

Dietary intervention as a therapeutic for cancer

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Funding information

Ministry of Education, Culture, Sports, Science, and Technology of Japan, Grant/Award Number: 20K17203 and 19H01036; Japan Agency for Medical Research and Development, Grant/Award Number: 20cm0106174h0001

Abstract

Cancer metabolism is influenced by availability of nutrients in the microenvironment and can to some extent be manipulated by dietary modifications that target oncogenic metabolism. As yet, few dietary interventions have been scientifically proven to mitigate disease progression or enhance any other kind of therapy in human cancer. However, recent advances in the understanding of cancer metabolism enable us to predict or devise effective dietary interventions that might antagonize tumor growth. In fact, evidence emerging from preclinical models suggests that appropriate combinations of specific cancer therapies with dietary interventions could critically impact therapeutic efficacy. Here, we review the potential benefits of precision nutrition approaches in augmenting the efficacy of cancer treatment.

KEYWORDS

cancer metabolism, cancer therapy, dietary intervention, nutrient, precision nutrition

1 | INTRODUCTION

Metabolic alterations are a hallmark of cancer (Figure 1). Studies conducted over the past two decades have established that critical metabolic changes seen in cancer include enhanced uptake of carbon sources, namely glucose and glutamine, relative to non-dividing normal cells.¹ Cancer cells actively consume these nutrients to meet high anabolic demands related to nucleotide and lipid production.² Often these mechanisms coincide with production of antioxidants. Catabolic metabolism is also upregulated in cancer. Relative to normal cells, cancer cells do, indeed, upregulate oxidative mitochondrial metabolism (TCA and oxidative phosphorylation).²⁻⁶

Many metabolic activities are conserved among cancers; however, several studies have identified metabolic traits specific to certain cancer types, which are either related to specific genetic alterations or to cells/tissues of origin.⁷⁻¹¹ Intriguingly, some cancer-type-specific metabolic activities show narrow requirements for a particular nutrient, which represents a unique vulnerability of that cancer to therapeutic targeting based on that nutrient.¹²⁻¹⁴

It is clear that both tumor and non-tumor cells are influenced by the availability of nutrients in their microenvironment¹⁵ (Figure 2). In vivo, the concentrations of many circulating nutrients, which are synthesized de novo or absorbed due to dietary intake, are regulated systemically, although concentrations of some nutrients in the tumor interstitial fluid reportedly differ from those seen in plasma.¹⁶ In addition, some nutrients required by cancer cells are generated by gut microbiota.¹⁷

Cancer patients often show great interest in dietary changes that may mitigate disease progression or augment therapy effects. However, we still lack rigorous clinical evidence supporting the effectiveness of dietary therapies in treating cancer, and the rationale for recommending dietary change is often not solid. Thus, some patients are, unfortunately, cheated by deceitful business practices due to their high motivation to improve survival. Therefore, it is critical for cancer researchers to rigorously evaluate the current status of nutritional approaches to combat cancer. Here, we discuss recent preclinical analysis of the connection between dietary modification and cancer metabolism and report studies that provide a rationale

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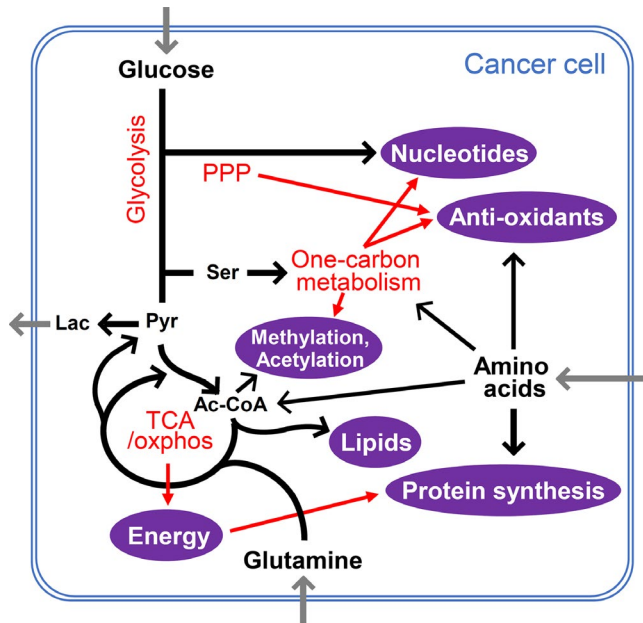


FIGURE 1 Summary of metabolic pathways in cancer cells. Tumor cells consume more glucose and glutamine than do non-proliferating normal cells. Both nutrients either fuel central carbon metabolism (glycolysis, the TCA cycle, and oxidative phosphorylation [oxphos]) to produce energy or are converted into building blocks of macromolecules, such as nucleotides, some amino acids, and lipids. The pentose-phosphate pathway and one-carbon metabolism also generate antioxidants such as NADPH and glutathione. Acetyl-CoA (Ac-CoA) is an intermediate in the TCA cycle, a substrate for lipids and an acetyl donor in protein acetylation. Note that TCA cycle and oxphos activity in cancer cells is higher than in normal cells, and that some lactate (Lac) is derived from glutamine.⁹ Amino acid (AA) uptake is also upregulated in cancer cells. AA serve as building blocks of proteins, but some also play important roles in metabolic pathways in cancer cells. Note that protein synthesis and RNA/DNA synthesis consume high levels of energy.⁶⁸ Pyr, pyruvate

for combining a specific diet with existing therapies in selected cancer types.

2 | CALORIC RESTRICTION, FASTING, AND FASTING-MIMETIC DIETS

Calorie restriction (CR) is the only dietary intervention proven to improve health and extend lifespan in mammals,¹⁸ and its benefits likely include lowering the incidence of malignancy. Studies of CR in cancer have a long history: a century ago Moreschi and Rous found that lowering calorie intake delays tumor growth in mouse transplantation models.^{19,20} Although there are many protocols to accomplish CR, the simplest and most popular is fasting. Combined with conventional chemotherapy, short-term or intermittent fasting significantly improves therapeutic responses in mouse xenograft models of human glioma, neuroblastoma, melanoma, and breast cancer.²¹ However, because long-term fasting or CR promote body weight loss, and cancer patients are often frail, short-term or intermittent

rather than long-term regimens are viewed as preferable in this disease context.

The recently developed fasting-mimetic diet (FMD) is an alternative and interesting approach to achieve CR. FMD strategies are based on lower caloric intake, with consumption of lower levels of sugar and protein but higher consumption of unsaturated fat relative to a normal diet. Periodic adherence to FMD reportedly mediates metabolic effects similar to those seen in prolonged fasting.²² Caffa et al (2020) show FMD synergizing with treatment with a CDK4/6 inhibitor, an estrogen receptor-signaling blocker (fulvestrant), or both to treat hormone receptor-positive breast cancer in mouse transplantation models.²³ These synergistic effects are robust and the combined therapy promotes long-lasting tumor regression in mouse models. An FMD approach is currently being evaluated in clinical trials for HER2-negative breast cancers.²⁴ Mechanisms of CR, fasting, and FMD are complex, and systemic responses by the host include reduction in circulating glucose, insulin, and IGF-1 levels, as well as activation of AMPK and autophagy.²⁵

3 | KETOGENIC DIET

The ketogenic diet, an approach originally developed to mitigate epilepsy,²⁶ has also attracted the attention of cancer patients. This diet is high fat and very low in carbohydrates and similar to FMD in terms of low sugar, which may in part explain mechanistic similarities to CR and fasting (Figure 3). Specifically, host responses to the ketogenic diet include lowering of circulating glucose and insulin levels and enhanced beta-oxidation of fatty acids in the liver that produce ketone bodies. The ketogenic diet has been shown to enhance radiotherapy or chemotherapy responses in mouse xenograft models of human lung cancer,²⁷ although clinical trials in cancer patients have had mixed results.^{28,29}

Nevertheless, a recent preclinical study in mice showed the potential of combining a ketogenic diet with PI3K inhibition.³⁰ PI3K mediates many pro-oncogenic signals, mainly through the PI3K-AKT and PI3K-mTOR axis, and PI3K activation is one of the most common events in human cancers. PI3K is, thus, a promising therapeutic target in cancer, but clinical trials of PI3K inhibitors have also shown mixed results, possibly due to emergence of resistance mechanisms. Using mouse allograft models of pancreas cancer and acute myeloid leukemia and xenograft models of bladder cancer, Hopkins et al reported disruption of the feedback mechanism that mediates resistance to PI3K inhibition.³⁰ PI3K is downstream of insulin and its inhibition promotes hyperglycemia by decreasing glucose uptake by normal tissues. High blood glucose, in turn, stimulates insulin release from the pancreas, re-activating PI3K in tumor cells and conferring resistance to PI3K inhibitors. As one means to perturb this feedback mechanism, these authors fed model mice a ketogenic diet and observed enhanced efficacy of PI3K inhibition relative to similarly treated mice fed a normal diet.³⁰

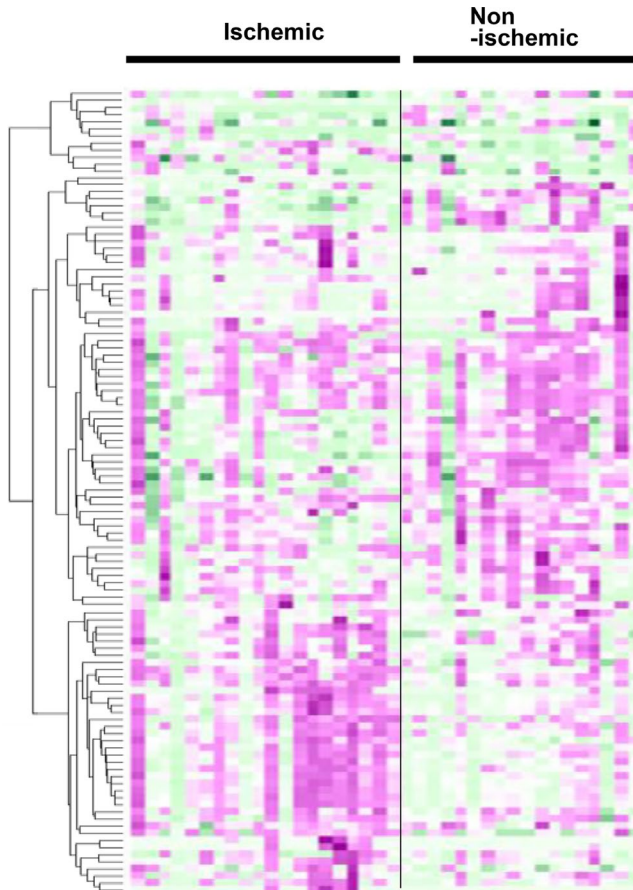


FIGURE 2 Rapid changes in the lung cancer metabolome after ischemia. In patients, lung tumors were resected either by lobectomy or partial resection at the time of surgery. In lobectomy cases, tissues underwent 15–20 min ischemia due to ligations of pulmonary arteries and veins prior to tumor removal (see reference 15 for details). In contrast, blood flow to the tumor was preserved until tissue removal in cases of partial resection. Shown is a heatmap comparing metabolome data of ischemic (lobectomy cases) versus nonischemic (partial resection cases) lung tumors (modified from Kikuchi et al, 2020)¹⁵

4 | POTENTIAL BENEFITS OF FRUCTOSE RESTRICTION

Both ketogenic and FMD diets lower blood glucose. However, unlike glucose, fructose is not scored as a sugar in blood tests. Tumor cells take up fructose via the GLUT5 transporter and metabolize it in the glycolytic pathway. It is well known that the Western diet and sugar-sweetened beverages contain very high levels of fructose, and increased consumption of fructose parallels the prevalence of obesity worldwide. Fructose has the same energy as glucose, but its glycation activity is at least 10 times higher than that of glucose, suggesting potential harmfulness of this sugar. Epidemiological studies have correlated fructose consumption with tumor incidence, particularly in the colon.³¹ Importantly, such studies have served as a warning about the hazards of high-dose fructose consumption. However, a recent study in *Apc*^{-/-} mouse models showed that more typical daily intake of fructose even at moderate doses boosts colon

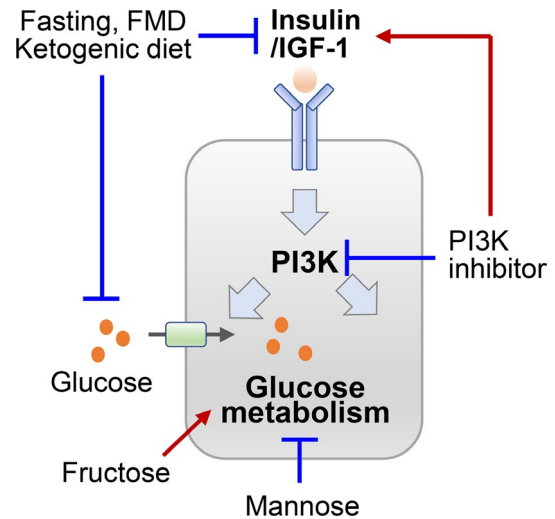


FIGURE 3 Diet can directly or indirectly alter glucose metabolism. Insulin activates PI3K, which stimulates both glucose uptake and other tumorigenic pathways. Treatment with a PI3K inhibitor causes hyperglycemia due to systemic blockade of insulin action, leading to hypersecretion of insulin from the pancreas. High levels of circulating insulin reactivate PI3K in tumor cells. These feedback mechanisms result in resistance of tumor cells to PI3K inhibition. A ketogenic diet suppresses insulin levels and antagonizes the resistance to PI3K inhibitors. FMD, fasting-mimetic diet; IGF-1, Insulin-like growth factor 1; PI3K, phosphoinositide 3-kinase. Note that fructose is protumorigenic. Mannose accumulates as mannose-6-phosphate (M6P) catalyzed by hexokinase and then inhibits various metabolic pathways, including glycolysis, the TCA cycle, and the pentose-phosphate pathway (see text for details)

tumorigenesis.³² These results imply that fructose intake by cancer patients should be carefully monitored, although to our knowledge there are no reports of positive effects of fructose restriction.

5 | MANNOSE SUPPLEMENTATION

Mannose is an epimer of glucose taken up by the same transporter as glucose. Mannose is a substrate in glycan synthesis and is, thus, important for glycosylation of certain proteins. Mammalian cells can synthesize mannose from glucose, and the source of mannose *in vivo* has been assumed to be glucose. However, a study in rats using a stable isotopomer showed that nearly 90% of orally administered mannose is rapidly absorbed and used to synthesize glycosylated proteins in many tissues.³³ In sharp contrast to fructose, emerging evidence indicates that mannose supplementation could serve as a therapeutic for acute urinary tract infections in women³⁴ and autoimmune diabetes in mice.³⁵

In addition, Gonzalez et al (2018) reported that mannose supplementation delays tumor growth and induces tumor regression when combined with chemotherapy in mice.³⁶ Mannose is metabolized in tumor cells and accumulates as mannose-6-phosphate (M6P) in glycolysis catalyzed by hexokinase.³⁶ The presence of M6P then inhibits activities of downstream metabolic pathways, including glycolysis,

the TCA cycle and the pentose-phosphate pathway, overall resulting in downregulation of glucose metabolism (Figure 3). The fact that deleterious effects of mannose appear limited to cancer cells is likely due to higher expression of glucose/mannose transporters on tumor cells relative to normal cells, which, therefore, increase mannose uptake in tumor cells.³⁶ The same study provided evidence that low expression in tumors of phosphor-mannose isomerase, which converts M6P to the glycolytic intermediate fructose-6-phosphate, predicts a positive response to mannose supplementation therapy. Mannose is readily available at pharmacies, and, thus, mannose supplementation has been presumed feasible and safe. Further study is needed to investigate the full potential (and limitations) of mannose supplementation therapy as a cancer treatment.

6 | AMINO ACID RESTRICTION AND SUPPLEMENTATION

Although many national cancer organizations worldwide, including the National Cancer Institute (NCI), in the USA encourage patients to follow a high protein diet during therapy, several studies report that restriction of dietary protein slows tumor growth in animal models.³⁷ In fact, in humans, high protein intake is linked to cancer and overall mortality.³⁸ Thus, limiting protein intake may benefit some cancer patients. The potential beneficial effects of a low protein diet include reduction in blood IGF-1 and PI3K-mTOR signaling, as is seen in CR, FMD, and ketogenic diets.³⁸ Meanwhile, the amino acid content of animal and plant proteins is not equivalent. Based on emerging understanding that amino acids have a differential impact on tumor cells, the content of specific amino acids is likely a more relevant concern in cancer than overall protein intake.

The 20 amino acid (AA) building blocks of all proteins are classically divided as essential (EAA) and non-essential (NEAA). However, several recent metabolic studies argue that amino acid classification should be context-dependent.³⁹ For example, because NEAA can be synthesized *de novo* in normal and cancer cells, the assumption has been that the exogenous supply of NEAA is of little concern. However, certain cancer subtypes show higher dependency on exogenous NEAA, which could serve as a targetable vulnerability. It is also noteworthy that EAA and NEAA are not just the building blocks of proteins but play important roles in synthesis of other macromolecules, in redox homeostasis, and in modifying both protein and DNA, and all of these activities are relevant to cancer cell growth and survival. Below, we discuss selected studies of manipulation of dietary amino acids as a means to enhance cancer therapy.

7 | METHIONINE RESTRICTION AND HISTIDINE SUPPLEMENTATION

One-carbon metabolism links the folate cycle with the methionine (Met) cycle (Figure 4). The folate cycle is important for synthesis of nucleotide precursors, whereas the Met cycle produces S-adenosyl methionine

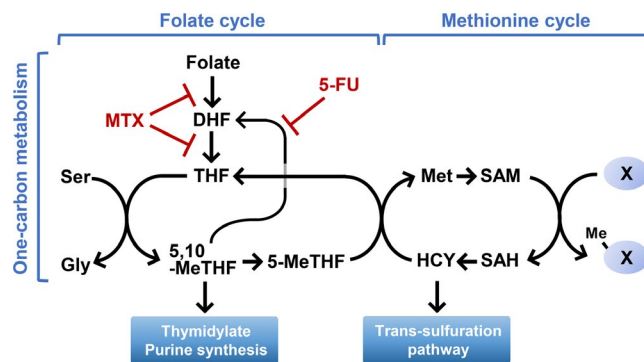


FIGURE 4 One-carbon metabolism links the folate cycle with the methionine cycle. In this pathway, the methyl group (one-carbon unit) of serine (Ser) is transferred to metabolites in the folate and then methionine cycles. S-adenosylmethionine (SAM) functions as a universal methyl donor for methylation of proteins and nucleotides (denoted as X). The anti-cancer drugs 5-fluorouracil (5-FU) and methotrexate (MTX) block folate metabolism. DHF, dihydrofolic acid; HCY, homocysteine; SAH, S-adenosyl-homocysteine; THF, tetrahydrofolic acid; 5,10-MeTHF, 5,10-methyleneTHF; 5-MeTHF, 5-methylTHF

(SAM), a donor of methyl groups in protein and DNA methylation.⁴⁰ One-carbon metabolism consumes the EAA Met and has been a target of anti-cancer drugs such as 5-fluorouracil (5-FU) and methotrexate (MTX). A study in mice showed that restriction of dietary Met augments the efficacy of 5-FU treatment or radiation therapy against patient-derived xenografts of colorectal cancer and autochthonous soft-tissue sarcomas.⁴¹ Met restriction rapidly alters the plasma levels of metabolites in Met, purine, and pyrimidine metabolism in mice and in human volunteers.⁴¹ In addition to Met, the folate cycle (and, hence, one-carbon metabolism) requires serine Ser, as will be discussed below.

Methotrexate inhibits dihydrofolate reductase in the folate cycle and reduces tetrahydrofolate (THF) levels. A CRISPR screen conducted in a leukemia cell line followed by metabolic analysis led to the unexpected finding that histidine (His) catabolism activated by His supplementation decreases the THF pool and increases the sensitivity of leukemia cells to MTX.⁴²

8 | BRANCHED-CHAIN AMINO ACIDS

Three branched-chain amino acids (BCAA) (leucine, isoleucine, and valine) are all EAA among proteinogenic amino acids. BCAA activate mTOR signaling and protein synthesis and are catabolized to fuel the TCA cycle in both normal and cancer cells.⁴³⁻⁴⁵ BCAA supplementation is used clinically to mitigate hepatic encephalopathy and promote wound healing after cancer surgery. Although BACC serve as an essential energy source in several malignancies,^{7,44,45} some clinical studies report that BCAA supplementation benefits liver cancer patients and is associated with prolonged event-free survival.^{46,47} Whether high levels of circulating BCAA are beneficial or harmful to patients is context-dependent, and further studies are needed to address these questions.

9 | SERINE/GLYCINE RESTRICTION

Ser is an NEAA synthesized through the Ser synthesis pathway (SSP), a branch from glycolysis. Ser functions in one-carbon metabolism as a one-carbon donor for folate and is also a precursor of glycine (Gly), a direct substrate for glutathione synthesis. Thus, Ser plays important roles in nucleotide synthesis, methylation, and redox homeostasis.^{48,49} A recent study also highlights the Ser function in sphingolipid diversity to support tumor cell growth.⁵⁰ Given these key functions, the demand for Ser by cancer cells is high, rendering some cancer cells dependent on exogenous Ser. Recent studies have extensively investigated effects of dietary Ser restriction on tumor growth and therapy. In mouse models, a Ser-free diet (as well as a Ser-free and Gly-free diet) reduces circulating Ser levels and delays the growth of colon cancer, lymphoma, myeloleukemia, and mammary tumors.^{51,52} Synergy between Ser restriction and biguanide treatment, which reduces blood glucose, has also been reported against autochthonous models of mouse lymphoma and colon cancer.⁵¹ By contrast, Kras-driven pancreatic cancer does not respond to Ser restriction,⁵¹ as activated Kras upregulates the expression of genes encoding SSP enzymes, thereby activating de novo Ser synthesis. In addition, some cancers reportedly show amplification of SSP genes and are, thus, less sensitive to Ser restriction.⁵³ Collectively, a tumor's SSP activity seems to be a key determinant of susceptibility to Ser restriction. In addition to Kras, the transcription factor NRF2, which is frequently activated in cancer, upregulates a set of SSP genes.⁵⁴ Thus, NRF2-activated cancers are also likely unresponsive to Ser restriction therapy.

10 | CYSTEINE/ARGININE/ASPARAGINE DEPLETION

Although not dietary approaches, we briefly note three therapies (either under development or already successful) intended to target NEAA availability.

Cysteine (Cys) can be generated by the transsulfuration pathway, but cancer cells also use exogenous cystine, the oxidized form of Cys. Cystine taken up by the cell surface xCT cystine/glutamine exchanger is rapidly converted to Cys. Many tumor cells have high Cys demands because Cys is a glutathione substrate and, hence, is important for maintaining low levels of oxidative stress.⁵⁵ L-cyst(e)inase, which degrades both Cys and cystine, is an artificial enzyme developed following saturation mutagenesis of the human cystathionine gamma-lyase.⁵⁶ In mice, administration of recombinant L-cyst(e)inase reduces circulating cystine levels and suppresses growth of human prostate cancer lines.⁵⁶

The NEAA arginine (Arg) is synthesized by the urea cycle, and certain cancers, including some liver cancers and melanoma, show loss of expression of the enzyme responsible for de novo Arg synthesis and are, thus, dependent on exogenous Arg.^{57,58} Recently, several arginine (Arg)-degrading agents, have been developed, the most advanced being ADI-PEG20, a PEGylated form of recombinant microbial Arg deiminase, which degrades Arg to citrulline and ammonia.¹⁴ Potential

anti-cancer effects of this reagent are currently being evaluated in clinical trials (ClinicalTrials.gov, <https://clinicaltrials.gov/>).

Finally, there is a class of clinical reagents degrading circulating asparagine, among them L-asparaginase. These drugs have already shown significant success even as a monotherapy in the treatment of acute lymphoblastic leukemia.⁵⁹ Other types of cancers are less responsive to this approach.⁶⁰

11 | CONCLUSION

We have reviewed studies that suggest that dietary intervention could have a therapeutic effect in cancer treatment. Due to space limitations, we have not summarized additional papers indicating that diet impacts cancer in two other highly significant ways; namely, by modulating immune activity and by altering the composition of gut microbiota. Relevant to the former, we refer interested readers to several excellent reviews of the relationship of diet to anti-tumor immune responses or immunotherapy.⁶¹⁻⁶³ Readers interested in literature relevant to the microbiome are encouraged to consult reviews of this emerging field.⁶⁴⁻⁶⁷ Most studies summarized here suggest that dietary interventions could serve as adjuvant therapies for cancer, rather than standalone treatments, and these combination therapies are summarized in Figure 5. We also note that dietary

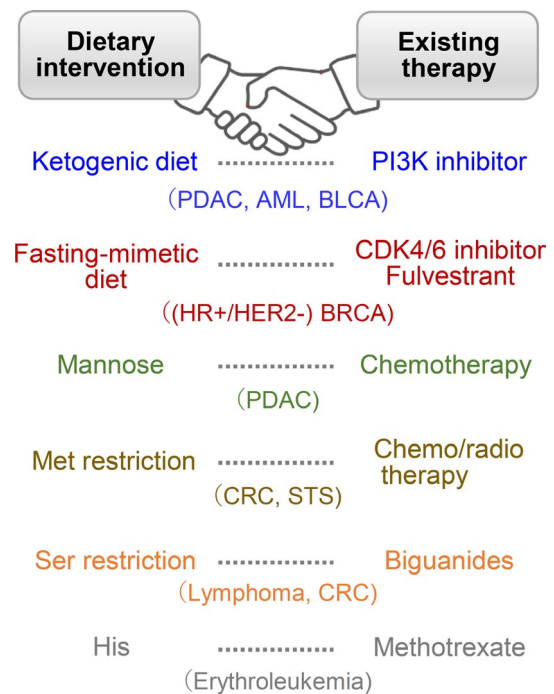


FIGURE 5 Precision nutrition approaches enhance cancer therapy. Preclinical studies indicate that specific dietary modifications (left) serve as adjuvant therapies with existing cancer therapies (right). Potential target indications of each therapy are shown in parentheses. AML, acute myeloid leukemia; BLCA, bladder carcinoma; BRCA, breast cancer; CRC, colorectal cancer; HR, hormone receptor; PDAC, pancreatic ductal carcinoma; STS, soft-tissue sarcoma

modifications most often have positive effects in the context of a specific cancer, and there is likely no universal diet beneficial to all cancers or all cancer treatments.

Many questions remain relevant to the connection between diet and metabolism in vivo. Changes in diet composition alter metabolism systemically, and those changes can be difficult to recapitulate in in vitro cell culture. Along these lines, we should pay more attention to nutrient compositions of culture media, which do not always resemble environmental conditions in vivo.

Given that dietary interventions are commonly applied to treat many metabolic diseases, it is impressive that Otto Warburg argued the concept that 'cancer as metabolic disease' almost a century ago. Some dietary interventions now appear so promising that detailed clinical assessment is soon anticipated.

ACKNOWLEDGMENTS

We thank M. Oh-uchi for help with preparation of the manuscript. This work was supported by KAKENHI grants from the Ministry of Education, Culture, Sports, Science, and Technology of Japan to MM (20K17203) and NT (19H01036), and by a P-CREATE grant from the Japan Agency for Medical Research and Development to NT (20cm0106174h0001).

DISCLOSURE

The authors have no conflict of interest to declare.

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How to cite this article: Morita M, Kudo K, Shima H, Tanuma N. Dietary intervention as a therapeutic for cancer. *Cancer Sci*. 2021;112:498-504. <https://doi.org/10.1111/cas.14777>