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Cellular Starvation as a Strategy in Cancer Cell Treatment: Mechanisms, Evidence, and Therapeutic Implications

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Abstract. Cellular starvation is a cancer therapeutic strategy based on the premise that nutrient deprivation can differentially affect cancer cell survival. Nutrient deprivation encompasses a variety of modalities such as systemic dietary restrictions in fasting and caloric restrictions, pharmacological nutrient starvation mimics, and specific nutrient-depleting compounds. Nutrient deprivation can target key nutrients including glucose, amino acids, and fatty acids. Cancer cells often exhibit heightened reliance on specific nutrients or nutrient classes, and such nutrient dependencies, termed "metabolic addictions", represent viable opportunities for targeted therapeutic approaches. Cancer metabolic alterations are not only involved in driving malignant transformation but are also dictated by the tumor microenvironment and further shape the tumor-immune microenvironment. Furthermore, metabolic rewiring of cancer cells and cancer-stroma interactions have been shown to modulate redox balance, enhance antioxidant capacity, and impact cellular responses to oxidative and other stresses.
Metabolites derived from glucose, glutamine, fatty acids, and other classes of biomolecules serve as building blocks to sustain the rapid growth and proliferation of cancer cells. Cellular metabolism, especially glucose and lipid metabolism, is tightly coupled to the tumor microenvironment and actively shapes the tumor-immune landscape. Therefore, targeting cancer metabolism and the interconnectedness of cancer cells with the tumor microenvironment holds substantial therapeutic promise.
Distinct cancer cell types carry out remarkably different metabolic rewiring programs during tumorigenesis and adapt diverse strategies to survive under adverse microenvironments. Nutrient deprivation therapy has the capacity to hamper tumor growth and overcome chemoresistance synergistically when combined with chemotherapeutics.

Keywords: Cellular starvation, Cancer, Cancer treatment, Free treatment, Cell therapy

1. Introduction

The discipline of cancer biology sheds light on the processes that can transform normal cellular proliferation into the hyper-proliferative febrile pathology characteristic of cancer (Ebrahim *et al*., 2016). These processes are responsible for modifications in the rates of synthesis and degradation of cellular macromolecules (proteins, nucleic acids and polysaccharides) that are requisites for the transition. The rate of synthesis is limited primarily by the accessibility of metabolic intermediates entering into metabolic pathways such as glycolysis or the Krebs cycle. Access to metabolic intermediates is determined by cellular input activity (modulated both at the transporter and the metabolic pathway enzyme level) and the competing energy- and carbon-requiring biosynthetic pathways employing them (Wang *et al*., 2022). The replenishment of metabolic intermediates occurs through the use of vitamins, amino acids and other metabolic Co-factors that enter through the cellular membrane and that can be regarded too as metabolic supporters. The embedding of these terms (energy, carbon, and metabolic co-factors) in a first derivative of a prospective total synthesis modulation law with respect to time enables the possible deducing of an elaborated first synthetic equation (Silva *et al.*, 2025).

2. The Concept of Cellular Starvation in Cancer Biology

The metabolic alterations that accompany the malignant transformation of cells are among the first observed hallmarks of cancer, and they have been the subject of extensive investigations. Tumor cells tend to display a high

basal level of glycolysis, a phenomenon known as the Warburg effect, even when oxygen is plentiful and oxidative phosphorylation would be preferred. Other cancer-associated metabolic dependencies include the utilization of glutamine as a preferred amino acid (glutamine addiction), and a reliance on intratumoral fatty acid oxidation. These alterations are termed metabolic dependencies. During progressive tumorgenesis under nutrient-rich conditions, the tumor microenvironment undergoes concomitant pathological changes, including the increased production of reactive oxygen species (ROS) and a pro-inflammatory environment, accompanied by an upregulation of HIF-1α pathway and metabolic reprogramming. These ongoing processes drive cancer cell survival, proliferation, immune evasion, and the development of metastases. Under deprivation conditions of major nutrients (e.g., glucose, amino acids, lipids), metabolic dependencies are still retained, but the accompanying metabolic reprogramming is counterintuitive to the Warburg effect and can be tumor-selective (Wang *et al*., 2024).

On the other hand, pre-tumorigenic cells toggle their metabolism toward oxidative phosphorylation instead of increased glycolysis under nutrient-rich conditions due to a distinct metabolic profile, and are reportedly less tolerant to metabolic stress than both normal and cancer cells when deprived of glucose. These endogenous factors dictate the varied responses of cancer cells to nutrient deprivation. In cancers with loss-of-function mutations in SETD2, the oxidative phosphorylation phenotype is preferentially adopted, and together with a switch of glutamine dependency to alanine dependency and promiscuous acquisition of alternative routes, cancer cells exhibit high-level nutritional plasticity in the absence of nutrient deprivation. Thus, nutrient deprivation has emerged as an intervention strategy aimed at cancer therapy. Cancer cells may adapt to nutrient deficiency by triggering a series of stress-coping responses that promote survival, but the underlying signalling pathways activated under nutrient-limiting conditions, which are reminiscent of those exerted by several types of fasting and dietary reformulation, differ markedly from those activated during general deprivation stress (Ibrahim *et al*., 2021).

3. Metabolic Dependencies of Cancer Cells under Nutrient Deprivation

The depletion of essential nutrients can compromise the growth of cancer cells by inducing cellular stress and triggering reprogramming of metabolic pathways. According to what was indicated by Cell Metabolism Research Group, (2022) a broad range of nutrient-deprivation strategies targeting glucose or other essential metabolites without impacting normal tissues is being evaluated in experimental and clinical research as a potential means to combat cancer. Although some nutrients support proliferation, cancer cells often develop atypical dependencies on additional nutrients, either to sustain proliferative synthetic demand or to cope with metabolic by-products generated by active metabolism and enhanced uptake (Endicott *et al*., 2021).

Almost all tumor cells undergo significant metabolic reprogramming, which is essential to sustain their growth and promote continuous proliferation; during the process of tumor development, they often experience severe nutrient deprivation. This occurs because the consumption of nutrients by the rapidly proliferating tumor cells frequently exceeds the supply of those nutrients, leading to a critical imbalance. The mechanisms underlying nutrient uptake and utilization are crucial as they play pivotal roles in driving specific onco-phenotypes during the complex process of tumor evolution. These unique nutrient dependencies—which are typically not used by normal, healthy cells—constitute noteworthy vulnerabilities and subsequently offer alternative options for cancer treatment when combined with traditional therapies. Among these, the most significant and prominent metabolic alteration that is closely associated with tumorigenesis is the Warburg effect (Reid & Kong, 2013). This phenomenon highlights the dependence on increased nutrient uptake and a specific metabolic outlet, particularly the altered [serine + glycine] to [one-carbon] flux, which has been observed distinctly in individual tumors. The four principal categories of nutrients that have been identified are glucose, glutamine, lipids, and one-carbon nutrients, each playing a vital role in the sustenance and progression of these malignancies (Birsoy *et al*., 2014).

4. Mechanistic pathways activated by starvation and their cancer-specific effects

The concept of cellular starvation has been reinterpreted in contemporary cancer biology, focusing on the withdrawal or depletion of essential nutrients rather than a general lack of cellular energy. Nutrient metabolites serve not only as substrates for cellular processes but also as signaling molecules that modulate cellular behavior through specialized pathways (Lv *et al*., 2024). Glucose deprivation (a classic model used historically) remains an example of such nutrient starvation, but additional paradigms capitalizing on various nutrient dependencies

characteristic of tumor cells have emerged, including amino acid scarcity, lipid limitation, hypoxic stress, and impairment of mitochondrial metabolism (Hughson *et al*., 2012).
The differential reliance of malignant versus normal cells on specific nutrients creates therapeutic opportunities. Tumor-specific nutrient dependencies that cytostatically or cytotoxically inhibit cancer cells have been described in the context of glucose, glutamine, serine, lipid, and heme metabolism. Importantly, while fasting reduces nutrient supply throughout the body, pharmacological strategies have been engineered that affect only the tumor. Nutrient-withholding active ingredients are increasingly being sought that deplete nutrients needed for proliferation and selectively target tumor cells while sparing normal tissues (Lv *et al*., 2024).

5. Preclinical evidence for starvation-based interventions

Certain combinations of fasting and a variety of chemotherapeutics can establish a synergy that greatly enhances the killing of tumor cells without harming normal cells. For example, short-term fasting or the fasting mimetic molecule mTOR inhibitor rapamycin can sensitize a panel of triple negative breast cancer (TNBC) cell lines to a variety of chemotherapy agents whilst protecting normal mammary epithelial cells. Metabolomic profiling shows that TNBC cells are unable to mount the expected metabolic shift following fasting, although normal mammary cells do. These findings were recapitulated in orthotopic mouse models, where cycles of fasting or rapamycin with chemotherapy greatly inhibited tumor growth and metastasis without overt toxicity and protection of normal tissues (Pateras *et al*., 2023).

Experiments have also shown that fasting or rapamycin sensitizes tumors driven by mutant p53 to cisplatin through enhancement of ROS-mediated toxicity, supporting the broader utility of these strategies across genotypes. Selective pressure imposed by various fasting strategies leads to acquisition of resistance mutations that confer autonomy of key metabolic genes, as evidenced by Drosophila models. Candidate genes have been identified that predict whether a tumor will become resistant following fasting, which helps inform decisions regarding the timing and nature of the starvation strategy employed in tandem with chemotherapy (Nencioni *et al*., 2018).

Preclinical evidence for suppression of the HIF-1 pathway during fasting has also been reported, permitting synergistic action of anti-angiogenic agents such as bevacizumab. Reprogramming of multiple metabolic pathways by fasting lowers the levels of an Esterase 1 metabolite that promotes tumor growth, while coordinates expression of lipid metabolic enzymes in the opposite direction from hypoxia, further supporting the use of fasting. Continued investigation of candidate fasting regimens across a wider spectrum of cancer types and chemotherapeutic agents is warranted, particularly modeling the effect of perturbations at successive time points on growth prior to applying combination therapy. Studying the impact of re-feeding intervals on subsequent agent selection will help to optimize real-world treatment protocols (Fasano *et al*., 2023).

A systematic assessment of cancer cell and tumor metabolism under these conditions is therefore essential for charting both the hazards and opportunities offered by cellular starvation to strategic cancer treatment (Nencioni *et al*., 2018).

6. Clinical approaches leveraging cellular starvation

Tumor starvation therapy aims to inhibit cancer cell growth by depriving nutrient availability (Seyfried *et al*., 2017). The underlying rationale is based on two observations. First, cancer cells demonstrate abnormal metabolic dependencies that render them acutely sensitive to starvation of specific nutrients; second, certain tumors exhibit ferocious uptake of specific nutrients and readily utilize tumor-derived nutrients post-starvation, highlighting the importance of timing. Temperature effects in the tumor microenvironment and immune ecosystem modulation further accentuate the growth advantage of nutrient-rich environments in parallel with enhanced sensitivity to nutrient-depleting therapy (Yang *et al*., 2020). Approaches to implement starvation therapy include dietary glucose restriction and pharmacological agents that mimic specific nutrient deprivation. So far, these strategies have exhibited acceptable safety and tolerability profiles, as well as promising signals of anti-cancer efficacy in early clinical trials (Vernieri *et al*., 2022).

7. Challenges, limitations, and safety considerations

Tumors are heterogeneous entities in multiple ways, and disruption of cancer cell metabolism can have off-target effects on normal tissues or cells residing within tumors. The stage of disease, number and types of coexisting tumors, and other patient characteristics may significantly impact a patient's ability to engage in starvation-based therapies (PubMed., 2022). Regulatory approval and patient access to therapies that exploit metabolic starvation require deep understanding of cancer metabolism along with patient stratification and monitoring strategies to select individuals who are most likely to benefit. An emerging focus on pathway- and cell type-specific effects may facilitate the development of combination treatment strategies that exploit the therapeutic potential of starvation without inducing injurious effects on normal and non-targeted tumor cells (van Gisbergen *et al*., 2021).

8. Integrative strategies: combining starvation with conventional therapies

Many cancer therapies are predominantly cytotoxic to indiscriminate normal tissues and thus are associated with dose-limiting toxicities. Biological elements that either amplify the therapeutic efficacy of the cytotoxic or protect normal tissues are urgently needed to improve anticancer therapy effectiveness. Various starvation therapies are being integrated into existing therapeutic paradigms to enhance sensitivity toward conventional chemotherapeutics and radiotherapy, or their counterparts are preclinically validated to explore their feasibility in combination. Screening and mechanistics underscoring starvation therapies are essential for combining starvation treatments with traditional therapies for advanced cancer patients. Starvation therapy involves the targeted deprivation of critical nutrients such as glucose, amino acids, or lipids to inhibit tumor proliferation. Initial screenings of four individual nutrients spotlight glucose and glycine nutrient starvation as being able to remove the protection bestowed by the classical DNA-damaging chemotherapeutic agent doxorubicin by leveraging the drug-induced DNA repair response (PubMed., 2024). A chemical library screen identifies diverse small molecules that selectively starve cancer cells of vital nutrients, whereupon the clinically approved metabolic inhibitor sorafenib is validated in combination with doxorubicin treatment to synergistically restrict glioma proliferation (ScienceDirect., 2025). The capability of sorafenib to promote both acute autophagy and sustained mitophagy in cancer cells unveils a mechanism whereby the starvation of both glucose and oxygen is induced, which sensitizes cells to doxorubicin treatment through the concurrent bolstering of the harmful unfolded protein response and the repression of DNA repair. Metabolic analyses and a nutrients scoreboard consistently reveal that a multidrug-resistant prostate cancer cell line deprived of glucose, cysteine, and methionine displayed the highest survival rate, while a corresponding organoid model on a microfluidic chip permitted real-time and noninvasive assessments of the nutrient depletion process and allowed the systematic evaluation of conventional anticancer drugs across cancers with distinct nutrient dependencies (Zhang *et al*., 2024a). Such screening strategies and knockout libraries leveraging unique nutrient patterns also pinpoint distinct cellular metabolic pathways that can be exploited to circumvent the reliance of highly aggressive pancreatic cancer cells on glucose and the substantively protective effect of oxidative phosphorylation against metabolic targeting (Wang *et al*., 2022).

9. Biomarkers and Patient Stratification for Starvation-Based Therapies

Cancer cells reprogram their metabolism to support rapid growth and proliferation. They usually develop strong dependency on one or several nutrients to maintain growth, and acquire resistance to therapies targeting these nutrients. Cells under metabolic starvation often activate adaptive response pathways to manage this stress. Biochemical pathways regulate glycosylation of proteins involved in nutrient transport, maintaining flux through them even when the nutrient of interest is limited. Starvation approaches are centered on depriving certain nutrients that cancer cells rely on for surviving. This treatment strategy could potentially be pursued independently or in combination with starvation approaches. Biomarkers can be defined either at the molecular or metabolic level to inform such stratification (Zhang *et al*., 2024b). Relevant patients could be selected based on the following parameters: pathway activation (AMPK, HIF-1α, mTOR, nutrient availability), nutrients required for survival and growth (glucose, glutamine, cystine, fatty acids), and tumor metabolic profiles (Warburg effect). Further stratification frameworks could support decisions on which regimen and combination would be used, as the starvation aspect could be delivered from dietary restriction or fasting-mimicking protocols or by administering drugs that clamp one particular nutrient selectively (Barbeau *et al*., 2020). Advanced diagnostic technologies ordered by the FDA and their respective providers are already available in clinical settings, and are thus ready for diffusion in oncological cancer wards to facilitate the implementation of therapeutic starvation, and assays designed to assess nutrient status or tumor metabolic activity could be performed to draw even more limited patient cohorts (Lv *et al*., 2024).

10. Future Directions and Research Gaps

Cellular starvation is increasingly regarded as a potential therapeutic strategy for cancer treatment. In preclinical models, cancer cells exhibit both distinct vulnerabilities and adaptive mechanisms under starvation through specific nutrient deprivation. These concepts have been successfully applied to design approaches and regimens that exploit nutrient deficiencies with therapeutically relevant effects. Nevertheless, many mechanistic aspects remain largely unexplored, limiting the robustness of conclusions and treatment prioritization (Keulers *et al*., 2024).

Cellular starvations represent a promising, although still underexplored, therapeutic approach for cancer treatment. It entails targeting intrinsic vulnerabilities of tumors that arise from their metabolic rewiring and elevated nutrient demand to promote selective pressure and killing. The considerable body of mechanistic knowledge accumulated in the last decade combined with a growing portfolio of experimental models and translational research efforts has already laid the foundation for fostering this unique therapeutic strategy and warrant the focused pursuit of the question it addresses. Prioritizing research targeting the natural history of solid tumors during nutrient deficiency and the interplay between different deprivation modalities will enable the development of effective starvation-based therapies both as stand-alone treatments and in combination regimens. Addressing how nutrient availability and other environmental factors sculpt tumor evolution, clonal diversity and metabolic strategies opens the door to personalized and adaptive approaches for confronting tumors (Nakhjavani *et al*., 2016).

Cancer cells have acquired the ability to grow under adverse nutrient supply either by obtaining more nutrients from the microenvironment or by exploiting their own internal nutrient stores. In view of targeting these opposing metabolic strategies, understanding the evolution of solid tumors from nutrient-rich to nutrient-poor environments in terms of temporal sequence and the emergence of adaptive metabolic rewiring has become essential. Efforts are required to clarify the conditions that determine whether tumor mutations promote growth, support selective advantage under restriction or confer no benefit. As multiple alternative and parallel resistance mechanisms to cancer therapies remain available to tumors, identifying starvation-based approaches that elicit higher fitness costs than conventional treatments will complement and increase the overall therapeutic window of these methods (Galluzzi *et al*., 2011).

Clinical targeting of nutrient support, either by altering provision of circulating substrates or disrupting key uptake mechanisms, represents the first onslaught of candidate starvation interventions in progress. Priority should be afforded to preclinical programs that actuate widely available fasting or caloric restriction mimetics with straightforward administration schedules (Martinez-Outshoorn *et al*., 2017)

11. Conclusion

Starvation has several distinct effects on cancer cells, offering a compelling rationale for therapeutic interventions that specifically target nutrient metabolism in these cells. Such selective pressures can be exerted in a variety of ways, including glucose restriction and amino acid deprivation, both of which are crucial for the survival and proliferation of tumor cells. The underlying rationale for this approach is based on the observation that tumor cells exhibit a greater dependence on certain nutrients compared to their normal, healthy counterparts. Currently, different types of fasting and fasting-mimicking approaches are being actively investigated in the field of cancer research. These innovative strategies aim to maintain a sufficiently low recommended dietary allowance (RDA) of certain essential nutrients, without necessitating prolonged adherence to conventional fasting regimens. Consequently, such methods broaden the applicability of fasting-related approaches for cancer treatment. Furthermore, the notion of combining established anti-cancer therapies with non-inhibitory strategies—which could potentially be exacerbatory—holds significant promise, particularly in multi-component systems; starvation-based approaches adhere to and reflect this principle effectively.

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