Mini Review
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Can protein restriction set up T lymphocytes favorably for their activation against pathogens through MYC?

Abstract

One area that presents a significant threat to global health is infectious diseases. With increasing prevalence of antibiotic-resistant bacteria,[1] opportunistic infections are a growing concern for human societies. In 2009, there were 89,000 deaths caused by pneumonia, septicemia, and influenza virus in the United States alone.[2] Antibiotic-resistant bacteria increase the risk of secondary infection that is associated with many standard medical procedures such as organ transplantation, chemotherapy, dialysis, and elective surgery.[1] The deceleration of new drug discovery suggests that acute preventative strategies strengthening host immunity prior to such procedures are of strong interest.

Keywords: global health, organ transplantation, influenza virus, pneumonia, septicemia

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Introduction

Since Clive McCay's first discovery nearly 80years ago,[3] studies of dietary restriction-a reduction in nutrient intake without malnutrition-in a diverse array of organisms have revealed it to be an effective way to extend lifespan and promote broad-spectrum improvement in health during aging.[4] While research has begun to unravel the mechanisms underlying how dietary manipulation modulates longevity, our understanding of how it affects individual health parameters, including immune function, remains limited. Early studies that focused on manipulation of total calories produced mixed results. Drosophila studies have variably reported detrimental, protective, or no effect of food dilution or reduced food intake on host survival following bacterial infection.[5–7]

Mammalian studies indicate that adaptive immunity appears improved in calorie-restricted animals, but survival outcomes of host animals infected with pathogen are considerably more variable. For example, calorie restriction has been reported to improve T-cell function in humans[8] and to promote antigen presentation, antibody production, and T-cell proliferation in response to influenza vaccination.[9] However, it aggravated mortality of young and aged mice in primary influenza infection[10,11] and promoted survival following murine retrovirus infection.[12] Similar outcomes are observed following bacterial infection where calorie restriction exacerbated mortality from sepsis[13] but improved survival of mice infected with Salmonella.[14] In contrast, protein restriction has produced more consistent outcomes that indicate enhanced protection from pathogenic infection. For example, a diet containing one third the protein in a normal diet suppressed the expression of hepatitis B virus and hepatitis B virus-induced liver injury in mice.[15] Low-protein diets also ameliorated mortality of guinea pigs from bacterial peritonitis[16] and protected mice from malaria infection.[17]

Then, how does protein restriction protect animals from pathogen? A "metabolic boost" might be a key adaptation that takes place under protein restriction. In T-cell activation, Myc functions as a metabolic switch to promote anabolic metabolism including aerobic glycolysis and glutaminolysis, which allows antigen-primed T-cells to go through a rapid proliferation by generating building blocks for nucleic acids and phospholipids with a limited nutrient supply, as intumor cells.[18]

Intriguingly, protein restriction has been shown to increase the Myc abundance[19] and myc over expression improves poor survival outcomes of fruit flies fed high protein diets,[19] suggesting that Myc plays an important role in favoring the post-infection survival of protein-restricted host animals. However, given that protein restriction had no impact on cellular immunity in Drosophila,[19] it remains to be seen whether Myc regulates the host metabolism more broadly beyond T-cell activation.

The protein restriction-Myc signaling relationship may have evolved to utilize glucose more efficiently during protein restriction, thereby meeting high energy demand during infection. For example, c-Myc increases cellular glucose uptake by up regulating the transcription of glucose transporter Glut1,[18] and transgenic over expression of c-Myc promotes hepatic glycolysis and cellular utilization of glucose.[20] Drosophila studies also support this notion. Li et al. reported that the consensus Myc binding site is highly enriched in genes that responded to amino acid starvation in larvae.[21] Furthermore, myc over expression stimulated glucose disposal in larvae fed a high sugar diet and prolonged their survival under starvation.[22]

These studies raise the possibility that increased glucose utilization through protein restriction-Myc signaling might act to maximize energy production in the face of limited amino acid availability and abundant carbohydrate. It warrants further investigation to test whether effective utilization of glucose, which is facilitated by Myc, could contribute to favorable survival outcomes of protein-restricted animals following infection.

Conclusion

Aligning with the public efforts to reduce the mortality risks from opportunistic infections, it will be of future interest to investigate

whether acute protein restriction prior to standard medical procedures such as surgery would decrease the mortality risks of susceptible human populations by increasing surgical stress resistance[23] and boosting innate immunity against secondary bacterial infection, as shown in a Drosophila study.[19] Myc improving the post-infection survival of protein-restricted animals and also playing an important role in T-cell activation, it will be informative to investigate whether protein restriction enhances T-cell activation following bacterial infection through Myc.

Given that protein restriction benefits much more than the host immune response to improve its metabolic health[24] and extend the rodent's lifespan,[24] it will be a priority to find optimal protein restriction diet regimes for humans, which would maximize our health benefits. High-protein, low-carbohydrate diets have become popular as a weight loss strategy due to their suppressive effects on appetite.[25] High protein diets are also recommended to septic patients due to a net increase in protein catabolism during sepsis.[26] However, long-term adherence to high-protein, low-carbohydrate diets has been associated with high mortality risk from cardiovascular diseases.[27] Considering beneficial effects of protein restriction on immunity, cardiovascular health, and longevity, high protein diets should be cautiously called for their public application and balanced diets that incorporate wholesome carbohydrates should be more encouraged instead.

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Conflict of interest

Author declares that there is no conflict of interest.

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