Annals of Medicine and Medical Research

Review Article
Published: 24 Jun, 2023

Are We Ready? The Paradox of Nutritional Interventions for Gastrointestinal Cancer

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Abstract

Increasingly literature has demonstrated the promising effects of dietary interventions as adjunctive anti-cancer treatment. However, the precise mechanisms of how diets influence cancer metabolism and the interactions in the tumor microenvironment are still not fully understood. Current studies are mainly focused on the experimental animal models, with conflicting and mixed results. Factors such as the different cancer types, hereditary features and the nutritional status of the host are all possible explanations. Herein, we gather the current evidence on several mainstream nutritional strategies in the treatment of gastrointestinal oncology, reviewing both benefits and risks, and hopefully contribute to the directions of future research.

Keywords: Dietary interventions; Cancer; Autophagy; Fasting; Oncology; Tumor microenvironment (TME); Glycolysis; Cachexia

Introduction

In recent decades, more and more attention has been paid to the oncology field and many breakthrough advances have been made. Until now, cancer is still the second leading cause of death in the United States. Moreover, Gastrointestinal (GI) cancers account for about 20% of all cancer diagnoses, with colorectal cancer ranking first [1]. Unfortunately, outcomes remain very poor. The medical cost and death toll attributed to cancers have grown dramatically making it become a major public health issue urgently needs to be addressed. Researchers are looking for better therapies to fight cancer apart from routine cancer treatments, such as surgery, radiation, chemotherapy, and immunotherapy.

Since cancer cells avidly rely on a continuous supply of nutrition's to support their growth and proliferation, therefore, disrupting the nutrition supply may hinder tumor growth. Therefore, nutritional interventions may also be considered as powerful tools for cancer treatment or functioned as adjuvant cancer therapies.

Protocols such as fasting, amino acids restriction have reported potential and exhilarating benefits among cancer therapies. However, studies conducted mainly on animal models or due to the small sample size, the exact mechanisms and effects are not fully elucidated and there are still many unanswered questions awaiting.

This review attempts to provide insight into several trending nutritional interventions targeting on gastrointestinal tumors and its possible limitations.

Overview of Tumor Metabolism Mechanism

In terms of metabolism, 70% to 80% of cancer cells prefer glycolysis rather than oxidative phosphorylation even when the oxygen is sufficient. It is also known as aerobic glycolysis. Unlike normal cells, only a small portion of glucose is utilized through the Tricarboxylic acid (TCA) cycle for ATP production in cancer cells. At first glance, it's not an efficient and reasonable way--only 2 ATP molecules per glucose was produced through the process. Cancer cells use nutrients for various biosynthesis and NADH production, thus maintaining the redox homeostasis and reducing ROS production. Therefore, enhanced glycolysis is reported to induce the resistance of CRC cells to 5-FU chemotherapy [2]. Similarly, mammalian cells are found to use the Tricarboxylic acid (TCA) cycle in G1 phase, while preferring glycolysis in S phase [3]. Practically, cells use this mechanism to support faster cell proliferation and growth.

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Received Date: *06 Jun 2023*
Accepted Date: *19 Jun 2023*
Published Date: *24 Jun 2023*

Citation:
Wang K, Zhang G, Li Y. Are We Ready? The Paradox of Nutritional Interventions for Gastrointestinal Cancer. Ann Med Medical Res. 2023; 6: 1061.

Since the glucose levels are essential for the survival and growth of many types of cancer, many therapeutic strategies are targeting glucose metabolism. At the hormonal level, the anti-tumor effect and cellular protection for non-cancer cells due to the reduced IGF-1 and insulin levels, to some extent. Compared with the normal cells, cancer cells tend to over express the insulin receptor. The hepatic IGF-1 production is reduced due to the low insulin levels which could cause Growth Hormone (GH) resistance in the liver. The IGFBP 1 (IGF-Binding Protein 1) promotes the binding to the circulating IGF1, thereby decreasing the IGF1 bioavailability [4]. The hepatic FGF21 (Fibroblast Growth Factor 21) expression is also induced during the starvation, which is responsible for cutting down the serum insulin and prevent the insulin resistance [5]. Thus, the downstream IGF1/AKT and mTORC1 pathways is downregulated, while some antioxidant and protective enzyme gene transcription upregulated. The lowering glucose level blocks the normal cell cycle of healthy cells or promotes them into a low division state, whereas the cancer cells are not impacted, making them more vulnerable to the chemotherapy. These effects are known as the differential stress resistance [6].

Energy Restriction

Calories restriction (CR)

CR refers to the long-term reduction of 20 to 40 percent of the total calories of the daily diet while providing essential nutrients to the organism to ensure that it does not suffer from the malnutrition. Therefore, CR is also called dietary restriction [7]. The CR has manifested its potent ability to promote the Intestinal Stem Cell (ISC) regeneration and increase its both numbers and functions in mammals [8]. The CR also reported the beneficial impact on the gut microbiota, the abundance of some probiotic microbes is also increased in CR, like *Bifidobacterium* and *Lactobacillus* spp. [6].

The incidence of cancer dramatically reduced in rhesus monkeys undergoing 30% CR, with the gastrointestinal adenocarcinoma being the most common one [9].

Intermittent fasting (IR)

The intermittent fasting refers to a diet that one individual intakes calorie on limited time while the rest period of time maintaining fasting state or just a little bit food intake. Keeping food intake within 16 h a day, every other day or 5 to 6 days per week are common IR patterns. The forms of Time-Restricted Feeding (TRF) and Fasting-Mimicking Diet (FMD) also belong to the IR. To achieve better adherence and feasibility, the concept of FMD emerged, it refers to a plant-based diet that is low in protein and carbohydrates, with relatively high in fat. According to an article published in Nature Communications, the patterns like fasting or calorie-restricted, low-carbohydrate, low-protein diets in rodents are all included in FMDs [10]. About 50% of colorectal cancers carry the KRAS mutations, even more than 90% possibilities in PDAC, indicating the poor prognosis and the challenges for drug resistance [11]. Vitamin C is viewed as a classical antioxidant, it is reported promoting the HIF-1α degradation, thus upregulating the activity of Pyruvate Dehydrogenase (PDH) in mitochondria and boosting the TCA cycle in KRAS mutant CRC [12]. When combined with the FMD, it exerts higher anti-cancer efficacy by accumulating excessive ROS, meanwhile, presenting lower toxicity when compared with oxaliplatin chemotherapy alone. The role of FMD in reversing the HO-1 over-expression stimulated by VC is the core part of this synergistic effect [13]. Subsequently, leads to the restored CD8+ T cell and suppressed the regulatory T cell functions.

Short-term fasting (12 h to 48 h) has proven to improve the life quality of cancer patients and shown to reduce the cellular DNA damage caused by cytotoxic agents. The 24 h of fasting before the abdominal radiation made the mice with pancreatic tumors more tolerant of the increased radiation dose. Probably because the fasting promotes the ISC renewal [14]. Also, the autophagy is enhanced meditated by the low serum IGF1, which upregulates AMPK-a main activator of autophagy. Trentesaux et al. found that the fasting stimulates autophagy so that promoting the survival in Lgr5+ISC and preserving the integrity of intestinal epithelium meditated by Atg7 (Autophagy-related protein 7). The ISC demonstrated more resilient when undergoing high doses of oxaliplatin and doxorubicin treatments. Despite the fact that, the Lgr5+ISC cannot directly sense the energy change, mediated by the Paneth cells instead [15]. The increased autophagy induced by the fasting is also reported to downregulate the CD76 expression and cut down the production of adenosine. Finally, it inhibits the M2 macrophage polarization, which is responsible for secreting immunosuppressive cytokines like IL-4, IL-6, and IL-10 and prompting tumor immune evasion in colorectal cancers [16,17]. Increasing literature also suggests fasting as a promising tool in Hepatocellular Carcinoma (HCC) treatment [18]. The fasting sensitizes the HCC cells to sorafenib, a potent multi-kinase inhibitor. The maintenance of p53 signaling is the key player in this effect. In addition, fasting is able to prevent hepatic stellate cells from activation [19].

A case series evaluated the patients with different types of cancer who fasted for different hours before undergoing chemotherapy, with minor discomforts like hunger and dizziness reported. And the chemotherapy-related events were largely reduced [20].

Calorie restriction mimetics (CRM)

However, it is infeasible and unreasonable to strictly maintain the CR. Scientists put forward the concept--calorie restriction mimetics. The CRM is a range of compounds having the similar metabolic and physiological effects of CR. That's to say the CRM can activate the signaling pathway the same as the role of CR, and do not require the same restriction [21]. Glycolysis inhibitors, NAD+ precursors, polyamines and polyphenols are all promising CRM candidates. But data on CRMs in clinical application are relatively limited, for fear of safety. It is reported that polyamine is involved in the colorectal tumorigenesis [22]. Resveratrol is a well-known natural polyphenolic compound with various effects including antioxidant, anti-inflammatory, and anti-tumor properties. It disturbs the mitochondrial metabolism of SW620 colon cancer cells. Specifically, resveratrol induces the breakdown of the mitochondrial electron transport chain, causing excessive ROS production and then elicited the cancer cell death [23]. It also shows the enhanced curative effect of the 5-FU chemotherapy, and simultaneously, reduces the side effects. As for the pancreatic cancer, the resveratrol inhibited the expression of *NAF-1*, a gene loci that regulates the autophagy and positively associated with the pancreatic tumorigenesis and invasion [24]. It also reported anticancer activity in HCC.

Till now the studies evaluating ER's effect performed on humans are limited, also with different cancer variants, mainly focusing on melanoma or gynecological cancers like breast cancer. According to statistics at the end of the year 2021, the clinical trials merely performed on CRC patients are relatively scarce [25]. It is worth noting that the current clinical studies have not shown robust evidence on long-term fasting or CR targeting at cancer patients [26,27]. And concerns of

weight loss, cachexia, poor adherence arouse [28,29]. Strikingly, the chronic CR did not influence the circulating IGF1 levels. In addition, whether these encouraging findings representing some relatively mild tumor types worth more explorations. More stratified and categorized studies are warranted in the future.

Noteworthy, the appropriate timing to start chemotherapy is important, it is mentioned that reserving at least 24 h to 48 h between the anti-cancer treatment and recovery from the fasting state in case of the combination of the noxious chemicals and regrowth signal to increase carcinogenesis and cause the abnormal tissue growth [30]. One study demonstrated the epithelial-mesenchymal transition increased and the tumor size enlarged in mouse models of CT26 colon cancer cells after the 4 weeks of periodic IF. Whereas, the similar results were not found in the consecutive CR group [31]. It is speculated that the IF may cause the subjects to overeat during refeeding, which is considered as an instinct. One study measured several parameters in mice and humans before and after fasting, respectively. Only to find that the gene expression at PBMCs (Peripheral Blood Mononuclear Cells) and the lipid composition of erythrocyte membranes changed more significantly in the mice group than in human ones, even in the same length of fasting. That enables the mice getting more resilient during chemotherapy. The higher basal PUFAs (Polyunsaturated Fatty Acids) composition in the cell membranes indicates the lower-level insulin-responding gene expression, yielding milder response to the chemotherapy. Furthermore, scientists demonstrated that fasting for 48 h provides stronger protection from the chemotherapy toxicity than the 24-h period [32]. Interestingly, based on the different responses to the starvation, one study indicated that due to the species physiological differences between mice and humans, the 24 h fasting and refeeding cycle is approximately equivalent to the 5-day period in humans [33].

Circadian rhythms also matter, they influence body metabolism in an intrinsic but inexact manner. One study showed the hepatic circadian clock gene expression is consistent with the time restricted feeding, while not in the skeletal muscle. The mice fed during inactive phase group became lazier and presented with increased hypothalamic orexigenic related genes expression, higher insulin peak and leptin resistance [34]. Previous studies revealed the frequency and time to peak of cortisol changed after fasting or TRF in humans [35]. Therefore, performing TRF at different eating windows of a day should take into account the different hormonal changes and more rigorous and well-controlled studies are required [36].

In conclusion, it remains to be fully investigated when it comes to specific conditions such as gender, host health conditions, tumor types, timing and duration of interventions in cancer patients undergoing ER [37,38].

Ketogenic Diet (KD)

The ketogenic diet is characterized by low-carbohydrate, high-fat consumption with adequate protein intake. By mimicking the fasting state, the fats are served as the primary energy source for the human body, and fatty acids are transformed into ketone bodies with the process of the β-oxidation in the liver, including acetone, acetoacetic acid and Beta-Hydroxybutyric Acid (BHB). With the sense of satiety, the KD is proposed as an effective tool for weight loss. With the deepening of researches, the ketogenic diet also has great potentials in the treatment of tumors. It exerts its pivotal and diverse roles in the following different ways [39].

Reducing the insulin/IGF-1 levels

Firstly, Ketogenic diet can affect glucose metabolism of tumor cells and reduce the insulin and Insulin-like Growth Factor (IGF) levels, which are the potent stimuli in tumorigenesis. Subsequently, the PI3K/Akt/mTOR signaling pathway is down-regulated. In addition, glucose intake limitation leads to the inhibition of the lactate/pyruvate cycle in tumor cells, which can stimulate angiogenesis through HIF-1 mediated trans-activation of VEGF, thereby inhibiting vascular angiogenesis [40].

Anti-inflammatory effects

Studies have also shown that the KD diet could inhibit NLRP3 inflammasome assembly, which is identified to suppress the inflammatory cytokines maturation and secretion in colorectal cancer [41]. Also, the deactivate the NF-κB pathway to exert the anti-inflammatory and pro-apoptotic roles [42,43]. One study found that combined with the chemotherapy, the curative effects of pancreatic cancer were dramatically improved and the metabolism of the tumor cells was disrupted [44].

Other anti-tumor growth effects

Additionally, the ketone bodies, and particularly BHB, can inhibit histone deacetylation and increase DNA methylation, which may be helpful in blocking tumor growth *via* epigenetic modifications [45]. Moreover, the reduced glucose availability passively prompts cancer cells to use the oxidative phosphorylation to produce ATP, while the normal cells still could rely on the TCA cycle to maintain their initial energy status. This phenomenon is called the anti-Warburg effect. In turn, the mitochondrial dysfunction of cancer cells leads to the cellular ROS accumulation, increased oxidative stress in colon cancer models [30].

The conflicts

When there is a lack of energy, hepatocellular carcinoma cells can upregulate the expression of the ketolytic enzyme 3-oxoacid CoA-transferase 1, inducing the tumor cells to use ketone bodies to enhance their growth. Other studies also support the fact that the ketogenic diet may stimulate tumor growth in some cases. The elevated circulating acetoacetate, triggered by high ketone body intake, causing BRAF V600E mutant-dependent MEK1 activation may be the possible explanation [46]. BRAF V600E mutation is found in colorectal cancer, melanoma, and leukemia. When it comes to the PDAC, it usually occurs at the head of the pancreas, which will affect its exocrine functions. It secretes digestive related enzyme thus negatively influencing lipid metabolism due to the tumor compression [47]. Of interest, scientists found BHB is the culprit of the liver metastasis in PDAC, for it acts as a major fuel to support tumor growth even under harsh nutritional conditions [48]. Recent work by another group has also reported the long-period of KD would result in the myocardial fibrosis, meditated by the increased SIRT7 expression. Accompanied with the reduction of the mitochondrial biogenesis and eventually leads to selective cardiac fibrosis and apoptosis [49]. Many clinical trials on KD did not have robust outcomes and results, due to the poor compliance especially for patients with late-stage cancers. The constipation, vomiting and fatigue are the most commonly reported side effects of KD. Additionally, what we cannot neglect is that the levels of apoB containing lipoproteins are elevated in patients who adopt the long-term ketogenic diet, which is a strong risk factor for cardiovascular diseases [50].

Notably, the basal ketone bodies levels were found to be discrepant

between men and women after fasting, with higher levels in women [33]. Taken together, despite the KD has shown encouraging and quite a lot of benefits in tumor growth inhibition and has enhanced the efficacy of multiple antitumor therapies in GI cancers. The efficacy of KD may be influenced by cancer subtypes, (whether it is lipid-addicted tumor), host genetic characteristics, or tumor differentiation status. More studies targeting different stages and types of tumors *in vivo* are needed [51].

Both the CR and KD diet could alter the insulin-IGF1 axis, lowering the serum glucose levels, thus exerting anti-tumor growth role. However, a recent study found in pancreatic ductal adenocarcinoma cells of rat's models, only the CR fed group slowed the tumor growth, though both groups showed the decreased glucose levels. Of interest, the similar consequences were also found in non-small cell lung cancer [52]. Further studies indicated this differential effect is mediated by lipid composition. The CR could inhibit the Stearoyl CoA Desaturase (SCD) activity, which is capable of converting the Saturated Fatty Acids (SFAs) into Monounsaturated Fatty Acids (MUFAs), leading to MUFA to SFA ratio decreased. While the ratios were not changed in KD group. And when palmitic acid was added to the KD group, the tumor growth was impaired [53,54]. Interestingly, the palmitic acid is found to promote metastasis in oral carcinoma and melanoma of animal models by altering the methylation of histone, and thus activating the Schwann cells [55]. Therefore, it is speculated that it is the specific lipid composition that really matters. Another paper also mentioned that unlike the fasting, the KD did not drive the host into a starvation status and with the absence of refeeding step, it's less likely to see the metabolic plasticity in the KD [56].

The Low Protein Diet

Roasted or fried foods rich in protein such as fish and meat can be the mutagens and carcinogens [57]. One study found that too much intake of dietary protein may increase the levels of the ammonia in the intestine, which is a strong inducer for colorectal carcinoma. While other studies support the view that it is the high calories that promote tumorigenesis. But these findings above are not consistent with the consequences detected in the older adults. The sources of protein may matter, studies show higher plant-based protein consumption is associated with a decreased risk for multiple diseases and mortalities, like cardiovascular disease and cancers [58]. Japan is famous for longevity worldwide; a study based on Japanese population concluded the typical Japanese model of diet. It is characterized by high consumption of seafood, dairy products, plant proteins, mainly the soybeans [59]. Intriguingly, a cohort study demonstrates that when subjects were divided into two groups by age, those who consumed large number of proteins at the age of 66 and above had obvious decrease in cancer mortality, regardless of the total calories intake and whether it is animal proteins [60]. LongoSo et al. assumed that is due to the poor absorption of protein intake in elderly people, so the elderly may benefit from the diet rich in protein [61]. It is very common to see the sarcopenia in cancer patients, and it is relevant to various complications and adverse prognosis. Another study found when patients with late-stage gastrointestinal cancer took more than 1.6 g/kg/d proteins; the overall survival was prolonged, although the Handgrip Strength (HGS) was not improved. Furthermore, it is the total protein intake, rather than the BACC that reflects the skeletal muscle quality [62]. On the contrary, other studies found the BACC's protective role in enhancing the skeletal muscle satellite cell activity [63]. Notably, the monitor of renal function is advised during the high protein diets, considering the metabolites of proteins would aggravate the burden of the kidneys [64].

Cancer-associated cachexia

The definition of cachexia is an unintentional body weight loss of more than 5% over the previous 6 months due to the imbalanced state between catabolism and anabolism. Cachexia is very common in cancer patients, especially in advanced cancers [65]. Meanwhile, gastrointestinal cancers are the most affected, with more than 80% prevalence in Pancreatic Cancer (PC) [66]. It is reported the altered gut microbiota, increased gut barrier permeability and disrupted lipid metabolism induced by the tumors all contributed to the development of the cachexia [67]. In cancer patients, the tumors are intended to grab nutrients to meet its own demand for its growth and proliferation and disrupt the host metabolism. The core features of cachexia are the excessive proteolysis of skeletal muscle and lipolysis of adipose tissue and it may even happen on the obese patients, called the sarcopenic obesity. The cancer cachexia is triggered by multiple factors, like the reduced energy intake by the side effects of anticancer therapies and the tumor burden itself, cytokines storms. Pro-cachectic circulating molecules including TNF-α, IL-6, IL-1, and activin A, derived from the tumor microenvironment can act on both tissues and the Central Nervous System (CNS) [68], which affects the appetite and metabolism. More recently, the CNS has been suggested as the pivotal driver in cancer cachexia progression. Additionally, IL-8 is identified as a predictive marker in the PC prognosis, elevated with the cancer progression accordingly [69]. Until now, the standard treatment and guidelines for cancer cachexia were still not available [70]. The current nutritional treatments revolve around the stimulating the appetite and gaining weight. It is recommended that the cancer patients consume adequate amount of food with high-protein and high-calories [71]. Therefore, there is a concern that the amino acid restriction or protein restriction for cancer therapy may aggravate the muscle mass loss during cachexia. More studies over one specific amino acids or composition of proteins needed further investigation. Theoretically, the KD with high fat, low carbohydrate and sufficient protein can reduce the risk of occurring cachexia in cancer patients. However, its efficacy on cancer-related cachexia is still remains elusive [65]. One study revealed that the aging mice fed with KDs maintain the muscle mass [72], whereas, Nakao et al. revealed the long-term KDs lead to muscle atrophy and protein proteolysis in rodent models [73]. In this experiment, the autophagy and atrophy-related genes are upregulated while protein synthesis related gens are downregulated. The comprehensive therapy solutions that multi-dimensionally target the pro-cachectic related pathway and combined with the nutritional and suitable exercises interventions may be prospective.

Amino Acid Intervention

Amino Acids (AA) are not only materials for protein synthesis but also involved in a wide range of biosynthetic pathways as key intermediate metabolites. AA provides essential nutrients for tumor growth and participates in the tumor immune evasion by reprogramming AA metabolism [74]. In recent years, approaches targeting on amino acid availability -deprivation or supplementation, have been considered as promising and useful adjuvant therapeutic strategies for cancer treatment in both preclinical and clinical studies [75]. For example, asparagine depletion by means of asparaginase enhancement has demonstrated good efficacy in the treatment of acute lymphoblastic leukemia and colorectal cancer [76,77]. It is important to note that the serum AA level is disturbed and its levels are found decreased in patients with gastric and colorectal cancer

[78].

EAAs (Essential Amino Acids)

EAAs consist of 9 kinds of AA, refer to a set of AA cannot be endogenously produced by human body but must be acquired through dietary supplementation. A specific EAAs-enriched diet impairs cancer growth in xenografted mouse models [78]. It facilitates BCAA oxidation, inhibits cancer cell glycolysis and upregulates the ATF, subsequently induces the ER stress, and strongly suppresses the mTOR pathway. Finally leading to cancer apoptosis, however, not affecting the non-cancer cell [79].

Methionine

Methionine has multiple essential biological effects like protein biosynthesis, one-carbon metabolism and redox balance. A bulk of studies have demonstrated the exhilarating benefits of Methionine Restriction (MR) in terms of suppressing autoimmune diseases, treating metabolic disorders, and anti-cancer treatments [80]. For instance, when combined with the methionine restriction, the efficacy of 5-FU chemotherapy in the 5-FU resistant colorectal cancers was elevated by disrupting the one-carbon and nucleotide metabolism so as to blocking the tumor cells entering the S/G2 cell cycle [81].

On the other hand, a study revealed that in mouse colon cancer cells, under the low level of methionine condition, the tumor cells are more capable of using the methionine than the CD8+ T cells by highly expressing the methionine transporter SLC43A2. Lack of material caused reduced H3K79 dimethylation and STAT5 expression, leading to the normal T cells immunity to cancer hampered [82]. Of note, the dysfunctional T cell reversed after receiving the methionine supplementation. So, this experiment sparked a provoking concern that the dietary methionine deprivation may weaken the immune system's anti-cancer immunity [83]. Another concern is the proangiogenic effect mediated by the MR, which may increase the chances of tumor metastasis [84]. In this work, the VEGF expression was activated by MR and the endogenous H2S production was boosted. Collectively, the enhanced glycolysis provides enough nutrients for the endothelial-driven angiogenesis. Moreover, one study found the MR altered the gut microbiota, and decreased the excretion of H2S from feces [85].

BCAA (Branched-Chain Amino Acids)

Leucine, isoleucine and valine are belonging to the Branched-Chain Amino Acids (BCAAs). More and more research has shown that BCAAs are essential nutrients for cancer proliferation and tumors use them as energy source and carbon source in various biosynthetic pathways. The accumulation of BCAAs resulting from the suppressed activity of BCAAs catabolism is positively correlated with hepatocellular carcinogenesis through the enhancement of mTORC1 activity. And in animal models, the BCAAs restriction was found to have an inhibitory effect on the PDAC progression [86]. Strikingly, one study discovered a sex-specific effect on longevity of dietary BCAAs restriction in mice, with the advantage favoring the male mice [87]. Of interest, a study based on large-scale Japanese population found that a high-BCAAs diet was associated with lower risks in colorectal adenoma, an early stage of CRC [88]. Consistently, a national cohort manifested that as the higher dietary BCAAs consumption, the lower all-cause mortality [89].

Leucine (Leu)

Unlike the other amino acids, the metabolism of the BCAA is mainly in skeletal muscle. Leucine, a member of the BCAA family, is essential for muscle maintenance by modulating protein synthesis and decreasing proteolysis through the activation of mTORC1 [90]. However, a recently published study suggested the beneficial effect of the leucine restriction on patients with CRC. Wang and colleagues found one subtype of regulatory B cells, highly expressed the Leucine-trna Synthetase 2 (LARS2) genes, showed a nutritional preference for Leu and were involved in the CRC immunoevasion. The leucine-induced regulatory B cells promote the reprogramming of mitochondrial metabolism, increasing the regeneration of mitochondrial Nicotinamide Adenine Dinucleotide (NAD+), making the Tgfb1 transcription increased. Then the interactions with the FoxP3posTreg cells were enhanced *via* the Tgfb1 dominant. While the Treg cells are associated with the poor prognosis in cancer patients [91]. However, simplistically complete inhibition of leucine intake resulted in the increased mouse mortality. In response to this, the researchers proposed an intermittent leucine intake scheme, which showed both better outcomes and successfully inhibited tumor development [92].

Glutamine

Glutamine is the most abundant non-essential amino acid in human body and is also an essential component, function as nitrogen donor for cancer cells. To meet the need for rapid proliferation, tumor cells have to use another energy source---glutamine, which generalizes ATP through glutamine-driven oxidative phosphorylation. In CRC patients carrying PIK3CA mutations are more dependent on glutamine [93]. So, with the enhancement of tumor cell metabolism, its consumption of glutamine also increases, which made the depletion of glutamine. In hepatoma cell and pancreatic cancer cells also found the similar patterns. Theoretically, restraining glutamine intake can inhibit tumor growth, but tumor cells will adapt to the chronic low glutamine levels in the long term. Undernutrition deprivation conditions, the KRAS-mutated PDAC tumor cells become more dependent on macropinocytosis and autophagy to reuse energy from the extracellular fluids [94,95]. In addition, neighboring cells like infiltrating immune cells could provide nutrients through metabolism [96]. Mestre-Farrera et al. found tumors tend to migrate and invade nutrient-rich adjacent tissues when there is low glutamine microenvironment [97]. Of note, with the aid of the branched chain amino acid transferases, some glutamine-deprived pancreatic cancer cells could still utilize nitrogen through transamination reactions. This hallmark is called the metabolic plasticity. The cancer cells manifested increased growth, maintaining the activity of the mTORC1 and preventing Glutamine Synthetase (GS) from degradation. Surprisingly, these alterations are epigenetic and reversible [98,99]. And the glutamine depletion is also shown to be involved in the progression of CRC with Apc mutation through hyperactivation of Wnt/β-catenin signaling, thereby stimulating the tumor migration and invasion [100,101]. And it was shown that supplementing with aKG (alpha Ketoglutarate), a downstream catabolic by-product of glutamate, was effective in inhibiting the WNT signaling activation in the CRC. Pre-treatment glutamine levels are also a reliable predictor for overall survival and progression in CRC patients [101,102]. Therefore, scientists pointed out that a novel therapy coupled glutamine or αKG supplementation with anti-proliferative drugs that simultaneously suppressed metastasis and tumor growth would be a viable therapeutic approach [103]. Similar to this, another paper also revealed that a certain concentration of glutamine is essential for cytotoxic CD8+ T cells exerting its roles in the TME of malignant salivary gland tumors. And the *ATG5* is the

key gene for tumor cells to adapt to a low glutamine environment through the activated autophagy [104]. In some glutamine-addicted tumors, it is assumed that supplementing with glutamine may ward off the glutamine from being stolen by the tumor itself. Scientists found that simply inhibiting glutamine utilization or using BPTES, a glutaminase inhibitor, both upregulated the PD-L1 expression and Fas/CD95 signaling in cancer cells, thus prompting increased PD-L1 binding to the *PD-1* receptor in the phenotype of colorectal cancer xenografts. The latter is expressed on the surface of immune cells. The T cell meditated anti-tumor immunity was impaired. Until when the combination with the anti-PD-L1 antibody therapy, increasing the CD8 T cell infiltration and impair the tumor growth [105]. The similar findings were also detected in bladder cancer and renal cancer [106]. In conclusion, the complex interactions between immune cells and cancer cells in the TME offer a rational explanation for the low-response or invalidity of the amino acid's inhibition in some cancer-treatment scenarios.

It is reported that there is quite a number of cancer patients receiving chemotherapy or radiotherapy were affected with the mucosal damage, which is very painful and suffering. The Oral Mucositis (OM) is the most common one, characterized by the ulcers in the oral mucosa. The mucositis may lead to local infection, activating the pro-inflammatory response, resulting in malnutrition. All these factors only make the situation worse and negatively affect the efficacy of subsequent treatment [107]. A study found that the topical use of glutamine could mitigate the injury caused by Gastrointestinal (GI) tract related chemotherapy and radiation and help tissues to heal during the anti-cancer treatment [108]. Also, adding with the disaccharide's supplementation may promote the glutamine absorption. Another study indicated that the parenteral glutamine supplementation could help restoring serum albumin levels and reducing inflammation in patients undergoing gastrectomy for gastric carcinoma [109]. Numerous studies have proven the glutamine's multiple and indispensable function on the gastrointestinal tract, it can stimulate the synthesis of glutathione (protecting cells from oxidative stress), maintain the normal mucosal integrity, and enhance the host immune responses (fuel for immune cells like lymphocytes) [110].

High Salt Diet (HSD)

The persistent *H. pylori* infection is associated with the peptic ulcers and gastric cancers [111], due to various pathogenic mechanisms, like the powerful ability to adapt to the harsh acidic environment through the formation of the biofilm [112], the ability to express urease thus producing the Ammonia (NH3), and some virulence factors, including the Cytotoxin-Associated Gene A (CagA) and Vacuolating Cytotoxin A (VacA) [113].

One study found that the increased consumption of highly salted food would do damage to mucosal barrier, thus enhancing the *H. pylori's* role of gastric colonization and increased intestinal permeability [114]. A meta-analysis concluded that the high salt intake significantly increased the risk of gastric cancer, as well as the processed food [115]. The composition of the intestinal microbiota was also found to be altered in the high salt diet rats, leading to a reduction in Lactobacillus and Prevotella NK3B31. Even though no evident physiological changes of the intestinal tract were observed in this four-week trial [116]. Meanwhile, the high consumption of salted food like pickles may also contain large amounts of the carcinogenic N-nitroso compounds [117].

A multitude of studies have demonstrated that the HSD is the culprit in many diseases, such as the hypertension and autoimmune diseases. It could aggravate the colitis in mice by promoting the gene expression of many pro-inflammatory factors [118]. However, the HSD doesn't always negatively affect the host health and drive tumor progression. When fed with the salt from the Shinan sea salt, researchers found that it could slow down the colon cancer progression induced by the high fat diet in mice [119]. It may meditate by inhibiting the *PD-1* expression and up-regulating the NK cell activation [120]. Also, the HSD made the intestinal permeability increased, promoted the location of *Bifidobacterium* in the tumor tissue, contributing to the NK cell activation, enhanced the tumor immunity. Similarly, in the Enterotoxigenic Bacteroides Fragilis (ETBF) infected mouse models, HSD inhibits colorectal oncogenesis *via* reducing the IL-17A and iNOS expression [121]. In addition, another study indicates HSD results in regulating the Myeloid-Derived Suppressor Cells (MDSCs) differentiation, reinforcing its function and activating T cells, thus enhancing T-cell-mediated anti-tumor responses. Ultimately, the immunosuppression state is reversed [122,123]. To sum up, these controversial studies above may indicate that the effect of high salt diet on tumors may depend on the different types of tumors and tumor microenvironments; we cannot simply extrapolate one experimental finding to other conditions [124,125].

Discussion and Future Directions

Our understanding of diet and nutrition therapies for cancers is still in its infancy. Data on the efficacy and safety of a specific dietary still inconsistent. The crosstalk between tumor cells and immune cells and the distribution of nutrients in the TME are extremely complicated and difficult to figure out. Firstly, these experiments were mainly conducted on animal models, considering the physiological difference; experimental results cannot be simply extrapolated to other subjects. Moreover, we cannot absolutely restrict one specific kind of protein or vitamin intake, and all the factors mixed together make the results not so convincing. So more well-designed, long-period, larger sample size of clinical trials in this field are warranted in the future. Weighing the benefits and risks, more "personalized treatment" based on a patient's specific oncogenic mutation profile is urgently needed. It is also recommended that proper and regular aerobic and resistance exercise during cancer treatment may improve the quality of life and reduce related adverse events [126]. Taken together, with the efforts of both oncologists and nutritionists, the dietary modifications are very promising approaches to improve the life quality and prolong the lifespan of cancer patients.

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