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Discover the Role of Calorie Restriction in Cancer Immunotherapy

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Abstract

Nowadays, the development of cancer immunotherapy has brought breakthrough results in treatment. However, understanding of the limitations of this therapy remains unclear. While the significant role of dietary energy intake in regulating cancer progression and host immunity is widely acknowledged, the impact of dietary Calorie Restriction (CR) on anti-tumor immune responses remains uncertain. Investigating this, we utilized an immunogenic B16 melanoma cell expressing ovalbumin (B16-OVA) to assess the effect of the CR diet on tumor growth and host immune responses. Furthermore, we evaluated whether the CR diet influenced the effectiveness of cancer immunotherapy, specifically anti-PD-1 monoclonal antibody (anti-PD-1 Ab) treatment. Our findings indicate that the CR diet notably decelerated B16-OVA tumor growth without altering $CD4^+$ and $CD8^+$ T cell infiltration into the tumor. Despite *in vivo* depletion of $CD8^+$ T cells facilitating tumor growth in the control diet group, no significant change occurred in the CR diet group, with or without $CD8^+$ T cell-depletion. Moreover, under CR conditions, anti-PD-1 Ab treatment lost its efficacy to suppress tumor growth, accompanied by the activation and metabolic shift of $CD8^+$ T cells. In conclusion, our study suggests that restricted energy intake in cancer patients may impair $CD8^+$ T cell immune surveillance and diminish the efficacy of immunotherapy.

Keywords: Cancer immunotherapy • Anti-tumor immune responses • T cell immune surveillance • Calorie restriction

Introduction

The role of physical condition, including energy/food intake, diet, exercise and weight, has been studied extensively in cancer progression. Diets high in calories, saturated fats and refined sugars are associated with increased cancer risk and faster tumor growth, while diets high in fruits, vegetables and whole grains are associated with reducing the risk of cancer and improving cancer outcomes [1]. Regular exercise has been shown to reduce inflammation, improve immune function and hormone regulation and slow cancer growth. In contrast, obesity is known to be associated with an increased risk of certain types of cancer and support aggressive tumor growth [2]. The correlation between physical condition and host immunity has also been studied recently. It has been reported that malnutrition and an unhealthy diet, characterized by a low intake of fruits, vegetables, and micronutrients, impair immune function and increase susceptibility to infections. On the other hand, a diet rich in nutrients and phytochemicals, such as flavonoids, carotenes and vitamins, is known to increase immune function and reduce inflammation. Physical activity has also been shown to improve immune function by enhancing immune cell circulation and reducing inflammation. Contrarily, obesity and a sedentary lifestyle were reported to impair immune function and increase the risk of infection. Recent findings suggest the effect of dietary calorie intake has significant impact on cancer disease and therapy. In general, Calorie Restriction (CR) is defined as the 20% to 40% reduction of the average daily caloric intake without incurring malnutrition or the deprivation of essential nutrients and has been reported to affect cancer prevention and therapy. In this study, we aim to investigate the effect of Calorie Restriction (CR) on anti-tumor immune responses in an immunogenic preclinical cancer model. We conducted a preclinical study using an immunogenic tumor model with B16 melanoma expressing Ovalbumin (B16-OVA) and tested for the effect of CR on the host anti-tumor immune responses. B16-OVA model is one of the most well-established models used to monitor host $CD8^+$ T cell dependent immune response. In addition, the effect of CR on immunotherapy with Immune Checkpoint Blockade (ICB) was studied. Although the CR diet delayed tumor growth, the host anti-tumor immunity and the response to anti-PD-1 treatment were poor due to the alteration of $CD8^+$ T cells' number and function. These findings may contribute to

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understanding the response to ICB under energy restriction in cancer patients.

Description

Based on pivotal study of patients diagnosed with cancer cachexia, we observed ICB treatment results in statistically significant differences between the control group and the cachexia group [3]. To understand the importance of physical condition, particularly energy intake, in cancer progression, we studied the effect of CR on anti-tumor immune responses in the immunogenic B16-OVA melanoma model. CR significantly slowed down the tumor growth of B16-OVA without affecting both $CD4^+$ and $CD8^+$ T cell infiltration into the tumor. While the *in vivo* depletion of $CD8^+$ cells accelerated B16-OVA tumor growth in the normal diet group, there was no significant change in the tumor growth of the CR group with or without $CD8^+$ cells. Considering anti-PD-1 Ab lost its efficacy to suppress tumor growth under the CR condition along with the metabolic suppression of $CD8^+$ T cells, the energy restricted physical condition in cancer patients may impair $CD8^+$ T cell immune surveillance and the efficacy of immunotherapy [4].

It has been known that CR reduces cancer risk and improves outcomes in preclinical and clinical studies. Calorie restriction activates molecular pathways that enhance cellular defenses, promote DNA repair and reduce oxidative damage, which may contribute to its anticancer effects. Additionally, CR has been shown to enhance the effectiveness of cancer treatments such as chemotherapy and radiation. Indeed, some studies have demonstrated that calorie restriction can improve immune function and reduce inflammation, potentially contributing to increased health [5,6]. Several studies have also provided evidence indicating that calorie restriction can enhance immune function and alleviate inflammation, leading to potentially improved overall health. CR has been shown to prevent mitochondrial dysfunction and enhance mitochondrial efficiency by reducing oxidative stress and inflammation, promoting mitochondrial biogenesis and improving mitochondrial quality control mechanisms. Therefore, CR may improve cellular metabolism and energy production, reduce cellular damage and contribute to improved health and longevity [5,6].

Conclusion

Contrary to the role of CR in cancer suppression, patients with sarcopenia or cachexia resulting from chronic caloric deficits may have a poorer response to immunotherapy, lower progression-free survival and lower overall survival rates, according to some studies. In line with our findings, those patients also showed a reduction in immune cell infiltration into the tumor microenvironment and impaired T cell activation. Therefore, it must be critical to balance between calorie restriction and maintaining an adequate calorie intake to avoid negative impacts on immune function and the subsequent response to cancer therapy.

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