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Fighting Cancer Using a New Weapon: Diet Intervention in Cancer Metabolism

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Abstract: Cancer, as a disease with a high mortality rate, unfortunately, cannot be completely overcome. Current anti-cancer strategies often have insufficient efficiency and significantly negative effects on healthy cells. However, recent studies have shown that targeting and regulating tumor metabolism through appropriate diets combined with other anticancer strategies is a potential way to decrease the tumorigenesis rate and inhibit tumor growth. This review mainly introduces the effects of various diets on health, summarizes the cancer metabolism, and outlines the interventions of tumor growth from the perspective of dietary regulation, which provides a theoretical basis for clinical practice and practical guidance for daily life.

Keywords: Cancer metabolism; Diet intervention; Caloric restriction; Cancer therapy

1. Introduction

Most people believe that diet is just a source of energy, but there are many other functions of diet that are less well known. Many common diets, such as the ketogenic diet, high or low protein diet, caloric restriction and high-fat diet, have been shown to be clinically effective in many diseases further demonstrating that the proper use of diet is necessary to maintain a healthy state. With the widespread use of these diets, scientists have found that diets can also be clinically effective for the treatment of many kinds of diseases. For example, the ketogenic diet (KD) is a very low-carbohydrate and high-fat diet. The reduction of carbohydrate increases the level of ketone body and induces a metabolic condition called ketosis, which converts fat into ketones rather than glucose and increases the efficiency of energy production [1]. Properly using the KD can effectively decrease body weight and also can improve the symptoms of cardiovascular diseases and type II diabetes. It can even decrease blood sugar and lipids and inhibit the growth of tumor cells [2]. However, if not used properly, the KD induces a high level of ketone body, which could cause serious complications, such as renal insufficiency [2]. Another example that is similar to low-carbohydrate diets is the high-protein diet, which can also lead to significant weight loss and improve blood lipids in overweight patients [2]. Because the body can achieve positive nitrogen balance with the increase of lean mass and loss of fat under the high-protein[3]. But protein overload can also be very damaging to the human body [4]. Thus, studies have found that the low-protein diet also presents an improvement in retarding the progression of chronic kidney disease by balancing the various indicators in the body [5].

Furthermore, Caloric restriction (CR) is a popular diet that causes weight loss and decreases the risk of age-related diseases and potentially cancer [6]. CR reduces oxidative stress and enhances autophagy [6]. Some drawbacks of CR are also caused hard to persist because it exposes patients to perpetual hunger, and patients can easily fall into malnutrition if they are weak or elderly.

Cancer is a disease that is very common but difficult to treat. Not only is it one of the leading causes of death worldwide, but the mortality rate is consistently increasing. One characteristic to define this disease is present on uncontrolled cell proliferation, which is a rapid increase in the number of cells as a result of over cell growth and cell division. The common cancer treatments include surgery, chemotherapy, radiotherapy, and targeted therapy. Unfortunately, these widely used treatments are often insufficient and destructive on healthy cells. For example, some chemotherapeutics can cause anemia, renal and liver dysfunction, hair loss and fatigue. Some studies have shown that tumor cells metabolize in a different way compared to normal cells [7]. The role of diet in suppressing tumor growth without harming healthy cells is not well-known. It deserves exploring whether changing metabolic patterns of cancer through mediating diet composition can assist in various treatment approaches to suppress the growth of tumor cells without affecting other normal cells. This article compares three major diets that have been shown to regulate tumor growth and briefly discusses how diets regulate tumor growth based on the differences of metabolic pattern in tumor cells and normal cells.

2. Cancer Metabolism

Rapid uncontrolled cell proliferation is a main characteristic of cancer. This occurs when metabolic alterations

accumulate in signaling pathways provide enough oxygen and nutrients to activate and enhance cell proliferation. The metabolic pathways must be activated under an appropriate microenvironment in order to achieve proliferation. These pathways rely on available nutrients to achieve cell maintenance, biosynthesis, and reduction-oxidation balance [8]. An appropriate microenvironment is needed to activate the pathways that signal for proliferation. Below is a concise graphic depiction from the article "Cancer Metabolism at a glance" [26], which describes major metabolic pathways employed by cancer cells to maintain survival and proliferation, and it also explains the nutrient utilization of cancer cells that used to complete the high demand of nutrient need of cancer metabolism. Starting with glucose, and followed with glutamine, serine and other amino acids, are all consumed nutrients and major contributors of cell metabolism. Under nutrient starvation, a limited supply of nutrients can lead to insufficient proliferation or even death of tumor cells. Cancer cells can develop into an important mode known as autophagy or "self-cannibalism" to obtain a sufficient amount of nutrients in a nutrient-deficient environment for survival [9]. Additionally, one study showed that rapamycin inhibits growth under nutrient-replete conditions, but actually promotes proliferation under nutrient-limited conditions due to enhanced lysosomal degradation of endocytose proteins [10].

In recent studies, the phenomenon reported by Otto Warburg has shown that "cancer cells consume tremendous amounts of glucose and metabolize the majority of the glucose into lactate even in the presence of oxygen", blocking glucose metabolism becomes a potential method to inhibit the proliferative effects of tumor[11][27]. Studies show that a compound called 2-deoxyglucose (2-DG) can accumulate 2-deoxyglucose-6-phosphate to inhibit hexokinase to slow glucose uptake of the cell [12]. However, since the dose of 2-DG is limited by the toxicity associated with symptoms of hypoglycemia, and the tolerable dose of 2-DG does not show sufficient effect of inhibiting cancer progression, it has not been used as a popular anticancer compound [13][30].

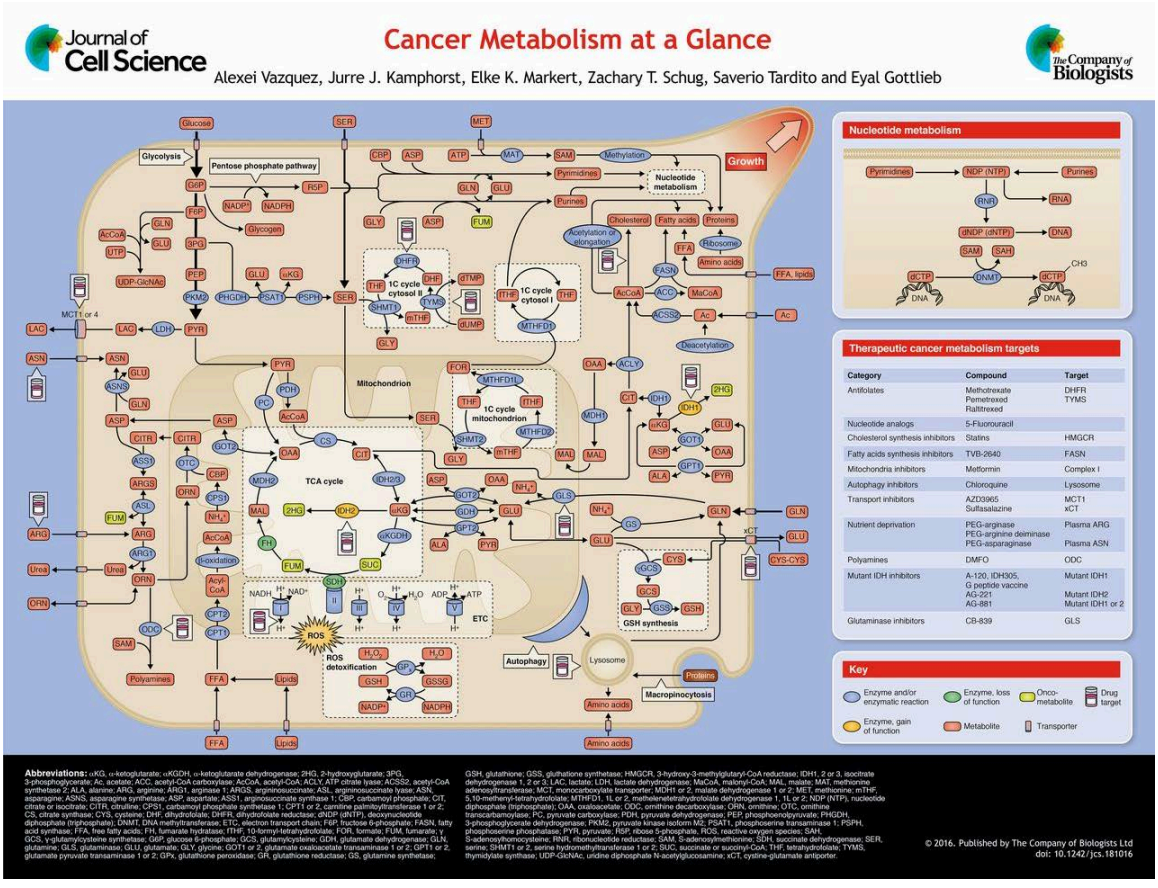

Figure 1. Cancer metabolism at a glance

Targeting de novo fatty acids might be an effective way to treat some cancers. Fatty acids are a key component of cell membranes, can also act as signaling molecules, and store energy. It was first discovered in the 1950s

that tumors are able to synthesize lipids, and a subsequent study determined that the large majority of lipids in tumor cells are synthesized de novo [14]. However, most human organs and tissues do not synthesize fatty acids de novo, except for adipose tissue, liver and lactating breast tissue, so inhibiting fatty acid synthesis is promising to treat all kinds of tumors[15][28]. And most diets mentioned in this review, such as ketogenic and low-fat, are low in fatty acids.

2.1. The effect of different types of diet on cancer risk and tumor growth

Ketogenic diet (KD) is shown by studies to potentially possess a tumor growth-limiting effect. One of the reasons is that because a period of low carbohydrate ketogenic diet may improve the metabolism of fat oxidation or breakdown and may therefore have a significant effect on obesity, which is a high risk factor for many disorders and diseases, including hypertension, type 2 diabetes, poor bone health, and cancers [1]. In a study, 39 obese patients were given a very low-calorie-ketogenic diet (VLCK) with only 4 grams carbohydrates and 15 grams protein , which is away less compared to the average 1,800-calorie diet that contains between 210 and 290 grams of carbohydrates and between 50 to 145 grams of protein each da,. During the one year follow-up process, 12 patients from VLCK group dropped out of the study in total because of the poor tolerance of hunger and the strong side effects of the diet. After 8 months of treatment, the maximum weight loss observed was 22.8 ± 11.4 kg in the group. And after the whole year follow-up in this VLCK diet group, more than 88% of patients lost more than 10% of their initial weight with well-preserved lean mass and less regained weight[16]. However, the mechanism of KD's weight loss effect is unknown yet [1]. The recent hypothesis is that KD reduces lipogenesis and increases lipolysis, inducing a greater metabolic efficiency to consume fats. Then, the alleviation of obesity can lead to significant benefits in reduction of cholesterol and blood triglycerides. In addition to reducing the symptoms of obesity, some animal studies indicate that KD can also slow tumor growth and delay tumor development, and increase the survival rate of patients. A study on mouse cancer models including different cancer samples indicated that the KDs enhance the efficiency of clinical intervention therapy like target therapy [17]. Moreover, a study in recurrent glioblastoma patients reported the effects of a combination of KD and other therapies, in which both the partial response rate and the tumor progression of the KD group are lower than the control group.

Researchers hypothesize that the Warburg effect in cancer cells has the potential to be targeted by increasing chronic metabolic stress, which occur due to the reduction in glucose levels accompanied by a reduction of insulin and/or Insulin-like Growth Factor (IGF) levels (signaling pathways contributes to tumorigenesis), provoked by dietary interventions such as KD and caloric restriction[17]. Furthermore, several animal model studies also show that the KD affects amino acid metabolism and urea cycle metabolites of cancer patients. Researchers suspect that the inhibitory effect of KD ontumor growth probably derives from the down-regulation of essential amino acids. Therefore, the ketogenic diet does show the evidence to combine other standard therapy or treatments to increase the therapeutic response and directly alter the metabolism of cancer cells to reduce the risk of cancer and inhibit the growth of tumors.

Another very popular type of diet called caloric restriction (CR) can effectively cause weight loss and reduce the risk of cancer. CR can decrease growth factors (GFs) and glucose in the blood to inhibit cancer growth, and less intake of nutrients can also limit the growth of cancer cells. CR without malnutrition can reduce oxidative stress and improve cellular autophagy (damaged cell decomposed itself in order to regenerate and reutilize the resources)[29], which are all associated with the inhibition of tumorigenesis which are essential components of the beneficial effects to reduce the risk of cancer[18]. Most data about the effects of CR are collected from rodents. Studies show that mice under CR lose weight and possess lower levels of circulating insulin, glucose, and circulating adipokines, which reflects the reduction in white adipose tissue (WAT) mass under restriction. CR can modulate autophagy and apoptosis which are all associated with the inhibition of tumorigenesis[31]. Autophagy is a self-degradation process that can be greatly up-regulated by lack of nutrients. It can prevent the accumulation of organelles and protein, thus contributing to prolonged life-span. CR has been demonstrated to dramatically up-regulate many autophagy genes, including ULK1, Atg101, APG12, GAPRAP/ GATE-16, autophagin-1, LC3, and beclin-1. Furthermore, reduction in food intake can increase the sensitivity of tumor cells to balance pro-apoptotic and anti-apoptotic proteins that helps to maintain human homeostasis, prolong lifespan and prevent apoptosis-mediated damage of normal tissues [18]. Studies have indicated that a total of four pathways are involved in the change of metabolism and the gradual shift from carbohydrate metabolism to lipid metabolism, and mediate the CR effects. They are the insulin like growth factor (IGF-1)/insulin signaling pathway, the sirtuin pathway, the adenosine mono-phosphate (AMP) activated protein kinase (AMPK) pathway, and mTOR pathway. These pathways may interact with each other to mediate different aspects of the response. Thus, CR can prevent cancer or even reduce tumor growth [18]. In summary, the combination of caloric and nutrient restriction, as well as caloric restriction mimetics (CRM), with the targeted drugs has displayed sufficient anti-

tumorigenesis activity and has a great impact on the suppression of the growth of the cancer cells [18].

However, some diets can also lead to a number of diseases like steatosis and inflammations, as well as cancer due to metabolic disorders and obesity. The combination of high-fat and high-carbohydrate diet will lead to more severe symptoms, including hyperglycemia, hypercholesterolemia, and higher levels of inflammatory mediators and lower levels of immune cells. Studies on mice show that there are many possible mechanisms that explain how HFD induced diseases occur. One of the mechanisms is lipotoxicity, which happens when murine adipose tissue stores excess calories and lipids are deposited into other organs after the use of HFD. The expanded organs under stress from excess energy also cause the inflexibility of metabolism and decreased autophagy, which all increase the risk of cancer. It has been reported that HFD promotes tumor progression in the small intestine of genetically susceptible, K-ras (G12Dint), mice independent of obesity and this process is related to the dysbiosis of gut microbiota. Butyrate could effectively attenuate the tumor progression through recruiting dendritic cells in the gut-associated lymphoid tissues [19].

2.2. The clinical application and potential of diet intervention on cancer therapy

Recently, choosing an appropriate diet for cancer patients has been attracting more and more attention. As we know, there are several sophisticated clinical cancer therapies, including surgery, chemoradiotherapy, targeted therapy, and immunotherapy. Patients under these therapies need enough energy to recover the function of their immune system and other organs. However, enough energy for the body also means abundant food for tumor cells. How to balance the beneficial and adverse effects of energy supplementation still remain to be solved urgently. It has been experimentally proved that some diets are beneficial to cancer therapy. However, because of the lack of well-controlled clinical trials, some of the dietary therapies have not been applied clinically, and some of them have been shown to be not as effective as in animal experiments.

Despite these difficulties from some clinical experiences, there are still some diets that have been shown to be effective in reducing the risk of cancer and slowing cancer growth. One of the dietary therapy is called the Gerson Therapy, which was developed by Max Gerson as a dietary approach to treat tuberculosis, but later was used to treat cancers by improving the health condition and eliminating toxins from the body. Following this diet, patients need to have a raw vegetarian diet for improving health condition, including drinking 13 glasses of fresh vegetable and fruit juices and various supplements, including iodine solution, vitamin B12, potassium, thyroid hormone, an injectable crude liver extract, and pancreatic enzymes [20]. To stimulate enzymes in order to eliminate toxins, the dietary program also encourages patients to take coffee, chamomile, or castor oil enemas. Salt, oil, berries, drinking water, and all preserved or processed food, as well as aluminum cookware or utensils, are not allowed in the program [20]. On the other hand, this dietary therapy also causes some side effects, including but not limited to loss of appetite, diarrhea, vomiting, fever, and pain on tumor masses. The consumed supplements and daily enemas may also lead to other serious side effects [21]. Therefore, although recent studies have shown that the advanced Gerson treatment diet program can achieve desirable results in slowing cancer growth, it is still not an effective plan for cancer patients who already suffer from side effects of diseases and treatments. Also, the high costs also make it hard for extensive application.

The other therapy is a cancer-prevention-related diet called American Institute for Cancer Research (AICR) Diet Therapy [22]. This diet therapy emphasizes a diet with various vegetables and fruits, foods low in fat and salt, and maintaining a healthy weight and being physically active. These recommendations make a positive impact on people's dietary habits and health conditions, which might reduce the risk of tumorigenesis [23]. Furthermore, the Mediterranean Diet has been praised highly for its beneficial effect on health. The relation between the Mediterranean Diet and cancer was determined through searching and screening hundreds of related papers and the results suggested that the Mediterranean Diet is associated with reduction in overall cancer rates as well as significantly lower rates of digestive tract cancers [24].

In terms of the mechanism of how different diets regulate tumorigenesis and tumor cell growth, some studies suggest that intermediate or final metabolites play an essential role. From recent perspectives, immunotherapy is currently the most promising approach to cancer treatment, which can directly kill cancer cells by activating the function of the immune system. The activity of immune cells will be directly affected by metabolism, for example, studies have shown that lactic acid can inhibit the function of immune T cells and provide tumor cells with a favorable microenvironment [25]. Therefore, modifying diets to improve the metabolic environment in the body can effectively improve the function of immune cells and possibly can prevent tumorigenesis or reduce the growth of tumor cells.

3. Conclusion

Nowadays, cancer is still an insurmountable disease in the world, even though many new therapies appear promisingly effective to some types of cancers. The unique metabolism of tumor cells has attracted more and more attention in recent years. Targeting tumors cells metabolism provides a new way to inhibit tumor growth specifi-

cally, without influence or less efficient on normal cells. The most direct and easiest way to mediate body metabolism is to regulate a component of daily diet. There already exist many typical diets affecting a person's state of health, including for metabolic dysfunction-related diseases, such as obesity, sarcopenia, diabetes, and even Alzheimer's disease. In recent years, with the deepening understanding of cancer metabolism, some diets have been found to affect cancer metabolism and slow tumor growth. Although some dietary studies cannot be applied clinically due to the low efficiency on animal experiments or the lack of control group, tumor metabolism can still be a main researching target of cancer therapy. In addition, in future experiments, with the continuous improvement of experimental methods and further understanding of tumor metabolism, researchers can better understand the relationship between diet and tumor therapy, thus contributing to the clinic along with other cancer clinical treatments.

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