Review

CellPress

The immunomodulating role of exercise in metabolic disease

Graeme I. Lancaster and Mark A. Febbraio

Cellular and Molecular Metabolism Laboratory, Baker IDI Heart and Diabetes Institute, Melbourne, Australia

A lack of physical activity is linked to the development of many chronic diseases. It is now well established that the immune system and inflammation play a central role in the development of numerous chronic metabolic diseases including insulin resistance, type 2 diabetes, atherosclerosis, nonalcoholic fatty liver disease, and specific types of cancer. Physical exercise elicits potent anti-inflammatory effects that are likely to account for many of the salutary actions of regular exercise on chronic metabolic diseases. Here we review the anti-inflammatory and immunomodulatory mechanisms by which the beneficial effects of exercise on chronic metabolic diseases may be mediated.

Inflammation at the nexus of metabolic disease

The World Health Organization has estimated that in excess of 1 billion people worldwide are overweight, with 300 million defined as clinically obese. Obesity is associated with the development of a cluster of chronic metabolic diseases such as insulin resistance, type 2 diabetes, atherosclerosis, nonalcoholic liver disease, hypertension, and some forms of cancer [1]. Physical inactivity is major contributor to the development of chronic metabolic diseases [2]. Furthermore, regular exercise prevents, or at least delays, the progression of a host of metabolic diseases including cardiovascular disease, insulin resistance, type 2 diabetes, and hypertension [2]. Indeed, it has been observed that exercise as a therapeutic intervention can be as effective as the medications that are prescribed for chronic metabolic diseases [3,4]. Although some of the beneficial effects of exercise in chronic metabolic diseases are likely to be attributable to an increase in energy expenditure and consequently a reduction in the accumulation of fat mass in individuals who consume calories in excess of their daily requirements, numerous studies have demonstrated that the salutary actions of exercise are independent of its effect on weight loss [5]. Exercise promotes numerous molecular and cellular changes in several tissues and these adaptations are likely to underpin many of the salutary actions of exercise.

Corresponding authors: Lancaster, G.I. (graeme.lancaster@bakeridi.edu.au); Febbraio, M.A. (mark.febbraio@bakeridi.edu.au).

Keywords: exercise; muscle; immune cells; inflammation; metabolic disease; anti-inflammatory.

1471-4906/$ – see front matter

 http://dx.doi.org/10.1016/j.it.2014.02.008

The past two decades have identified inflammation as a key nexus between obesity and the development of chronic metabolic diseases [1]. A plethora of studies have described how inappropriate activation of components of the immune system and induction of local inflammation in key cells and tissues underpins the development of chronic metabolic diseases. For example, in obesity the immune cell profile of the adipose tissue is substantially altered such that proinflammatory macrophages, neutrophils, and $CD8^+$ T lymphocytes accumulate, while regulatory T cells and eosinophils decrease, and initiate a state of local inflammation that contributes to the development of systemic insulin resistance. In cardiovascular disease, immune cells accumulate within the arterial vasculature and contribute to the formation of atherosclerotic plaques [6–8].

Exercise elicits potent and wide-ranging effects on the immune system [9,10], principle amongst these being its anti-inflammatory effects. Although exercise can be proinflammatory and has, in some instances, been associated with increased production of proinflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and C-reactive protein, this is typically only the case after extreme forms of exercise such as marathon running or Ironman triathlon, which are associated with muscle damage and even systemic endotoxemia [11,12]. However, in most instances exercise is anti-inflammatory in nature. The cytokine profile induced by exercise is classically anti-inflammatory, comprising marked increases in the levels of several potent anti-inflammatory cytokines such as IL-10, IL-1 receptor antagonist (IL-1ra), and IL-6 [12]. An elegant and powerful demonstration of the anti-inflammatory effects of exercise is the observation that prolonged cycling exercise reduced endotoxin-induced TNF-α production *in vivo* in humans [13]. Preventing or attenuating inflammation is likely to be an important mechanism by which physical activity and exercise protect against the development of chronic metabolic diseases [3,14].

Here we discuss some of the latest research on the anti-inflammatory effects of exercise in the context of chronic metabolic diseases (Figure 1), outline several novel hypotheses, and highlight areas for further research. Specifically, we discuss how exercise can impact on several tissues that are deleteriously affected in metabolic disease, such as adipose tissue – a key site in the control of systemic metabolism – and liver and skeletal muscle. We also discuss the role of exercise as a modulator of Toll-like receptor (TLR) function and how this may counteract some of the negative effects of obesity. Finally, we discuss the

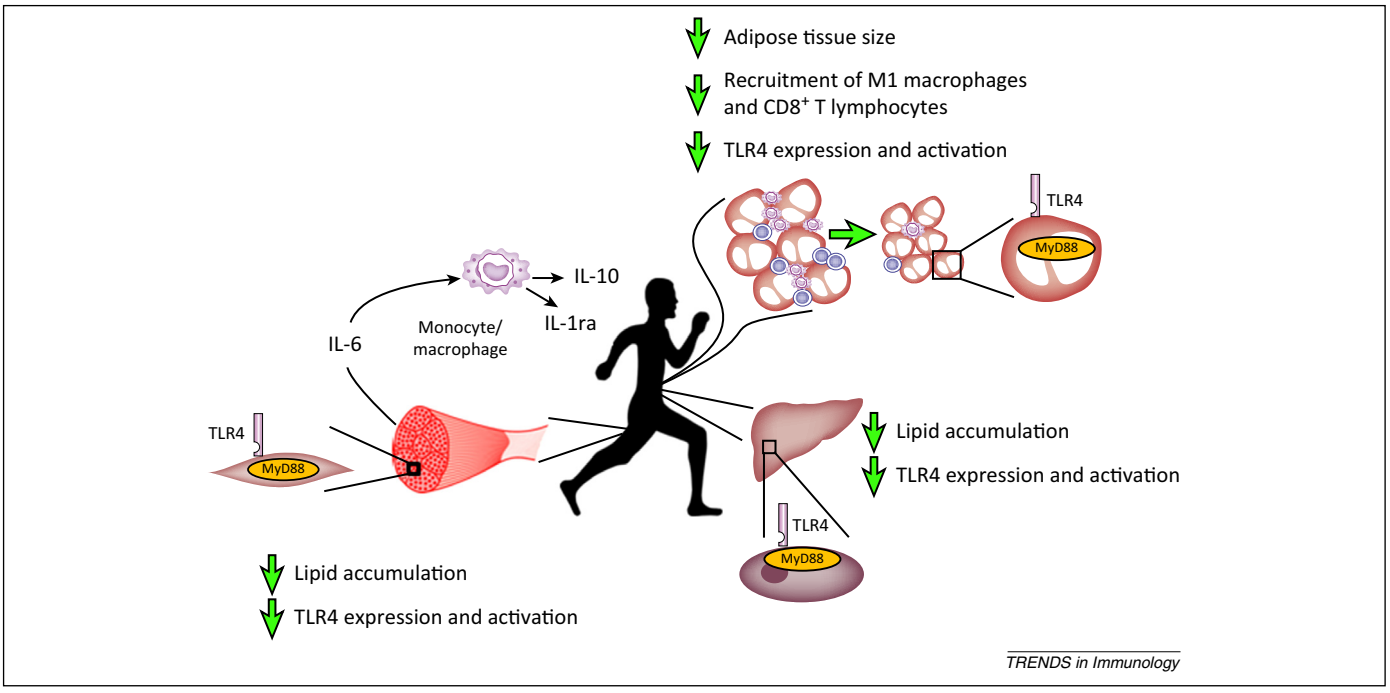

Figure 1. The anti-inflammatory effects of exercise in the context of obesity. As discussed in the text, exercise may mediate potent salutary actions in the context of metabolic disease via its anti-inflammatory effects. Given the proinflammatory effects of several lipids, limiting lipid accumulation, either by limiting the expansion of adipose tissue or by decreasing the accumulation of lipid in the skeletal muscle and liver, is likely to be a key anti-inflammatory effect of exercise. Furthermore, by inhibiting the expansion of adipose tissue, exercise limits the recruitment of proinflammatory M1 macrophages and $CD8^+$ T lymphocytes, cells known to promote insulin resistance. It is well established that exercising muscle releases myokines. The release of interleukin-6 (IL-6) from skeletal muscle and subsequent production of IL-1 receptor antagonist (IL-1ra) by monocytes and macrophages may represent an important anti-inflammatory action of exercise. Finally, exercise can decrease the expression and activation of Toll-like receptor 4 (TLR4) in several tissue and cell types and this may contribute to exercise's ability to protect against the deleterious effects of obesity.

role of IL-1β and the inflammasome in metabolic diseases and suggest that a primary anti-inflammatory effect of exercise may be via the inhibition of IL-1 signaling (Figure 1).

Obesity and adipose tissue-resident immune cells

A hallmark of obesity is a shift in the immune cell profile of the adipose tissue [8]. Thus, the proportion of resident M2 anti-inflammatory, alternatively activated macrophages [15], eosinophils [16], and $CD4^+$ T lymphocytes [17] decreases and the proportions of M1 proinflammatory, classically activated macrophages [15], neutrophils [18], B lymphocytes [19] and $CD8^+$ T lymphocytes [17] are increased. Mechanistically, this change in the adipose tissue immune cell profile initiates a state of local inflammation within the adipose tissue that induces both local and systemic insulin resistance. Remarkably, the targeted deletion of even a single immune cell type through genetic or antibody-mediated approaches can protect against the development of insulin resistance in mice fed a high-fat diet [17–20]. It is likely that the obesity-associated transition of the adipose tissue immune cell profile from principally anti-inflammatory cell types toward proinflammatory cell types is a key event initiating the development of local and systemic insulin resistance [8]. Several hypotheses have been proposed to explain the key events that lead to the shift in the adipose tissue immune cell profile in obesity [8]. The death of adipocytes within the adipose tissue, adipose tissue hypoxia, production of chemotactic factors, and increased free fatty acid (FFA) fluxes have all been proposed to regulate the obesity-associated shift in the immune cell profile [21]; however, in each instance adipose tissue expansion due to adipocyte hypertrophy is central. An increase in adipose tissue mass is a hallmark of human obesity. A key beneficial effect of exercise is via its effects on weight loss and/or the prevention of weight gain. Accordingly, by limiting the expansion of adipose tissue, exercise would be predicted to ameliorate obesity-induced changes in the adipose tissue immune cell profile and, importantly, contribute to the maintenance of whole-body insulin sensitivity.

Several studies have shown that chronic exercise training in mice fed a high-fat diet, which is associated with reductions in adipose tissue mass, results in a marked reduction in the levels of proinflammatory cytokines in adipose tissue compared with non-exercising controls [22–25]. Importantly, this reduction in adipose tissue inflammation following exercise training is associated with a substantial reduction in macrophage adipose tissue content [22–25], an effect that is probably attributable to a decrease in the recruitment of M1 proinflammatory macrophages [23,24]. Chronic exercise training was also associated with an increase in the expression of CD163, a marker of M2 macrophages [24]. Studies examining adipose tissue inflammation in humans following exercise are limited, but there is experimental support that a combination of diet and exercise reduces adipose tissue inflammation and macrophage recruitment [26], although others report little effect of endurance training alone on adipose tissue inflammation [27]. Of note, however, in this latter study, endurance exercise training increased the number of $CD163^+$ cells within the adipose tissue, indicative of increased