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Brief Commentary

Special issue on exercise immunology: Current perspectives on aging, health and extreme performance

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ABSTRACT

The aim of this special issue is to highlight outstanding exemplars of empirical research and review papers that reflect the breadth of current developments in exercise immunology. The contributions to this issue are categorized according to four major themes: (1) exercise and immune-aging; (2) the effects of acute exercise on cellular shifts and gene expression; (3) the effects of exercise on immune regulation during stress and disease; and (4) extreme performance and the impact of dietary counter measures on immunity. We discuss the papers appearing in this issue, in accordance with these major themes, and summarize their important contributions to this exciting and expanding field.

1. Introduction

Both physical activity and exercise, whereby the latter term is reserved for motivated physical activity (e.g., to alter body composition or athletic potential), are known to have profound effects on health, well-being and longevity. Notwithstanding, attempts to establish mechanistic links with the immune system is a fairly recent endeavor. Exercise immunology as a discipline came to prominence in the late 1980's through the formation of the International Society of Exercise Immunology (ISEI), with the overarching goal of fostering scientific research that aims to improve health and prevent and treat disease through exercise and physical activity.[1] There is general consensus that prolonged or vigorous bouts of exercise can impair immunity (e.g., increasing infection susceptibility and progression), whereas regular moderate intensity exercise may boost immunity (Nieman, 1994). This assertion was initially supported by observational studies, and more recently the underpinning pathophysiology has begun to unfold through a series of mechanistic studies involving animal models and human clinical trials (Walsh et al., 2011).

The deliberate attention for exercise immunology in this journal should perhaps come as no surprise. Besides the intrinsic behavioral and motivational nature of exercise, the broader psychoneuroimmunology (PNI) community has historically been captivated by the potent effects of physical activity on mood, cognition, motivation (e.g., fatigue), and associated neurobiological processes. There are also strong conceptual overlaps between the two 'behavioral immunology' sub-disciplines; e.g., in the way that neuroendocrine mechanisms have been proposed as key mediators of the effects on immunity. Hence, researchers from both fields tend to take careful note of each other's work, and significant cross-fertilization is apparent in terms of ideas, methods, and techniques. An illustrative example is the immune-enhancement theory, e.g., as formulated by Dhabhar and others (Dhabhar, 2009; Fleshner and Laudenslager, 2004), which in its original formulation emphasized the immunoenhancing effects of acute psychological stress. This framework was readily adopted by exercise immunologists, leading to a fundamental reinterpretation of the immune responses to acute exercise, which were hitherto largely perceived as being immunosuppressive (Edwards et al., 2007).

In 2005, *Brain, Behavior and Immunity* devoted a special issue on exercise immunology, edited by Dr. Jeffery Woods (Woods, 2005). A major theme of that issue was inflammation, which was elegantly exposited by linking the inflammatory regulatory effects

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[1] From here we will use 'exercise' as a general descriptor.

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of exercise with multiple organs, including the brain, skeletal muscle and liver, through a series of human and animal experiments involving cancer survivors, ultra-endurance athletes, and models of heat stress, viral infection and hypersensitivity responses (Woods, 2005). Back then, the inflammation-regulating properties of exercise were still somewhat enigmatic (e.g., what triggers the release of inflammatory factors, from which tissues, what are their main targets/functions?). It is encouraging to note that, almost a decade later, a number of these questions have been answered.

In the current issue on exercise immunology, a major cross-cutting theme once again emerges – that of human aging. Over one-third of the papers explicitly justify their research questions from the perspective of immunological aging or other age-related processes, such as impaired vaccination responses, reduced thymic output, cognitive decline, and in the interaction between exercise and viral latency (in particular cytomegalovirus infection). The latter topic reflects a very novel development, guided by evidence gathered over the last ten years that implicates latent infection with cytomegalovirus (CMV) in immunosenescence, and as a determinant of the functionality and composition of the T cell compartment (Pawelec et al., 2010). Moreover, even in the contributions that did not affirm as a primary aim to understand aging-related processes, the possible implications of the findings are often still elaborately discussed from that perspective.

Gene expression is another theme of the current issue that was not apparent in 2005. The recent expanding use of high throughput DNA and microRNA sequencing technology has undoubtedly facilitated this development, and an increasing number of scientific studies have been appearing in the literature assessing the effects of exercise on the expression of genes, gene pathways and microRNAs involved in inflammatory and disease processes. However, consistent with the aim of this special issue to highlight the breadth of current developments in exercise immunology, aging and gene expression were not the sole themes. While a number of contributions might be rubricated under more than one heading, we have identified the following four major topics to categorize the articles appearing in this special issue:

(i) Exercise, immunity and aging;
(ii) The effects of acute exercise on cellular shifts and gene expression;
(iii) The effects of exercise on stress and disease-related immune regulation;
(iv) The immune effects of extreme performance[2], and the impact of dietary countermeasures.

Here we synthesize the papers appearing in this issue in accordance with these themes, and summarize their important contributions to this exciting and expanding field of research.

2. Exercise, immunity and aging

Immunosenescence is a term used to describe the decline in the functioning of the immune system with advancing age. While this decline is apparent in both innate and adaptive immunity, the latter has been described in more detail and its signature features include, amongst others, reduced thymic output, lower circulating numbers of naïve T-cells, increased proportions of differentiated T-cells, and impaired responses to novel antigens (e.g., vaccination responses). There is ample evidence that latent infection with CMV, which is widespread in the population and typically asymptomatic, drives several of these changes, in particular the dramatic increase in numbers and proportions of differentiated T-cells in peripheral blood. It is specifically these differentiated cells that carry many of the characteristics of aging, such as short telomeres, impaired responsiveness to mitogens, and a high inflammatory potential as evidenced by a high propensity for tissue migration and the release of inflammatory cytokines. An excellent primer on the subject is provided in the invited review paper by Muller and Pawelec (2013), who in addition discuss the evidence on how age-related changes to immunity can be attenuated through different kinds of behavioral, psychological and nutritional interventions that capitalize on the inherent plasticity of the immune and neuroendocrine systems.

Intervening in age related immune decline is also a main focus of the review by Pascoe et al. (2013) on exercise and vaccination, a topic that has garnered a great deal of research attention in recent years. Vaccination is at the crux of preventing influenza and pneumonia related fatalities in older adults. It is inauspicious, however, that this intervention does not always elicit protective immunity in this group. Hence, there is a need to enhance vaccine responses through adjuvants that are cost-effective and free of debilitating side effects. Exercise immunologists have explored a variety of approaches, ranging from extended exercise-training programs (Woods et al., 2009) to administering vaccines immediately after a single exercise bout (Edwards et al., 2008). In a comprehensive review of human studies, Pascoe et al. (2013) conclude that most studies confirm benefits of acute or chronic exercise. They also note a need to examine these adjuvant effects in cohorts with known immune system impairment, e.g., in older adults or clinical populations. Another critical issue is that while adjuvant effects of exercise have been demonstrated for immune outcomes (e.g., antibody titers, *in vitro* stimulation tests), it still has to be determined if this translates to de facto protection by reducing the incidence or severity of those illnesses for which the vaccines are given as a prophylactic. By addressing these and related issues, this excellent review provides both an up-to-date overview of empirical findings as well as a clear agenda for human clinical trials in this area.

Two original research articles appearing in this issue are concerned with the effects of habitual high volume/high intensity training on thymic output. The thymus is essential for the production of naïve T-cells, but its output undergoes profound age-related decline starting as early as young adulthood. In the absence of 'new recruits', there is an increasing reliance on expansions within the existing T-cell pool to maintain T-cell diversity with advancing age. A large number of endocrine factors, including glucocorticoids and metabolic hormones, are known to affect thymic involution, so the idea of studying this process in an exercise context is compelling. Prieto-Hinojosa et al. (2014) compared thymic activity in young British national standard triathletes with that of healthy and non-elite age-matched controls, through the measurement of signal-joint T cell receptor excision circles (TREC) in circulating T-cells. They observed strikingly low TREC levels in the athletes (more so in the CD4+ than the CD8+ subset), suggesting that the demands of high-level endurance training may contribute to premature age-associated changes to the T-cell compartment. These findings were largely consistent with the findings reported in this issue by Moro-Garcia et al. (2013), who compared several immunological parameters between older and younger athletes with age-matched non-athlete controls. They likewise report lower TREC levels in young athletes exposed to exceptionally high training volumes compared to controls. However, in contrast to Prieto-Hinojosa et al. (2014), these differences were seen in CD8+ T cells but not CD4+ T-cells. These authors further show that lower thymic activity in athletes is accompanied by reductions in T-cell activation/proliferation, increased frequency of differentiated T-cells, and a lower CD4:CD8 T-cell ratio. These formative contributions

[2] The term 'extreme performance' has been used in this issue to denote those types of activities that would not typically be performed by the vast majority of the general population (e.g., intensive exercise training, marathon running, operating in adverse environmental conditions).