Introduction

In developed countries, metabolic syndrome is increasing rapidly due to changes in lifestyle such as inactivity and overeating. It is clear that inadequate physical activity can result in obesity, type 2 diabetes, atherosclerosis and nonalcoholic steatohepatitis (NASH). However, physical activity effectively prevents the development of metabolic syndrome. Therefore, interventions including exercise and nutrition that improve metabolic syndrome constitute important therapeutic strategies.

Recently, the innate immune system via macrophages and lymphocytes has been associated with the development of chronic inflammation, which is correlated with inducing insulin resistance, dyslipidemia and hypertension. Chronic inflammation is also associated with local inflammatory response in adipose tissue and liver. Tissue resident macrophages release inflammatory cytokines and reactive oxygen species, which induce systemic inflammation. Obese patients display high plasma levels of pro-inflammatory cytokines and oxidative stress biomarkers. Exercise has anti-inflammatory effects and may prevent the development of chronic inflammatory diseases. Regular exercise appears to reduce the plasma concentrations of inflammatory mediators such as pro-inflammatory cytokines and reactive oxygen species in obese patients. Therefore, increasing physical activity can lead to a reduction in systemic inflammation via a decrease in pro-inflammatory mediator secretion. To elucidate the mechanisms of chronic inflammation improvement and/or prevention in the local tissue due to exercise is important for the development of effective exercise therapy. This review provides information to elucidate the molecular mechanisms from the perspective of immune regulation of the improvement in chronic inflammation due to exercise.

Effects of exercise on local tissue inflammation in obesity

Obesity is associated with the pathogenesis of chronic inflammatory diseases, which in turn has been largely attributed to chronic local tissue inflammation in visceral adipose tissue. Several inflammatory mediators such as pro-inflammatory cytokines and chemokines are secreted from adipocytes and macrophages. Several important cytokines and chemokines are implicated in tissue dysfunction, including tumor necrosis factor (TNF)-α, interleukin (IL)-6, and monocyte chemoattractant protein (MCP)-1. Pro-inflammatory cytokines such as TNF-α is known to induce adipocyte death through activation of apoptosis signaling. Moreover, chemokines such as MCP-1 and macrophage inflammatory protein (MIP)-1, are responsible for activating and infiltrating macrophages in tissue area, which contributes to local tissue inflammation. There is evidence that the expression of pro-inflammatory cytokines and chemokines in adipose tissue and liver are...
increased in obese humans and mice\textsuperscript{11,12}. These inflammatory proteins can be released into the circulation, resulting in chronic systemic low-grade inflammation, which is associated with insulin resistance. Thus, these mediators are a marker for evaluating the inflammatory state of local tissue induced by obesity.

Several recent studies have examined the effects of exercise on reducing adipose tissue inflammation in obese mice. In mice on a high-fat diet for 16 weeks, endurance exercise has been shown to reduce gene expression of inflammatory markers (such as TNF-α and MCP-1) in visceral adipose tissue and liver\textsuperscript{13,14,19}. Vieira et al.\textsuperscript{19} also reported that 12 weeks of endurance exercise decreased gene expression of TNF-α and MCP-1 in the visceral adipose tissue in obese mice. Moreover, several studies have shown that gene expression of TNF-α and MCP-1 in visceral adipose tissue was reduced in voluntary exercising mice, even when the mice continued to consume a high-fat diet\textsuperscript{16,17}. Similarly, in humans, intermittent high-intensity exercise for two weeks reduced IL-6 protein levels in subcutaneous adipose tissue of obese individuals\textsuperscript{18}. Furthermore, a 15-week lifestyle intervention incorporating exercise and diet was associated with decreased gene expression of IL-6, TNF-α, and MCP-1 in subcutaneous adipose tissue of obese individuals\textsuperscript{19}. Also, obesity-induced muscle inflammation was reported\textsuperscript{20}. However, 12 weeks of combined endurance and resistance exercise resulted in decreased TNF-α and IL-6 gene expression in skeletal muscle of obese individuals\textsuperscript{21}. In addition, Jung et al.\textsuperscript{21} also reported that high expressions of TNF-α and IL-6 in skeletal muscle after high-fat diet were normalized after 3 weeks of endurance exercise. Taken together, these findings provide evidence to support that regular exercise reduces the development of local tissue inflammation associated with obesity.

Recently, it was shown that weight loss by caloric restriction and exercise resulted in improvement of adipose tissue inflammation\textsuperscript{22}. Exercise appears to be an important intervention for decreasing weight gain, but the contribution of weight loss from exercise in the reduction of adipose tissue inflammation is unclear. Indeed, data from several studies suggest that regular endurance exercise-induced weight loss resulted in a decrease in local tissue inflammation\textsuperscript{23}. However, it was shown that regular endurance exercise in obese mice decreased gene expression of pro-inflammatory cytokines in adipose tissue and liver without loss of weight\textsuperscript{23,24}. Therefore, the reduction of inflammation in both adipose tissue and liver might directly depend on regular exercise.

Preventive effect of exercise on chronic inflammatory disease

NASH is an important component of metabolic syndrome, which is characterized by insulin resistance, dyslipidemia, and hypertension. The innate immune system plays a key role in the development of NASH\textsuperscript{25}. Kupffer cells (also known as Browicz-Kupffer cells and stellate macrophages), hepatic resident macrophages, produce various pro-inflammatory cytokines and reactive oxygen species, which enhance hepatic inflammation and fibrosis\textsuperscript{26}. Chronic exercise may prevent or reduce the severity of NASH\textsuperscript{27}. In patients with NASH, physical activity level was negatively associated with the state of fibrosis\textsuperscript{28}; and chronic exercise reduces the serum aminotransferase levels as a marker of hepatic injury\textsuperscript{29}. Moreover, regular exercise training also improves serum aminotransferase levels and hepatic steatosis in obese mice\textsuperscript{30,31}. However, the mechanism of how exercise training attenuates the development of hepatic inflammation and fibrosis remains unclear.

A very recent study found that regular exercise drastically attenuates hepatic inflammation and fibrosis, indicating the positive effects of exercise on improvement of NASH. In the experimental model frequently used to induce NASH (high-fat diet and high-fructose water feeding), it was shown that the TNF-α protein content in liver was increased after a 16-week feeding, while 16 weeks of endurance exercise induced a significant decrease in hepatic TNF-α content\textsuperscript{24}. Similarly, Jung et al.\textsuperscript{21} reported that hepatic protein levels of IL-6 and TNF-α were elevated after a high-fat diet, but reduced after 3 weeks of endurance exercise. Furthermore, we showed that 16 weeks of endurance exercise induced decreases in collagen deposition and mRNA levels of fibrogenic markers such as collagen type 1 α and tissue inhibitor of metalloproteinase (TIMP)-1\textsuperscript{24}. Also, in a human study, Promrat et al.\textsuperscript{32} demonstrated that 48 weeks of exercise reduced steatosis and the inflammatory score in NASH patients. Taken together, these findings suggest that regular endurance exercise may prevent or improve NASH. Interestingly, recent studies observed that regular endurance exercise in diet-induced obese mice attenuated macrophage infiltration in the liver\textsuperscript{21,24}. A recent study proposed that macrophages play pathogenic roles in NASH, because macrophage-depleted mice showed both lower hepatic inflammation and fibrosis than normal mice\textsuperscript{33}. Collectively, our findings indicate that the reduction in hepatic inflammation and fibrosis by regular endurance exercise is associated with suppression of macrophage infiltration.

Changes in the number and subset composition of leukocytes

Adipose tissue consists of a variety of cell types including adipocytes, endothelial cells, and immune cells. Recently, it has been shown that the innate immune response mainly mediated by macrophages and lymphocytes is key to the inflammatory process in adipose tissue\textsuperscript{34}. Recent studies showed enhanced infiltration of macrophages and lymphocytes in high-fat diet-induced obesity in mice\textsuperscript{35,36}. Our studies and those of others showed that regular en-
Endurance exercise in obese mice reduced mRNA levels of macrophage markers such as F4/80 in adipose tissue\textsuperscript{13,15}. Furthermore, we also analyzed the characteristics of the cell types in adipose tissue by flow cytometry, and found that 16 weeks of endurance exercise in diet-induced obesity in mice decreased the cell number of macrophages and lymphocytes in visceral adipose tissue. Similarly, Xu et al.\textsuperscript{37} reported that 8 weeks of endurance exercise also acts to decrease macrophage contents in the visceral adipose tissue in obese mice. Interestingly, macrophage activation has been operationally classified into two separate polarization states\textsuperscript{38}. M1 macrophages produce inflammatory cytokines such as TNF-\(\alpha\) and IL-6. In contrast, M2 macrophages produce IL-10, which suppresses inflammation and oxidative stress. Lumeng et al.\textsuperscript{39} reported that mice with high-fat diet-induced obesity show a phenotypic switching from M2 macrophages to M1 macrophages in adipose tissue. On the other hand, cytotoxic CD8\(^+\) T cells produce chemokines such as MCP-1 and MIP-1\(\alpha\), which modulate the activation and infiltration of macrophages in adipose tissue\textsuperscript{34}. In contrast, helper CD4\(^+\) T cells produce cytokines such as IL-4 and IL-10, which suppress macrophage infiltration\textsuperscript{40}. Therefore, M1 macrophages and CD8\(^+\) T cells have been shown to play critical roles in the associated adipose tissue inflammation. Wasinski et al.\textsuperscript{41} reported that the number of CD8\(^+\) T cells in adipose tissue decreased after 6 weeks of endurance exercise. We also found that 16 weeks of endurance exercise decreased the cell number of M1 macrophages and CD8\(^+\) T cells, and changed the ratio of macrophage and T cell subsets in obese adipose tissue\textsuperscript{46}. In contrast to the decreased ratio of M1 macrophages and CD8\(^+\) T cells, the ratio of M2 macrophages and CD4\(^+\) T cells remained unchanged after 16 weeks of endurance exercise. Interestingly, this phenomenon was unique to visceral adipose tissue, because the macrophages and T cell subsets in the spleen and blood leukocytes did not change with 16 weeks of endurance exercise training. These results indicate that regular endurance exercise may improve adipose tissue inflammation by changing the number and subset composition of leukocytes (Fig. 1).

**Future prospects**

Aberrant action of the innate immune response, mainly by macrophages, is important for development of an inflammatory state of local tissue. Interestingly, it is reported that the adaptive immune system plays a key role in the development of chronic inflammation in visceral adipose tissue in addition to the innate immune system\textsuperscript{42}. Recently, several studies have investigated the role of specific subsets of T cells or B cells in adipose tissue. CD4\(^+\) helper T cell activation has been operationally defined as several separate polarization states such as Th17 and reg-

![Fig. 1](image.png)

**Fig. 1** Mechanisms of the anti-inflammatory effects of regular exercise.

Physical inactivity and overeating lead to an infiltration of inflammatory macrophages (M1) and CD8\(^+\) T cells into visceral adipose tissue. M1 macrophages and CD8\(^+\) T cells release pro-inflammatory mediators such as TNF-\(\alpha\), IL-6 and MCP-1, which increase risk for local and systemic chronic inflammation. Regular exercise induces change in the number and subset composition of macrophages and T cells, reducing the ratio of M1 to M2 macrophages and the ratio of CD8\(^+\) T cells to CD4\(^+\) T cells. M2 macrophages release anti-inflammatory mediators such as IL-4 and IL-10, which leads to a reduction in inflammation. Thus, regular exercise attenuates the development of diabetes and NASH.

TNF, tumor necrosis factor; IL-6, interleukin-6; NASH, nonalcoholic steatohepatitis.
ulatory T cells, which are associated with the induction of adipose tissue inflammation\textsuperscript{43}. Th17 cells were increased, while regulatory T cells which decreased in adipose tissue after feeding a high-fat diet\textsuperscript{44,45}. Th17 cells increase and these cells produce MCP-1, which induces macrophage infiltration and adipose tissue inflammation\textsuperscript{46}. In contrast, regulatory T cells have also been shown to inhibit macrophage activation\textsuperscript{47}. Furthermore, obesity has been shown to increase infiltration of mature B cells into visceral adipose tissue. Mature B cells also produce pathogenic IgG antibodies that cause the activation of T cells and macrophages\textsuperscript{48}. Thus, these results show that Th17, regulatory T cells and B cells potentiate macrophage and T cell polarization, which promote obesity-related local/systemic chronic inflammation (Fig. 2). Further work will be required to determine whether regular exercise affects the adaptive immune system via altering CD4\textsuperscript{+} helper T cells and B cell polarization.

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**Fig. 2 Development of obesity-related chronic inflammation via innate immune and adaptive immune systems.**

In early obesity, there is a shift in T cell populations towards Th17 cell polarization, and B cell infiltration of visceral adipose tissue. Helper T cells and B cells increase the recruitment of M1 macrophages and CD8\textsuperscript{+} T cells into visceral adipose tissue, and promote the aberrant action of the innate immune system. TNF, tumor necrosis factor; IFN, interferon; IL, interleukin; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein.

**References**


