible by focusing on metabolic enzymes or epigenetic regulators. Such strategies could enhance treatment efficacy and reduce the risk of resistance.

Keywords Metabolic Memory · Cancer Cells · Epigenetic Modifications · Transient Stressors · Therapeutic Resistance

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Introduction

According to the International Agency for Research on Cancer (IARC) in 2022, there were an estimated 20 million new incident cancer cases, 9.7 million cancer deaths, and 53.5 million cancer survivors five years post-diagnosis (Bray et al., 2024). Due to lifestyle risk factors and the aging trend in the population, it has been estimated that the number of new cancer cases will increase by more than 75% in 2050 (Bizuayehu et al., 2024). Iraq recorded an age-standardized cancer incidence rate of about 159 per 100,000 individuals in 2022, whereas in the Kurdistan Region, the Erbil Governorate's incidence rose from 64 to 160 cases per 100,000 individuals during the 2013–2019 period, with breast, hematological, colorectal, and lung cancers being the most prevalent among females (K et al., 2022, Salih et al., 2024).

Cancer cells are characterized by an extremely high level of plasticity that allows them to adapt to numerous environmental stresses (Ravindran Menon et al., 2020). This plasticity is due in part to their ability to reprogram cellular metabolism in response to oncogenic mutations, which support their growth and survival (Bhat et al., 2024). It is therefore important to understand the mechanisms that allow metabolic reprogramming in cancer cells in order to come up with new treatment strategies (Navarro et al., 2022). Cancer metabolism studies have indicated that cancer cells utilize altered metabolic pathways to meet their stringent energy demand and adapt to the unfavorable tumor microenvironment (Fendt et al., 2020, Yang et al., 2024a, Tufail et al., 2024). Metabolic reprogramming of cancer cells not only enhances survival and proliferation but also enables them to withstand stress and attain treatment resistance (Faubert et al., 2020).

The Warburg effect, defined by enhanced glucose uptake and glycolysis in the presence of oxygen, is a well-studied form of metabolic reprogramming in cancer cells (Fukushi et al., 2022). This process allows cancer cells to produce ATP and essential metabolic intermediates, thereby facilitating the biosynthesis of macromolecules while simultaneously promoting cellular proliferation, invasiveness, and drug resistance (Bose et al., 2021). Metabolic alterations in cancer-associated fibroblasts within the tumor microenvironment are often driven by oxidative stress, which is generated by hydrogen peroxide released by the surrounding cancer cells (Fedele et al., 2021). The ability of cancer cells to adapt their behavior and scavenge nutrients in the face of restricted availability represents an important feature of their metabolic flexibility (Kreuzaler et al., 2020). Cells utilize nucleic acids, proteins, and lipids for biosynthetic pathways, supporting cell growth and being associated with enhanced glycolytic activities and reduced oxidative metabolism (Zhu and Thompson, 2019, Hamid, 2025). During metabolic stress, cancer cells have the ability to launch a number of survival mechanisms, one of which is autophagy, through which they recycle intracellular contents to generate energy and maintain cellular homeostasis (Munir et al., 2019).

Recent advances in oncology have shed light on the phenomenon of metabolic memory, which explains how temporary metabolic stress produces an enduring genetic legacy in cancer cells and shapes their future behavior. Metabolic memory refers to the long-term maintenance of changed metabolic and phenotypic states despite removal of stressors like hypoxia, caloric restriction, and chemotherapeutic treatment (Dong et al., 2024, Biradar and Begum, 2025). The stressors are noted for causing persistent epigenetic modifications including DNA methylation, histone modifications, and alterations in noncoding RNA levels, all of which affect gene expression and increase tumor plasticity (Obeid and Damaghi, 2024, Shwani, 2025).

The epigenome is highly regulated by nutrition, environmental exposure, and oxidative stress, all of which contribute to tumor growth and resistance to therapy (Rubio et al., 2023). The metabolic changes in cancer are regulated by the key oncogenetic networks of HIF-1α, Myc, p53, and PI3K/Akt/mTOR, and thus highlight the complex interaction of genetic events and metabolic plasticity (Park et al., 2020). Thus, the epigenome serves as a memory of past stress experiences, allowing tumor cells to maintain a competitive edge and phenotypic heterogeneity even when a causative stressor is removed (Laisné et al., 2025). Such understanding of how transient stressors lead to long-lasting epigenetic modification is crucial in developing tailored regimens of treatment for purposes of preventing recurrence and resistance. Therefore, this review aims to synthesize and critically evaluate current evidence regarding how transient stressors induce metabolic memory in cancer cells via persistent epigenetic modifications. The objective is to elucidate the underlying molecular mechanisms, their implications for tumor progression and treatment resistance, and potential therapeutic strategies to address this phenomenon for enhanced cancer management.

Metabolic Memory: Concept and Mechanisms

Metabolic memory is the enduring cellular and molecular effect that persists after a transient disruption in metabolism such as hyperglycemia, hyperlipidemia, or hypoxia (Dong et al., 2024). Originally described in diabetic complications,

the phenomenon describes the manner in which transient episodes of metabolic stress induce sustained gene expression and lasting changes in cellular phenotype, even after return to normal metabolic states (Yang et al., 2024b). Unlike the rapid adaptive responses seen under the acute state, metabolic memory represents persistent reprogramming mechanisms that last for prolonged periods (Dong et al., 2024). More particularly in the field of oncology, metabolic memory provides tumor cells with the ability to survive numerous environmental challenges—e.g., nutrient starvation or oxidative stress—by maintaining a metabolic and transcriptional profile that favors tumor growth (Kreuzaler et al., 2020). Approximately 70% to 90% of solid tumors maintain the Warburg effect, indicative of how extensive long-term glycolytic reprogramming is in cancer cells (Cunha et al., 2023, Vaupel et al., 2019).

At the molecular level, metabolic memory is driven by a complex interplay between epigenetic modifications, metabolic reprogramming, and regulatory feedback mechanisms. The process is built on epigenetic modifications (Chen and Natarajan, 2022, Dong et al., 2024). Abnormal promoter hypermethylation is a common and important feature present in solid tumors, with methylation frequency in the gene RASSF1A in certain types of non-small cell lung carcinoma ranging from 16.7% to 85.7%, while remaining almost absent (0%–3.3%) in healthy tissues. In addition, promoter hypermethylation of the RASSF1A gene is recognized as one of the earliest epigenetic alterations in breast cancer and is detected in more than 60% of primary breast carcinoma cases, while other key genes such as BRCA1 also frequently show similar hypermethylation patterns (Kozomara et al., 2018). Also, in colorectal carcinoma, hypermethylation of DNA mismatch repair genes, such as MLH1, has been reported in up to 30% to 50% of what are reputed as sporadic cases (Farchoukh et al., 2016). In contrast, hypomethylation of oncogenes leads to stable deregulation of transcription (Bhootra et al., 2023). Gene abnormalities linked with mutations and chromatin remodeling are extremely prevalent in cancer, occurring in roughly 45% of tumors, and are of critical importance in the disruption of gene expression and in the progression of malignancy (Krishnamurthy et al., 2022). Histone modifications, such as elevated H4K16 acetylation or reduced H4K20 trimethylation, further influence chromatin accessibility and gene expression. The combined modifications activate glycolytic enzymes (e.g., HK2, LDHA) and inhibit mitochondrial oxidative genes in a long-lasting manner, enabling the metabolic transition called the Warburg effect (Shvedunova and Akhtar, 2022).

One of the most important and increasingly valued features of metabolic memory is the role of non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). These molecules are potent regulators of gene expression at the transcriptional and post-transcriptional levels (Statello et al., 2021). miRNAs, for example, can down-regulate translation or trigger degradation of mRNA transcripts involved in apoptosis, metabolism, and cell cycle regulation (Rac, 2024). Metabolic stress can cause stable changes in miRNA expression profiles, leading to long-term suppression of tumor-suppressive pathways or long-term activation of oncogenic ones (Alamoudi et al., 2018). lncRNAs, by contrast, can act as scaffolds or decoys for chromatin modifiers and transcription factors, thereby directing widespread epigenetic remodeling. These non-coding RNAs thus create a mechanistic bridge between transient environmental signals and long-term gene expression patterns (Bure et al., 2022) (*Figure 1*).

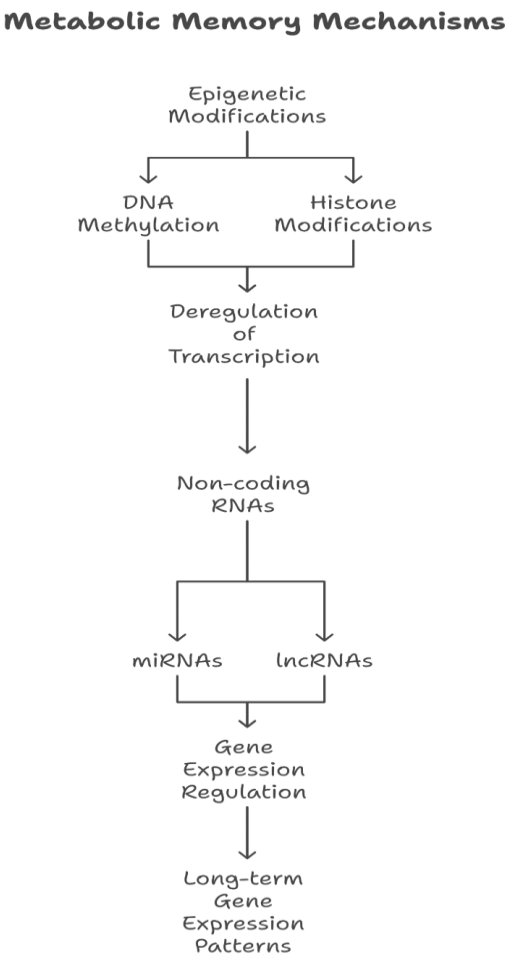

Figure 1: Mechanisms of metabolic memory in cancer cells.

In addition to the complicated process of epigenetic reprogramming, there is also a significant factor known as metabolic memory. This is aided by oxidative stress,

inflammatory signals, and cellular aging. All these factors combine to maintain a detrimental state that can be detrimental to health. Whenever the body is under stress, it forms reactive oxygen species, or ROS. This results in severe damage to the DNA and proteins of the cells, enhancing unhealthy responses to that stress. The inflammatory chemicals that are emitted during the process, as well as the premature aging of the cells, result in tissue not functioning as it should. This results in a detrimental cycle that aids in maintaining the memory state already formed.

Table 1: Transient Stressors and Their Role in Inducing Metabolic Memory in Cancer Cells

Transient Stressor	Acute Cellular Response in Cancer	Molecular/Pathway Involvement	Contribution to Metabolic Memory
Hypoxia	Acute oxygen deprivation leads to a switch from oxidative phosphorylation to glycolysis (Warburg effect), upregulating glucose transporters (e.g. GLUT1), and increasing lactate dehydrogenase activity.	Stabilization of HIF-1α under low oxygen activates transcription of glycolytic and angiogenic genes via PI3K/AKT/mTOR; AMPK activation balances energy stress.	Persistent HIF-1α activity causes chromatin remodeling and histone acetylation, reinforcing glycolytic phenotype and angiogenesis even after reoxygenation, contributing to tumor aggressiveness
Nutrient Deprivation	Triggers autophagy and lysosomal biogenesis to maintain intracellular energy and metabolite levels; suppresses protein synthesis and proliferation.	AMPK senses low ATP/AMP ratio, inhibits mTORC1, and upregulates SIRT1 to promote catabolic gene expression and enhance mitochondrial function.	These adaptations imprint transcriptional and epigenetic changes (e.g. deacetylation via SIRT1), leading to durable metabolic rewiring and stress-adaptive phenotypes
Oxidative Stress	Accumulation of ROS induces oxidative damage to DNA, lipids, and proteins, triggering apoptosis or stress responses depending on intensity.	NRF2 is activated, translocates to the nucleus, and promotes antioxidant gene expression; simultaneously, oxidative stress inhibits DNMT1, reducing DNA methylation globally.	This leads to epigenetic instability (global hypomethylation and local hypermethylation), promoting heterogeneity, therapy resistance, and clonal selection
Chemotherapy	Induces DNA and mitochondrial damage, oxidative stress, and metabolic shifts in surviving cells toward glycolysis and glutamine dependence.	Involves p53-mediated cell cycle arrest/apoptosis, NF-κB activation for survival, and reprogramming of mitochondrial and glucose metabolism.	Persistent metabolic reprogramming through transcriptional memory and histone modifications promotes drug resistance and tumor recurrence

Note: The table summarizes key transient stressors (hypoxia, nutrient deprivation, oxidative stress, and chemotherapy), their acute cellular responses, molecular pathways involved, and how they contribute to the establishment of long-term metabolic memory in cancer cells.

Transient Stressors Inducing Metabolic Memory

Transient stressors such as hypoxia, nutritional insufficiency, oxidative injury, and chemotherapy have a significant impact on cancer cell metabolic processes. These stressors induce various signaling cascades involved in stress responses, alter gene expression profiles, and change metabolic enzyme function; hence, it can improve cell resilience against repeated stressors (Al Tameemi et al., 2019, Tang et al., 2022). These adaptations, given sufficient time, will form the foundation for metabolic memory, which eventually influences cancer cell proliferation, survival, and treatment response (Chen et al., 2023).

Hypoxia, a common feature of solid tumors, triggers a series of metabolic adaptations, such as the increase of glycolysis, the decrease of oxidative phosphorylation, and the activation of hypoxia-inducible factor 1 alpha (HIF-1α)

(Dzhalilova and Makarova, 2021, Chen et al., 2023). This leads to multiple changes in cancer cells, including enhanced angiogenesis, metastasis, and resistance to therapy (Jing et al., 2019). Another common stressor in tumors, nutrient starvation, is that it leads to autophagy and other catabolic processes' activation, promoting the recycling of intracellular components for energy production (Bugajova et al., 2024). Oxidative stress, caused by an imbalance between the production of free radicals and the effectiveness of antioxidant defense systems, can cause damage to DNA, proteins, and lipids. Finally, this can lead to metabolic disorder and cellular apoptosis (Sasidharan Nair et al., 2021). While chemotherapeutic drugs are designed to kill cancer cells, they can also cause metabolic stress and create a condition of metabolic memory (Chen et al., 2020).

Acute stressors induce changes in metabolic processes, which are crucial for cancer cell survival and adaptation; therefore, they are an important factor in disease development and treatment resistance (Ferdousmakan et al., 2025). This transient stress can induce metabolic remodeling, which contributes to cancer progression. (*Table 1*).

Epigenetic Footprints of Transient Stressors-How transient stressors leave lasting epigenetic marks?

Epigenetic modifications play an essential function for mediating metabolic memory, hence laying the molecular foundation for long-term maintenance of modified metabolic states within neoplastic cells (Chen and Natarajan, 2022). Such epigenetic modifications involve DNA methylation and histone and noncoding RNA transcriptional regulation, all of which affect gene expression and chromatin structure without altering the inherent DNA sequence. As such, these modifications drive sustained alterations within expression levels of metabolic enzymes, signaling pathway functioning, and cell phenotypes, eventually leading to maintenance of metabolic memory (Bure et al., 2022).

DNA methylation, wherein a methyl group is added to cytosine bases, is an extensively studied epigenetic change with the potential to suppress gene expression18. Histone modifications like acetylation, methylation, phosphorylation, and ubiquitination can affect chromatin structure and gene transcription (Mortazavi et al., 2022). Non-coding RNAs including microRNAs and long non-coding RNAs function by regulating gene expression by binding to messenger RNA or interacting with enzymes involved in chromatin modifications (Statello et al., 2021).

Epigenetic processes allow metabolic memory to form and be maintained, offering novel targets for oncological interventions. Oxidative stress, known to cause multiple types of DNA damage, negatively influences DNA methyltransferase activity and produces global hypomethylation (García-Guede et al., 2020). Tumor suppressor genes may be silenced by hypermethylation as cancer progresses, whereas oncogenes may be activated by hypomethylation (Vaidya et al., 2025). These processes are strictly controlled to ensure precise gene expression and cellular homeostasis. Elucidation of how epigenetics and metabolism communicate with one another is required for the advancement of novel anticancer therapeutic strategies. In addition, most epigenetic alterations are reversible and can be targeted effectively by pharmacological inhibitors, and therefore they represent attractive targets for cancer therapy. Epigenetic treatments can re-establish normal gene expression and cell function, which prevents drug resistance and improves patient prognosis (Dai et al., 2024).

Metabolic and epigenetic research holds great promise for discovering novel therapeutic strategies for targeting fundamental mechanisms driving cancer progression and drug resistance (Garg et al., 2024). For example, aberrant epigenetic modifications have been found to have a strong association with tumor cell proliferation and confirm a crucial role for chromatin-modifying enzymes in oncogenic transformation (Tan et al., 2022). Environmental, dietary, alcohol consumption, and exposure to environmental toxins can disrupt epigenetic regulation, thereby increase cancer risk (Tiffon, 2018). Also, concurrent targeting of metabolic and epigenetic alterations can allow for more effective and personalized cancer therapy (Miranda-Gonçalves et al., 2018). As shown in (*Figure 2*), which briefly illustrates the epigenetic footprints of transient stressors, these brief exposures can leave lasting epigenetic marks.

Application Prospects for metabolic memory

Metabolic memory and transient stressors offer promising avenues for cancer therapy by influencing diagnosis, prognosis, and treatment. Interventions such as dietary restriction and pharmacological agents are being investigated to modulate cellular responses and overcome drug resistance (Eckerling et al., 2021). Simultaneously, Epigenetic alterations in the context of cancer therapy are an extremely encouraging avenue for specific targeting, with the potential to correct aberrant gene expression patterns and restore normal cell functioning (Perri et al., 2017). Their inherent reversibility on top of their sensitivity to drug treatment makes them attractive targets for oncologic therapy. Histone deacetylase inhibitors and DNA methyltransferase inhibitors are two main classes of epigenetic drugs approved for cancer therapy (Suraweera et al., 2025). These chemotherapeutic drugs act by opposing the abnormal histone acetylation and DNA

methylation patterns present in cancer cells, therefore causing gene expression alterations (Ilango et al., 2020). However, it should be noted that systemic therapy has proven to achieve best results when initiated simultaneously with cancer chemotherapy initiation, showing remarkable efficacy against early breast cancer and significant effects against metastatic cases (Agostinetto et al., 2022). As illustrated in (*Figure 3*). how incorporating an individualized treatment approach tailored to specific epigenetic and metabolic profiles can and will enhance therapeutic outcomes and optimize long-term disease control.

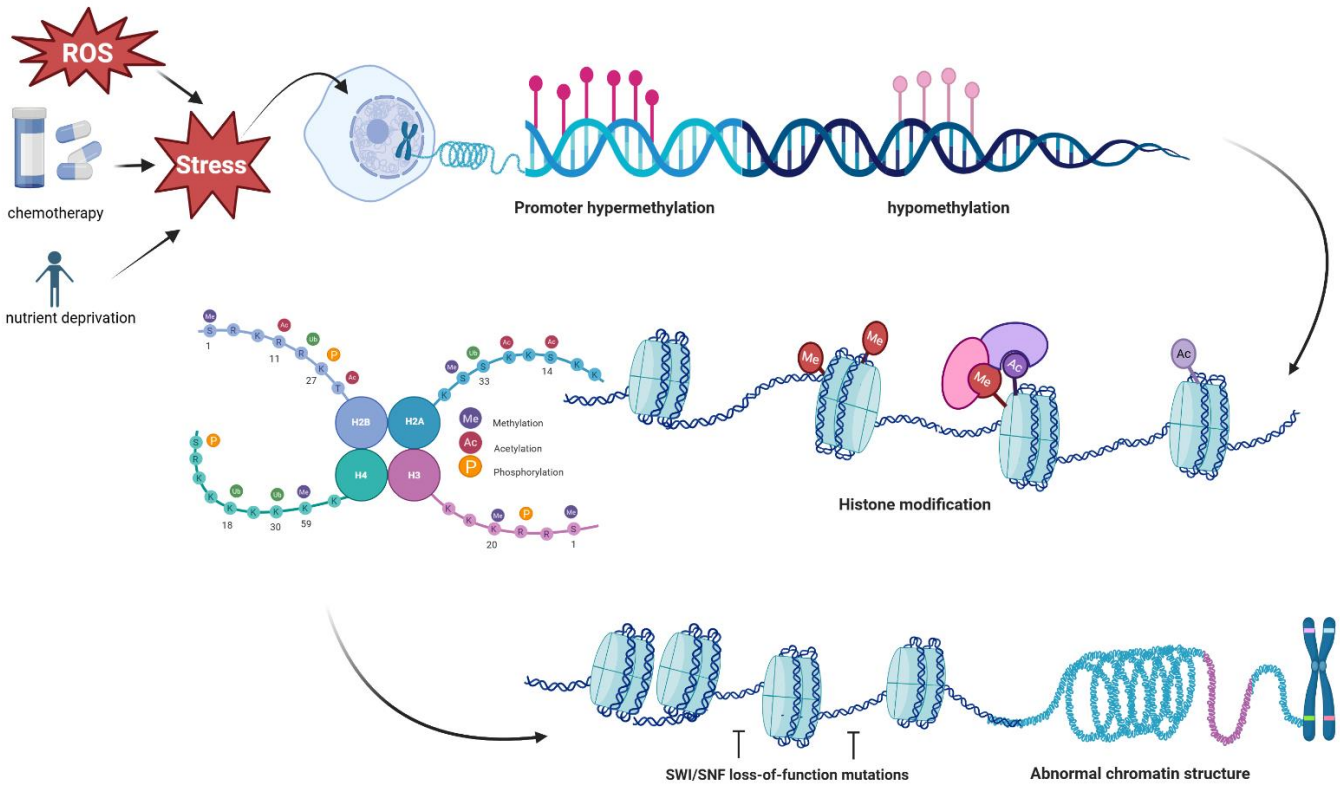

Figure 2: Epigenetic footprints of transient stressors in cancer cells.

These epigenetic drugs can either be used alone or combined with other therapy modalities, such as chemotherapies, targeted therapies, and immunotherapies, to enhance therapy efficacy (Morel et al., 2020). Significantly, combinations of HDAC inhibitors with other therapy options have shown encouraging developments in preclinical and clinical studies (Hontecillas-Prieto et al., 2020). Individualized epigenetic treatment tailors the treatment to the individual patient using their unique epigenetic profile, with specific focus on the particular epigenetic changes that are driving their cancer condition. Specific radio or nano-theranostics are being developed for targeted diagnostics (Sabit et al., 2025, Degrauwe et al., 2019).

Epigenetic approaches to cancer prevention by diet should be considered not only within the framework of the cancer continuum but also across the whole of the lifespan continuum (Montgomery and Srinivasan, 2019). Diminutive RNA non-coding entities, microRNAs (miRNAs), have the potential to regulate gene expression by targeting messenger RNA molecules (Finotti et al., 2019). Therapeutic applications involving miRNAs are also being developed, targeting cancer-related miRNAs specifically or replacing tumor-inhibiting miRNAs to restore their expression. Targeting dysregulated m6A regulators could be an attractive strategy for cancer therapy, similar to the

strategies targeting other epigenetic regulators (Zheng et al., 2022). Over-expression and suppression of microRNAs have the potential to alter cell fate and enable tumor progression (Mortazavi et al., 2022).

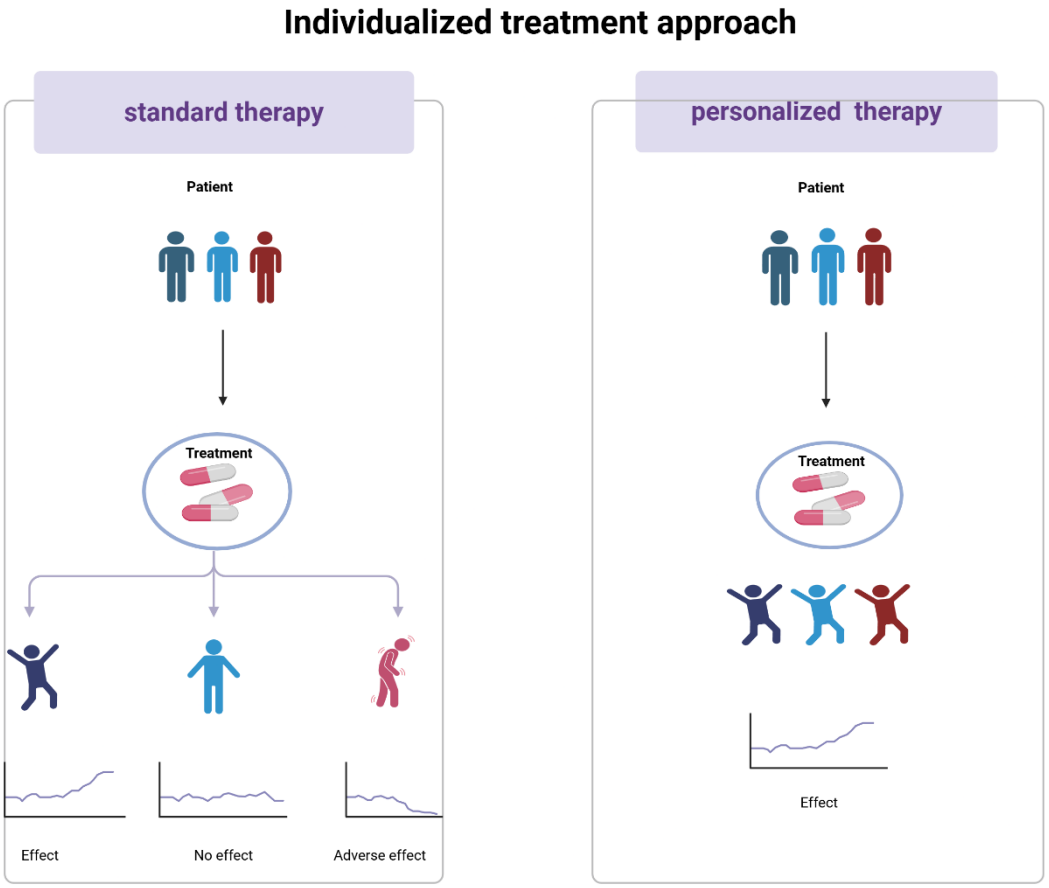

Figure 3: Individualized treatment approaches targeting metabolic memory.

Epigenetic alterations, such as DNA methylation and histone modifications, are key players in cancer development and progression (Ilango et al., 2020, Tan et al., 2022). Evidence confirms that these alterations may affect oncogene and tumor suppressor gene expression levels and hence alter the behavior of cancerous cells (Baylin and Jones, 2016). Targeted therapy, often given concomitantly with chemotherapy and other treatment regimens, aims to hinder cell proliferation and cell spreading of cancerous cells by targeting specific genes or certain proteins/enzyme targets present within cancerous cells or their surrounding tissue microenvironment (Mokhtari et al., 2017). Targeted drugs are chosen based on their interaction within specific target sites (Zafar et al., 2024).

In addition, these therapy methods have proven to be effective within clinical settings. Cancer management is being revolutionized, with new developments being introduced Metastatic cancers remain an uncontrolled clinical problem for most people, considering that inherent genomic instability of all cancer types predisposes them to resistance to both cytotoxic and target therapy strategies (Dhanyamraju, 2024). Combining epigenetic drugs with established treatment modalities can potentially reduce drug resistance, enhance treatment efficacy, and improve patient prognosis (Majchrzak-Celińska et al., 2021, Biradar and Begum, 2025). Therapeutic oncogene suppression has proven to be effective, yet mostly within the short term. Implementing a strategy that allows for monitoring of clonal evolution along with the timely implementation of adaptive therapy could result in greater control plus increased survival (Derbal, 2024).

Conclusion

Metabolic memory allows cancer cells to retain epigenetic and metabolic alterations caused by short-term stress, which promotes treatment resistance and disease progression. It is essential for policymakers and healthcare practitioners to prioritize the development of therapies that target these long-lasting changes to improve personalized cancer therapy. Future studies are needed to clinically confirm these mechanisms and develop combination therapies capable of efficiently counteracting metabolic memory and enhancing patient prognosis.

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Author Contributions Karez Abdulghany Omer: Conceptualization; Literature search and selection; Drafting the manuscript; Visualization. Huda Jaabar Jawhar: Methodological supervision; Critical revision of the manuscript; Validation of sources; Final approval.

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