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EDITORIAL

Targeting metabolism through exercise and nutrition to rejuvenate an aging immune system

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Abstract

Dysregulated metabolism is a hallmark of the aging process. Immune function is tightly controlled by cellular metabolism, and emerging evidence indicates that aged immune cells have alterations in metabolism that may promote aging-related disease. Lifestyle interventions including diet and exercise are potent strategies for targeting metabolic dysfunction in aging, but to date, only a few studies have examined the ability of exercise or diet to regulate immunometabolism, despite their well-known positive effects on healthspan and lifespan. Utilizing lifestyle modification as precision medicine to target age-related diseases through modulating immunometabolism is promising, but a great deal of work remains.

Keywords: Immunometabolism, exercise, diet, inflammaging, immunosenescence

Advancing age has long been associated with declining immunity, but the recent (and ongoing) COVID-19 pandemic has brought this to the attention of many outside the relatively small fields of biogerontology and geroscience. Aging impairs immune responses (broadly termed immunosenescence) and increases chronic inflammation (colloquially referred to as inflammaging) through a variety of mechanisms that have been reviewed in detail recently [1]. Various geroprotector drugs, especially mTOR inhibitors [2], have shown some promise in enhancing immunity in older adults. Nevertheless, well-validated therapeutic strategies for boosting immune responses during aging remain elusive. Lifestyle interventions such as physical exercise and dietary modification have received considerable attention as therapies to promote healthspan and lifespan, due in no small part to their multifaceted health benefits, low cost, and strong safety profile compared to many pharmaceuticals. To a large extent, these strategies are eustressors that affect cellular and systemic metabolism. Aging profoundly dysregulates human metabolism [3], so many of the benefits of diet and exercise are likely to derive from their metabolic effects.

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In recent years, it has become clear that cellular metabolic programs drive the phenotype and function of immune cells. While initial observations were made over half of a century ago [4], the rapid expansion in laboratories studying immune cell metabolism in the last two decades has led to an explosion in research in what is now termed immunometabolism. Immune cell metabolism is highly complicated and has been comprehensively reviewed elsewhere [4, 5], but in general, pro-inflammatory activation of immune cells such as T cells and macrophages is associated with activation of glycolysis, the pentose phosphate pathway, and fatty acid synthesis, while anti-inflammatory and pro-memory responses are supported by fatty acid oxidation and mitochondrial metabolism. Dysregulation of immunometabolism is, by extension, associated with a host of chronic diseases including age-associated diseases such as cardiovascular disease and cancer [5]. While immunometabolism is understudied in the context of aging, there has been some progress in this area in the last several years. In general, aged monocytes and macrophages have been observed to have reduced mitochondrial respiration and defective NAD^+ metabolism, and this is associated with increased inflammation [6]. Conversely, aged T cells have increased mitochondrial respiration, likely due to increases in the proportions of memory cells, and aging also dysregulates metabolic reprogramming during activation in T cells [7]. Strategies to normalize immunometabolism during aging may therefore have substantial utility as treatments for age-related chronic and infectious diseases.

In recent years, a variety of nutritional strategies have

been popularized which have been shown to improve health- and/or lifespan, at least in model organisms. For the most part, these are based either on some form of short-term fasting (*e.g.,* intermittent fasting, time-restricted feeding) or alterations in dietary macronutrient content. Low carbohydrate ketogenic diets (KDs) are the most prominent example of the latter, and dietary interventions currently have the best evidence supporting a dietary effect on immunometabolism. KD or supplementation with the ketone β-hydroxybutyrate suppresses inflammasome and monocyte activation during coronavirus infection in aged mice [8], and there is a significant body of work indicating that ketones alter cellular metabolic pathways associated with inflammation, including by suppressing glycolytic activation [9]. In addition to KD, other dietary strategies including intermittent fasting and amino acid restriction have anti-inflammatory effects [10], suggesting that dietary changes may be simple interventions that are efficacious in altering immunometabolism and capable of being used in a precision medicine context.

While physical exercise is well known as a driver of metabolic changes in skeletal muscle, heart, and other tissues, to date there is very little published research on its effects on immunometabolism. Long-term moderate aerobic exercise training is generally anti-inflammatory, at least when undertaken by individuals with low-grade inflammatory conditions (including aging) [11]. So far, the limited attempts to characterize metabolism in circulating immune cells have found few changes pre- *vs*. post-exercise, whether this is interrogated after a single exercise bout [12] or after a training intervention [13, 14]. However, exercise redistributes immune cells, thereby shifting their circulating proportions, and most exercise studies to date have examined heterogeneous peripheral blood mononuclear cell populations. This introduces a substantial likelihood of biasing results by measuring different cell populations before and after exercise. Some indirect evidence, primarily from gene expression studies, does suggest that exercise training could increase mitochondrial metabolism in circulating immune cells [11]. So far, though, this has not been conclusively demonstrated directly, and it remains to be demonstrated that exercise-induced immunometabolic changes are linked to the anti-inflammatory effects of regular exercise training.

To summarize, aging results in a multifaceted decline of immune function that promotes (chronic and infectious) disease susceptibility and systemic inflammation. Metabolic reprogramming drives phenotypic and functional changes in immune cells, and there is now emerging evidence that aging alters immunometabolism in ways that may cause immunosenescence and inflammaging. As inexpensive and effective strategies to target metabolism, physical exercise and dietary interventions hold tremendous promise for ameliorating aging-related diseases through immunometabolic reprogramming. While there is some published support for this, especially in the context of dietary interventions, substantially more work is needed to demonstrate that exercise and/or diet can be used to target immunometabolism for precision medicine.

Declarations

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