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Review

Caloric restriction - A promising anti-cancer approach: From molecular mechanisms to clinical trials

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ABSTRACT

Cancer is the second leading cause of death worldwide and the morbidity is growing in developed countries. According to WHO, >14 million people per year are diagnosed with cancer and about 8 million die. Anti-cancer strategy includes chemo-, immune- and radiotherapy or their combination. Unfortunately, these widely used strategies often have insufficient efficacy and significant toxic effects on healthy cells. Consequently, the improvement of treatment approaches is an important goal. One of promising schemes to enhance the effect of therapy is the restriction of calorie intake or some nutrients. The combination of caloric restriction or its chemical mimetics along with anti-cancer drugs may suppress growth of tumor cells and enhance death of cancer cells. That will allow the dose of therapeutic drugs to be decreased and their toxic effects to be reduced. Here the possibility of using this combinatory therapy as well as the molecular mechanisms underlying this approach will be discussed.

Contents

Abbreviations: Acetyl-CoA/CoA, acetyl-coenzyme A/Coenzyme A ratio; AMPK, AMP-dependent kinase; APL, autophagolysosome; ATG, autophagy-related gene; ATP/ADP, adenosine triphosphate/adenosine diphosphate ratio; CDK, cyclin-dependent kinase; CR, caloric restriction; CRM, caloric restriction mimetics; DDA, DNA-damaging agent; DSR, differential stress resistance; EMA, the European Medicines Agency; ER, endoplasmic reticulum; Erk 1/2, extracellular signal–regulated kinases 1/2; FDA, Food and Drug Administration; FOXO, forkhead box factors; FFA, free fatty acids; HDAC, histone deacetylase; HER2, human epidermal receptor 2; HbA1c, high cancer risk hemoglobin; GF, growth factors; GH, growth hormone; IGFBP-1, IGF-binding protein; IGF-I, insulin-like growth factor I; IRE1α, inositol-requiring enzyme 1 alpha; KD, ketogenic diet; LKB1, liver kinase B1; MAPK, mitogen-activated protein kinase; mTORC1, mammalian target of rapamycin complex 1; NADH/NAD^+, the ratio of reduced and oxidized nicotinamide adenine dinucleotide; NADPH/$NADP^+$, the ratio of reduced and oxidized NAD phosphate; Nrf2, NF-E2-related transcription factor; PERK, protein kinase-like endoplasmic reticulum kinase; PI3K, (phosphatidylinositol-3 kinase); PPARα, peroxisome proliferator-activated receptor α; PGC-1α, PPAR coactivator-1α; ROS, reactive oxygen species; Sirt1, sirtuin-1; TCA cycle, tricarboxylic acid cycle; TKI, tyrosine kinase inhibitor; Ulk1, Unc-51 like autophagy activating kinase 1; UPR, unfolded protein response; XPG, xenobiotic processing gene.

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1. Introduction

Overweight is one of the most serious problems of modern civilization which appeared with conditions of food oversupply. Nowadays, 39% of all adults are overweight and 13% are obese [1]. Worldwide, obesity has more than doubled since the 1980s; therefore, the incidence of diseases associated with overweight (cardiovascular and musculoskeletal disorders, diabetes and cancers) is growing continuously. Consequently, the control of body weight is becoming an increasingly more popular recommendation from the medical community. The reductions of food intake or diets without malnutrition have been reported to have clear positive effects on health and lifespan. For example, the life-span of yeast, nematode and flies has been shown to significantly increase as result of caloric restriction (CR) [2]. The similar correlation between CR and the prolongation of life has been demonstrated for rodents. However, controversial data were obtained in the studies of CR impact on primates. The major effect on age-related and all-cause survival has been demonstrated [3], but two other groups were not able to detect essential effects on mortality [4,5]. These discrepancies can be explained by the differences in experimental protocols and the individual features of tested animals.

The ability of CR to prolong human life is still under debate as no clear data supporting this idea have been presented. On the one hand, the longevity and low morbidity of Okinawans are associated with low-caloric diet typical for the Okinawan population [6]. Unfortunately, the quantitative model assuming the correlation between longevity and CR has still not confirmed the positive effect [7]. Moreover, the question of suffering from hunger and its potential negative effect on fertility is still remaining. Nevertheless, a number of studies have shown a set of benefits from low caloric intake. Thus, CR without malnutrition prevents obesity, diabetes and hypertension; it is able to reduce the risk factors for heart diseases, brain atrophy, musculoskeletal disorders (especially osteoarthritis), atherosclerosis and cancer [8,9]. Today, cancer is one of the most common causes of death and the morbidity is growing [10]. An increased body mass index (BMI) and a lack of sufficient physical activity not only correlate with the incidence of different tumors but may decrease survival after anti-cancer therapy and worsen prognosis in some cases [11,12]. At the same time, CR can attenuate tumorigenesis and enhance the death of cancer cells upon therapy due to the impact on body weight. The studies of spontaneous and experimentally induced oncogenesis have revealed that CR leads to a decreased incidence of breast, skin, intestinal, ovarian, hepatic and brain cancers [13,14]. Furthermore, the lower incidence of breast carcinogenesis (up to 50%) has been observed among women with anorexia nervosa and low BMI [15]. Since CR modulates many biochemical and metabolic processes on different levels, the mechanisms underlying the anti-cancer effect of decreased calorie intake are under investigation. CR modulates the level of metabolites altering the adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio, acetyl-coenzyme A (acetyl-CoA)/CoA ratio, the ratios of reduced and oxidized nicotinamide adenine dinucleotide NADH/NAD^+ and NAD phosphate NADPH/$NADP^+$. It promotes decreasing level of growth factors (GF) essential for cell growth and division [16]. Moreover, it can regulate apoptosis and autophagy [17,18]. Finally, nutrient restriction regulates hormonal status via controlling the level of glucocorticoids in serum, which influences various metabolic functions and activates anti-stress and anti-inflammatory pathways [19]. The modulation of the level of GFs plays a crucial role in the anti-tumorigenic properties of CR since growth hormone (GH) and insulin-like growth factor I (IGF-I) are the major postnatal extracellular regulators of cell growth and proliferation. It is known that GF-induced stimulation of mitogen signaling pathways (Ras, Akt) is a hallmark of cancer cells [20]. The increased concentration of IGF-I is associated with the high risk of development of breast, lung, colon, and prostate cancers [21,22]. Moreover, positive cross-talk between IGF-1 deficiency and decreased tumorigenesis correlates with the increased life-span of individuals with mutated genes of GFs or their receptors [2]. The modulation of GFs via the control of nutrition may have a high potential for cancer incidence decrease and improvement of anti-cancer therapy strategies.

Another benefit of CR in the context of anti-tumor therapy is an ability to promote adaptive mechanisms of normal cells in response to stress caused by treatment with anti-cancer drugs. Many anti-tumorigenic agents are able to introduce DNA damage and activate various mechanisms of programmed cell death; however, they have significant toxic effects on healthy cells. Accumulating evidence suggests that the combination of stress stimuli, such as DNA damage and CR, has a synergistic effect on cancer cell death, while the negative side effects on normal cells can be reduced. The phenomenon of differences in sensitivity of cancer versus normal cells to stress stimuli is called differential stress resistance (DSR). Consequently, the reduction of drug-mediated toxic effects via the combination of anti-cancer therapy with CR can be achieved not only through enhancement of the treatment efficiency and respective decrease of drug dosage but also through increasing the resistance of normal tissues to chemotherapy.

CR is able to influence hormone-dependent regulation of homeostasis as well as various pathways associated with tumorigenesis and cell death. Considering the ever-increasing interest in further understanding the mechanisms underlying potential therapeutic benefits of CR, here we made an attempt to summarize and critically discuss the available data obtained from clinical trials on the impact of CR or CR mimetics in anti-cancer therapy.

2. Caloric restriction and cell death

2.1. Biochemical changes during caloric restriction: role of caloric restriction on cancer cell metabolism

The reduction of nutrient intake (especially carbohydrates) results in various metabolic and biochemical changes, such as the modulation of ATP/ADP and NADPH/$NADP^+$ ratio, depletion of acetyl-CoA, decreasing blood concentrations of insulin, glucose, IGF-1 and other GFs [14,23]. Binding of IGF-1 and insulin to their receptors regulates glycolysis, contributing to cancer metabolism and tumor cell proliferation; therefore, the depletion of these factors under CR attenuates tumor progression [24,25]. In normal conditions, these interactions also lead to activation of proliferative signaling pathways including PI3K (phosphatidylinositol-3 kinase)/Akt/mTORC1 (mammalian target of rapamycin complex 1) and Ras/Raf/MAPK (mitogen-activated protein kinase) (Fig. 1) [26,27]. The PI3K/Akt/mTORC1 pathway is a major regulatory node that controls protein synthesis, cell cycle, growth and survival in response to extracellular stimulation. The hyperactivation of this pathway due to mutations has been detected in various types of cancer [28,29]. The decrease of its stimulation is one of the most advantageous effects of CR at the cellular level, which can potentially be used for anti-cancer therapy.

The inhibition of mTORC1 pathway under CR amplifies the activation of peroxisome proliferator-activated receptor α (PPARα) which is triggered by reducing glucose level and followed by lipolysis (Fig. 1). PPARα controls the transcription of genes regulating fatty acid oxidation and ketogenesis with the simultaneous reduction of glucose and glutamine consumption that allows cells to adapt to prolonged fasting [30]. The preferential usage of glucose as the main energy source in cancer cells has long been known as aerobic glycolysis or the Warburg effect [31]. Fast proliferating cancer cells seem to use the glycolytic pathway for production of metabolic derivatives which are used in biosynthesis of cellular components. A suppression of glycolysis was suggested to be one of the most promising strategies in anti-cancer therapy because this approach can be applied for many types of cancers irrespective of their origin. PPARα-mediated stimulation of lipid oxidation might possess anti-cancer properties, not only through inhibition of glycolysis but also through the production of free radicals by damaging mitochondria and triggering cell death [32]. Moreover, free fatty acids (FFA) appearing during PPARα-stimulated lipolysis may also induce