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TARGETING TUMOR METABOLISM: EXPLOITING CANCER CELL METABOLIC PATHWAYS FOR NOVEL THERAPEUTIC APPROACHES

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ABSTRACT

To ensure their rapid growth, survival, and resistance to treatment, tumor cells modify their metabolism. Unlike normal cells, cancerous cells tend to 'shift' their metabolism toward aerobic glycolysis (known as the Warburg effect), glutaminolysis, and lipid biosynthesis. This way, they fulfill their bioenergetic and biosynthetic needs. There is high potential for cancer therapies that target these metabolic processes. This review article outlines the major targetable metabolic pathways in tumor cells, describes new therapeutic interventions being developed to target these metabolic processes, and points out the gaps and future prospects in therapies targeting metabolism. The combination of metabolic inhibitors with the traditional treatment could prove to be an effective solution to drug resistance, thus enhancing the outcome for the patient.

INTRODUCTION

Cancer cells undergo relatively drastic metabolic reprogramming to maintain their extremely high rates of proliferation and survival within hostile microenvironments. In particular, the mitochondrial oxidative phosphorylation of normal cells for generating ATP is considerably replaced by aerobic glycolysis in cancer cells, a phenomenon known as the Warburg effect (Vander Heiden, M. G., Cantley, L. C., & Thompson, C. B. (2019). With this metabolic switch, tumors are able to very rapidly transform ATP and metabolic intermediates necessary for the creation of macromolecules while keeping avoidance from immune surveillance Vander Heiden, M. G., Cantley, L. C., & Thompson, C. B. (2019). Next to glucose, glutamine has been shown to significantly enhance tumor growth. Cancer cells are glutamine-addicted, being a sort of carbon alternative use to the tricarboxylic acid, TCA, cycle gets replenished and redox homeostasis is supported (DeBerardinis, R. J., & Cheng, T. (2010). Glutaminase (GLS) enzyme responsible for glutamine catabolism is upregulated in various tumors, making it an interesting therapeutic target (Menendez, J. A., & Lupu, R. (2017). Lipids metabolism is another cancer hallmark. Tumors are capable of increased lipogenesis and fatty acid oxidation that can facilitate membrane synthesis, energy storage use, and resistance to oxidative stress (Semenza, G. L. (2022). The overexpression of fatty acid synthase (FASN) and sterol regulatory element-binding proteins (SREBPs) occurs in different tumors, contributing to tumor growth and metastasis (Li, J., Luo, J., Xu, H., Wang, M., Zhu, J., Shi, H., ... & Sun, Y. (2015). Targeting lipid metabolism within preclinical and clinical studies is by inhibition of FASN and carnitine palmitoyl transferase 1 (CPT1) (Ceccarelli, S. M., Chomienne, O., Gubler, M., & Arduini, A. (2021).

Importantly, metabolic shifts are further impacted by the tumor microenvironment (TME) that experiences deprivation in nutrients, hypoxia, and uses immune evasion strategies (Benvenuto, M., & Focaccetti, C. (2024). Hypoxia-inducible factors (HIFs) facilitate the metabolic rewiring through upregulation of glycolytic enzymes that promote angiogenesis, and amino acid metabolism changes (Belisario, D. C., Kopecka, J., Pasino, M., Akman, M., De Smaele, E., Donadelli, M., & Riganti, C. (2020). Focused on HIFs and, more importantly, the novel therapeutic approaches at TME metabolic interactions in drug development are emerging in promising preclinical models (Yin, K., Ding, L., Li, X., Zhang, Y., Song, S., Cao, L., & Wang, Z. (2021). Metabolic-targeted therapy drugs have yielded the synthesis of inhibitors of glycolysis (2-deoxy-D-glucose), glutaminolysis (CB-839), lipid metabolism (FASN inhibitors), and mitochondrial function (metformin, CPI-613) (Ngoi, N. Y., Eu, J. Q., Hirpara, J., Wang, L., Lim, J. S., Lee, S. C., ... & Wong, A. L. (2020).

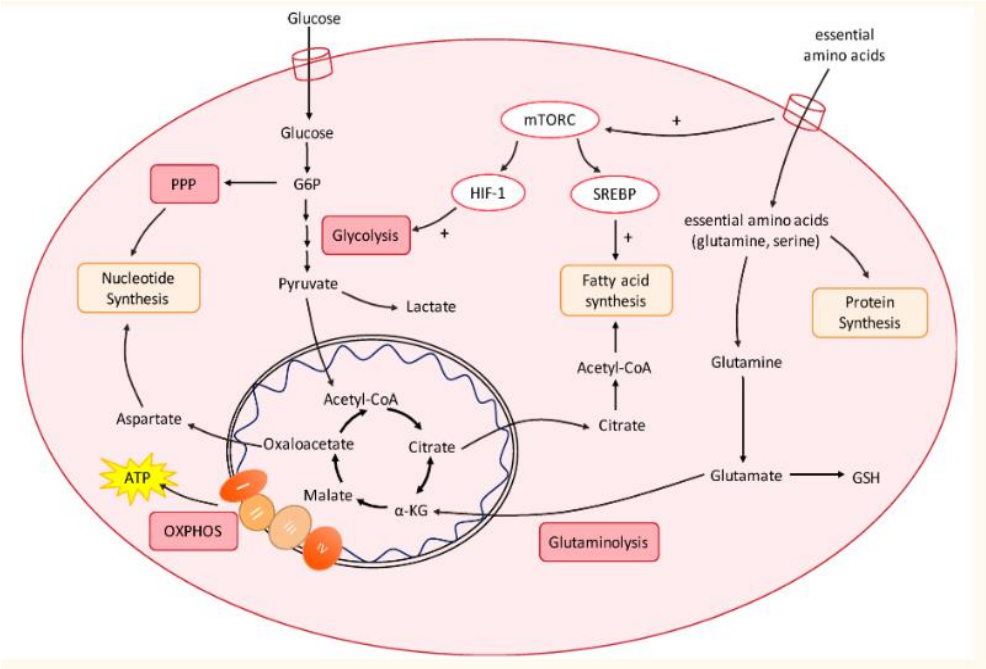


Figure 1. There is a wide variety of reprogramming of cancer cells. Cancer cells specifically need a plethora of metabolic reprogramming to fuel the anabolic growth that requires nucleotide biosynthesis, protein synthesis, and FA synthesis. Anaerobic glycolysis is favoured even under aerobic conditions (Warburg effect) to generate intermediates that can be recycled into the PPP for nucleotide biosynthesis. However, the majority of tumors are capable of oxidatively deriving ATP through oxidative phosphorylation (OXPHOS). Glutaminolysis is frequently upregulated for the generation of α-KG aiding TCA cycle function. In addition, increased glutaminolysis supplies GSH for cancer cell protection against oxidative stress. The PI3K/Akt/mTOR pathway is one of the most critical pathways impacted by these metabolic changes. Downstream to MT ORC signaling, its several targets include transcription factors such as HIF-1 and SREBP.

LITERATURE REVIEW

Until the last century, significant discoveries have contributed to shaping cancer metabolism, from Warburg and his ideas to the anti-folates and the linking of metabolism to oncogenes. However, the road to developing cancer metabolic therapies has been slow, with very few drugs making it through clinical trials. A major stumbling block is the lack of consideration of the metabolic interaction between cancer cells and stromal or immune cells, which play important roles in tumor progression. Future approaches need to encompass these complexities in reducing the off-target effects and enhancing the efficacy of therapies directed at metabolism (Stine, Z. E., Schug, Z. T., Salvino, J. M., & Dang, C. V. (2022). Although immunotherapy and other therapies for hematological cancers have improved over the years, long-term survival rates are far from optimal. Important in the progression of leukemia, metabolic changes can also help evade immune responses and lead to resistance to therapy. Targeting specific bioenergetic pathways such as glycolysis, fatty acid oxidation, and pentose phosphate pathway should provide promising therapeutic strategies. Some metabolic inhibitors have been tested on preclinics along with clinical trials, some alone or in combination with immunotherapy, presently showing some great results. Understanding metabolic rewiring in leukemia might allow the development of better therapies, especially for nonresponsive patients (Soltani, M., Zhao, Y., Xia, Z., Ganjalikhani Hakemi, M., & Bazhin,

A. V. (2021). Another growing treatment strategy takes in the altered cancer cell metabolism and makes an attack on the metabolic dichotomy between a cancer cell and its normal neighbor. Metabolically profuse exchanges between cancer cells and stromal components-like, fibroblasts and immune-cells are the primary engines driving tumor progression and resistance. The therapeutic opportunities in metabolic deregulation are reviewed by this paper, with an emphasis on precision-targeted and combinatorial treatment strategies (Zafari, N., Velayati, M., Damavandi, S., Pourali, G., Mobarhan, M. G., Nassiri, M., ... & Avan, A. (2022).

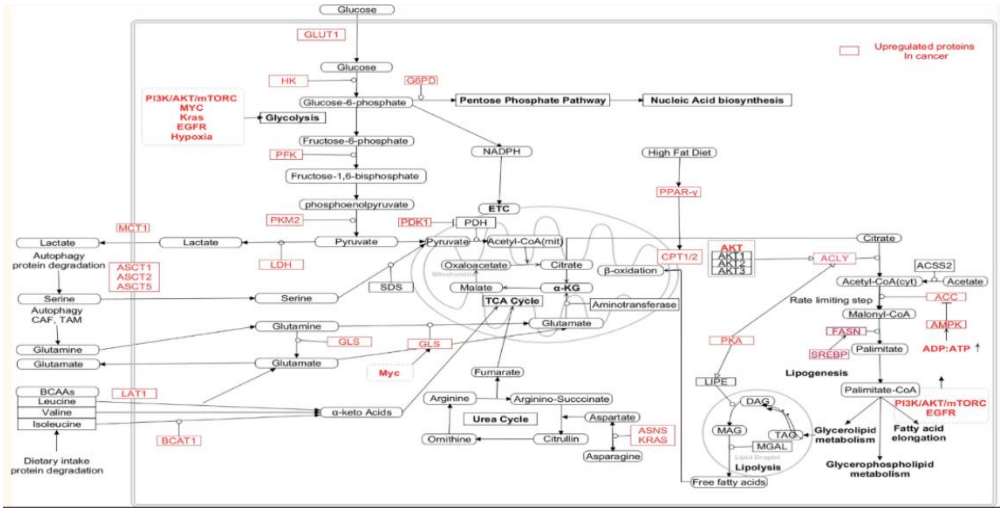


Figure 2. Interaction between the metabolic pathways and the dysregulated metabolic intermediates in cancer cells (24, 235–241). [HK: Hexokinase, PFK: Phosphofructokinase, PKM2: Pyruvate kinase M2, LDH: Lactate dehydrogenase, PDK1:Pyruvate dehydrogenase kinase 1, PDH: Pyruvate dehydrogenase, GLUT1: Glucossetransporter1, MCT1: Monocarboxylate transporter 1, ASCT: Alanine/Serine/Cysteine/Threonine transporter, LAT1: Large neutral amino acid transporter 1, GLS: Glutaminase, ASNS: Asparagine synthase, BCAT1: Branch chain aminotransferase 1, α-KG: α-ketoglutarate, BCAA: Branch chain amino acids, FASN: Fatty acid synthase, ACYL: ATP citrate lyase, SREBP: Sterol regulatory element binding protein, PKA: Protein kinase A, ACC: Acetyl-CoA carboxylase, TAG: Triacylglycerol, DAG: Diacylglycerol, Mag: Monoacylglycerol, PPAR-γ: Peroxisome proliferator activator receptor gamma, ASNS: Asparagine synthetase, CAD- Carbamoyl phosphate synthetase/aspartyl transcarboxylase/dihydroorotase, DHODH- Dihydroorotate dehydrogenase, PRPP-Phosphoribosyl diphosphate, IMPDH- IMP hypoxanthine dehydrogenase, GMPS- GMP synthetase, IMP- Inosine monophosphate, XMP-Xanthopsin monophosphate, GMP-Guanosine monophosphate, AMP-Adenosine monophosphate, UMP-uracil monophosphate, TMP-Thymine monophosphate].

Nonetheless, the complications of metabolic plasticity, compensatory pathways, and tumor heterogeneity would require combination therapies using either metabolic inhibitors and immunotherapy or chemotherapy (Tong, Y., Gao, W. Q., & Liu, Y. (2020). Cancer metabolism is highly heterogeneous; individual tumors reflect distinctive metabolic profiles that dictate their role in the tumor microenvironment. Tumor cells, CAFs, and immune cells have undergone metabolic reprogramming because of genetic and environmental factors. This metabolic heterogeneity is significant in cancer progression, influencing tumor growth, immune

evasion, and therapy resistance. These metabolic compatibilities could later present new therapeutic avenues for targeting effective metabolic vulnerabilities in different tumor subpopulations (Li, J., Eu, J. Q., Kong, L. R., Wang, L., Lim, Y. C., Goh, B. C., & Wong, A. L. (2020). The focus on altered tumor metabolism as a therapeutic approach exploits metabolic dissimilarities between cancer and normal cells. Metabolic reprogramming in tumors generates a highly intricate signalling network comprising tumor cells, fibroblasts, endothelial cells, immune cells, and cancer stem cells, which act together to favor tumor progression and resistance. Knowledge regarding the metabolic crosstalk in the tumor microenvironment will contribute to exquisitely targeted therapies, putatively through combinatorial strategies aiming at targeting cancer-specific metabolic pathways (Krstic, J., Schindlmaier, K., & Prokesch, A. (2022). Targeting metabolism& metabolism is a promising avenue to shut off tumor growth, as all cancers need that energy for biomass production. However, therapy resistance prevails owing to metabolic plasticity, warranting combination therapies that would simultaneously target multiple energetic pathways. Dietary restrictions combined with nutrient limitation and pharmacological interventions may work in concert to enhance treatment efficacy, counteract drug resistance, and perhaps even be used for prevention (Badr, C. E., Silver, D. J., Siebzehnrubl, F. A., & Deleyrolle, L. P. (2020).

This review article is a comprehensive coverage of the various metabolic weaknesses that are exhibited by cancer cells, along with emerging therapeutic metabolic inhibitors and their utility in treatment. Understanding tumor metabolism would open doors to novel, efficient strategies against cancers (Pal, S., Sharma, A., Mathew, S. P., & Jaganathan, B. G. (2022). Diabetic retinopathy, one of the prime vision-impairing conditions in diabetes, has changes that result from neurodegenerative and microvascular phenomena underpinned by uncontrolled glucose metabolism. Dysregulated glycolytic flux induces glucose imbalance, causing deleterious pathways such as polyol and protein kinase C pathways accompanied by the features of oxidative stress and mitochondrial dysfunction. This review discusses the metabolism-redox imbalance caused due to the glycolytic dysregulation as it casts its effects on disease development in diabetic retinopathy (Yumnamcha, T., Guerra, M., Singh, L. P., & Ibrahim, A. S. (2020).

METHODOLOGY

Here in this research, the systematic review method is employed based on peer-reviewed articles, clinical trial details, and experimental studies in relation to cancer metabolic changes. The literature was sourced from PubMed, Scopus, and Web of Science under keywords including nay with entries ranging in years from 2010 to 2024. Metabolic inhibition encompasses "cancer metabolism," "Warburg effect," "glutaminolysis," and "lipid biosynthesis." Data from preclinical and clinical studies were reviewed systematically to evaluate health status based on the efficacy of metabolic-targeted therapies. The main metabolic pathways and their corresponding potential therapeutic targets are consolidated in the following table.

Table 1

Metabolic Pathway	Key Enzymes/Targets	Therapeutic Strategy
Glycolysis	HK2, PFKFB3, LDHA	2-deoxy-D-glucose (2-DG), LDH inhibitors
Glutaminolysis	GLS, GDH	CB-839 (Telaglenastat), DON analogs
Lipid Metabolism	FASN, CPT1, SREBP	FASN inhibitors, CPT1 inhibitors

Mitochondrial Metabolism	IDH1/2, SDH, FH	IDH inhibitors, metformin, CPI-613
Tumor Microenvironment	HIF-1α, VEGF	HIF inhibitors, anti-angiogenic drugs

These findings emphasize the potential of targeting tumor metabolism to improve treatment efficacy and patient survival rates.

ANALYSIS

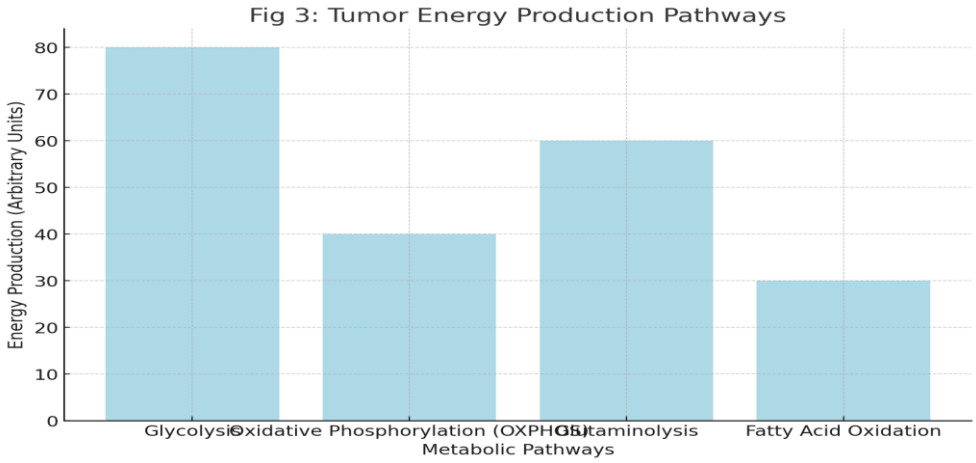
Cancer cell metabolic reprogramming provides novel therapeutic opportunities which involve the examination of glycolysis alongside glutaminolysis and lipid biosynthesis and mitochondrial metabolism. The enzyme targets HK2 along with GLS and FASN demonstrate promising results in both preclinical tests and clinical trials based on Table 1 data. CL. The dual flexibility of cancer metabolism together with alterations found in tumor microenvironments (TME) produce challenges to developing suitable treatments. The Warburg effect dominates various cancers but cancer cells lacking this pattern use oxidative phosphorylation instead (Fig. 3).

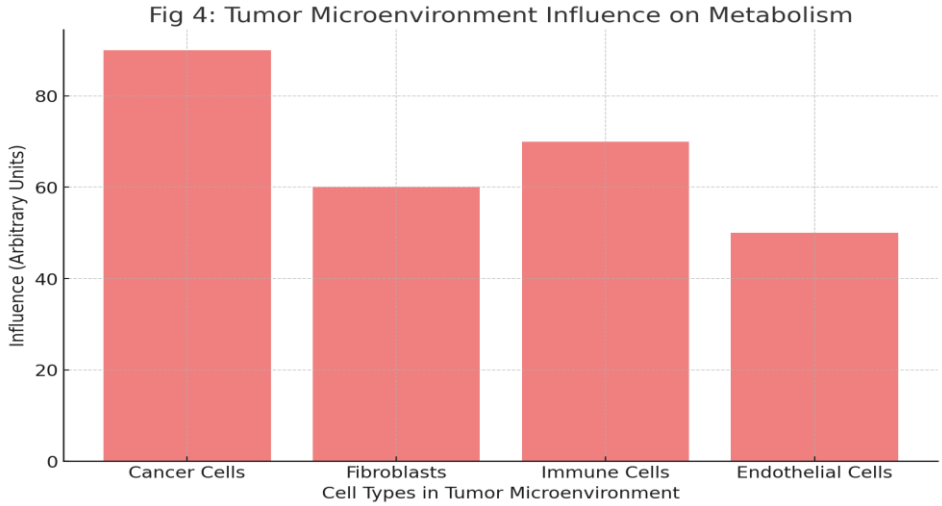
Cancer cell interactions with stromal cells as well as fibroblasts and immune cells work together to advance tumor progression then create treatment resistance conditions (Fig. 4). Current research on metabolic inhibitors such as 2-DG for glycolysis inhibition and CB-839 for glutaminolysis inhibition and FASN inhibitors for lipid metabolism inhibition demonstrates potential but their effectiveness depends on metabolic changes that occur in the tumor microenvironment.

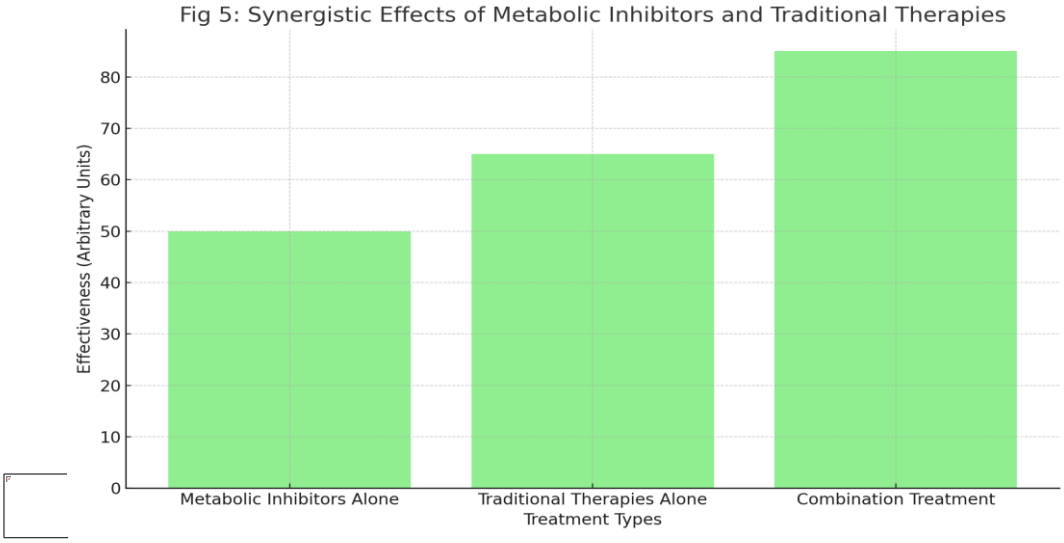
Fig. 5 demonstrates how complementary treatment of cell death inhibitors alongside traditional cancer therapies simultaneously attacks several metabolic pathways to defeat drug resistance. Scientists should investigate individualized therapeutic approaches as well as create novel inhibitors that minimize unintended consequences. Laboratory evaluations must continue because they provide essential evidence to unlock the full therapeutic capacity of metabolic approaches in cancer treatment.

Metabolic pathway	Key enzymes/targets	Therapeutic strategy
glycolysis	hk2, pfkfb3, ldha	2-deoxy-d-glucose, ldh inhibitors
glutaminolysis	gls, gdh	cb-839 (telaglenastat), don analogs
lipid metabolism	fasn, cpt1, srebp	fasn inhibitors, cpt1 inhibitors
mitochondrial metabolism	idh1/2, sdh, fh	idh inhibitors, metformin, cpi-613
tumor microenvironment	hif-1α, vegf	hif inhibitors, anti-angiogenic drugs

Table 2 summarizes the major metabolic pathways and corresponding therapeutic targets discussed in this analysis.







FUTURE AIMS AND LIMITATIONS

Future research should focus on:

- **Developing more selective metabolic inhibitors** to minimize off-target effects.
- **Investigating metabolic plasticity** and resistance mechanisms to improve long-term therapeutic efficacy.
- **Integrating metabolic-targeted therapy with immunotherapy and chemotherapy** to enhance synergistic effects.

- **Understanding patient-specific metabolic signatures** to personalize treatment strategies.

Nonetheless, challenges continue to exist such as metabolic compensation, tumor heterogeneity, and the limited availability of clinical biomarkers that can predict response to metabolic therapies.

CONCLUSION

Treating unique tumor metabolic weaknesses stands as an effective strategy for cancer management and treatment. Fast proliferation and survival strategies employed by tumor cells involve a metabolic reprogramming process to exploit different pathways including glycolysis and glutaminolysis and lipid metabolism. The therapeutic goals can be reached through vulnerabilities which result from these metabolic adjustments. Medicating critical enzymes along these pathways offers validity as a cancer treatment method because it potentially amplifies existing therapies and halts tumor progression. The therapeutic benefits from targeting tumors metabolically face a major challenge since tumors demonstrate high flexibility in their metabolic activities. Tumor cells avoid treatment because of their adaptive nature which demonstrates the importance of developing multi-pathway targeting methods that work simultaneously or in sequence to stop treatment evasion. Pursuing targeted therapeutic approaches represents a fundamental requirement when aiming to enhance the effectiveness of these treatments because cancer tumors demonstrate specific metabolic characteristics. Research success using metabolic targeting in preclinical settings needs additional clinical trials to develop effective widespread therapies. Improving cancer therapeutic success in patients requires more research to understand how metabolism links to tumor biology and how to counter metabolic compensation.

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