Exercise Regulates the Immune System

27

Jing Wang, Shuqin Liu, Guoping Li, and Junjie Xiao

Abstract

The profound effect of exercise on the normal functioning of the immune system has been well-known. Exercise and immune regulation are interrelated and affect each other. Exercise changes immune regulation by affecting leucocytes, red blood cells, and cytokines, etc. Regular exercise could reduce the risk of chronic metabolic and cardiorespiratory diseases, partially by the anti-inflammatory effects of exercise. However, these effects are also likely to be responsible for the suppressed immunity that make our bodies more susceptible to infections. Here we summarize the known mechanisms by which exercise—both acute and chronic—exerts its immune regulation effects.

Keywords

Acute exercise · Chronic exercise · Innate immune system · Adaptive immune system

J. Wang · S. Liu · J. Xiao (✉)
Cardiac Regeneration and Ageing Lab, Institute of Cardiovascular Sciences, School of Life Science, Shanghai University, Shanghai, China
e-mail: junjiexiao@shu.edu.cn

G. Li
Cardiovascular Division of the Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

27.1 Background

A complex network of cells and molecules construct the immune system, which function to protect our bodies from invading microorganisms, facilitate wound healing, and prevent disease. The immune system contains innate (nonspecific, nature) and adaptive (specific, repetitive) immunity, and both immune systems work synergistically in the overall immune response. In the immune response, adaptive immune cells function to release messenger molecules and cytokines that regulate immune system especially innate immune cell function, while cells from innate immune system help facilitate specific immune responses through antigen presentation [1, 2]. The immune system not only protects our bodies against infection but also influences other physiological systems and their processes, including metabolism, sleep/fatigue, tissue repair, mental health, and thermoregulation [3–5]. Based on the recognition that stress responses mediated through the endocrine and nervous systems play a key role in determining exercise-induced immune changes and that the immune system mediates many exercise effects, the exercise immunology has developed into its own discipline during the past four decades [6].

Compared with many branches of the exercise sciences, exercise immunology has quite a short history. The modern era of careful epidemiological investigations and precise laboratory studies

J. Xiao (ed.), *Physical Exercise for Human Health*, Advances in Experimental Medicine and Biology 1228, https://doi.org/10.1007/978-981-15-1792-1_27

began in the mid-1980s. The early work of David Nieman piqued the interest in the effect of exercise on the immune system, by reporting that people with a more serious commitment to regular exercise may experience less infectious episodes such as upper respiratory tract infections (URTI) than their sedentary peers because of both direct and indirect effects on immunosurveillance; conversely, those engaged in stressful race experience appeared to be at a greater risk of infection than those who remained sedentary [7–9]. Thus, the link between exercise and the immune system in people who exercise has become a prominent focus area in the sports science and medicine communities since the formation of the International Society of Exercise and Immunology (ISEI) in 1989 [10, 11]. It is generally recognized that regular moderate-intensity exercise is beneficial for our bodies, while prolonged periods of intensive exercise training can depress immunity [12]. The immune responses to exercise are organized, and specific immune cells are redistributed for defined functional purposes. Most studies about the effects of exercise on the immune system are focused on the impact of the chronic effects of exercise training as well as the acute bouts of exercise. Both acute and chronic exercise have shown significant response in the area of leukocyte redistribution, activity, trafficking, and function [11, 13]. The intensity, duration, and volume of exercise have been reported to influence the redistribution of immune cells into the circulation associated with exercise [14–17]. In most of the exercise immunology studies, which type of exercise training can improve immune function in athletes, the elderly, and diseased patients is of great concern. In this chapter, we will describe the effects of chronic and acute exercise on immune responses and some strategies for restoring immune function after exercise.

27.2 The Effects of Exercise on Innate Immune Cells

As one of the two main immunity strategies found in vertebrates, the innate immune system is also known as the nonspecific immune system or in-born immune system, which is a semi-specific and widely distributed form of immunity [18]. The innate immunity includes both cells and soluble factors, which represents the first line of defense against pathogens. Major cells of this immune system include neutrophils, macrophages, dendritic cells (DCs), and natural killer (NK) cells. Soluble factors of the innate immune system include complement proteins and antimicrobial peptides [19]. Beside these innate immune cells and factors, many host cells can also initiate responses to a pathogenic infection. Here we will focus on exercise and the innate immune cells and the inflammatory cytokines which constitute the products of these immune cells.

27.2.1 Exercise and Neutrophils

Neutrophils, as the first-line defenders against bacterial infection in innate immunity, has been a popular cell type to study in the field of exercise immunology. A single bout of exercise has a profound effect on the total number and composition of circulating neutrophils [11]. Following a bout of high-dose resistance exercise, the neutrophils may remain elevated and peak up threefold post exercise [20–23], whereas prolonged endurance exercise (0.5–3 h) may cause neutrophil count to increase up to fivefold [24]. Although the increased number of not only neutrophils but also other immune cells is often indicative of infection and inflammation, exercise-induced immune cell counts typically return to pre-exercise levels within 6–24 h after exercise cessation [25].

Regular exercise training studies in leukocytes reported that leukocyte count in blood circulation does not change, including that of neutrophils [26]. In endurance aerobic exercise training studies, neutrophil counts significantly decreased after exercise therapy in those with chronic inflammatory conditions. This count was correlated with percent changes in insulin sensitivity index, body mass index, maximal oxygen uptake (VO2max), and fasting triglyceride analysis [27]. Whether this effect is deleterious or beneficial is dependent upon the context. Of note, in a resistance exercise study, it was found that the change in the number of circulation neutrophils can occur more rapidly following a bout of higher-volume/lower-intensity (5 × 10 reps, 80%-1 RM) vs. lower-volume/higher intensity (15 × 1 reps, 100%-1 RM) resistance exercise [28]. However, in another high-dose resistance study, there were no detected changes in neutrophil count [29]. It is not clear till now to determine clearly why different exercise temporal profiles vary for neutrophils in the literature.

The change in the number of neutrophils in blood was rapid and profoundly raised the first time after acute exercise, followed by a second, delayed increase a few hours later, which was associated with both the duration and intensity of the exercise [16, 30]. These immediate and delayed neutrophilic leukocytoses induced by exercise are mediated respectively by catecholamine and cortisol [31]. The ability to adhere to the endothelium is the initial step of neutrophil migration to sites of infection or injury. However, acute intensity exercise was reported to enhance neutrophil chemotaxis and phagocytosis but not their ability to adhere to the endothelium [32, 33]. The acute bout of exercise could reduce the oxidative burst and degranulation of neutrophils in response to bacterial stimulation that can last for long times. Also, this exercise could increase the unstimulated neutrophil phagocytosis, degranulation, and oxidative burst activity [16, 30, 34]. All these results indicated that acute exercise might reduce neutrophils' ability to respond to exogenous stimulation but mobilize highly functional neutrophils into the circulation blood and increase spontaneous neutrophil degranulation [35]. Although there are more studies of neutrophils in acute and chronic exercise training, little is known about the influence of exercise training on neutrophil function, which needs further study.

27.2.2 Exercise and Monocytes/Macrophage

Monocytes are the largest type of leukocytes that circulate in the blood and then migrate into tissues, where they mature into macrophages and myeloid lineage dendritic cells. These maturations are essential in tissue regeneration, recovery, and repair through processes including promotion of minisatellite cell stimulation and phagocytosis [36]. Classical ($CD14^{hi}CD16^{-}$) and nonclassical ($CD14^{low}CD16^{+}$ or $CD14^{hi}CD16^{+}$) are two main populations of monocytes. The inflammatory nonclassical ($CD14^{low}CD16^{+}$) monocytes express 2.5 times as much cell surface TLR4 as the other classical monocytes, which is driven by TNF-α [37]. Regular exercise appears to reduce the number of inflammatory monocytes ($CD14^{low}CD16^{+}$) in blood at the resting state. In the studies of cross-sectional and longitudinal exercise training, people with physically training exhibit a lower percentage of inflammatory monocytes, lower surface TLR4 expression, and reduced circulation monocyte inflammatory responses to lipopolysaccharide (LPS) [38–43]. The anti-inflammatory effect of exercise on these monocytes in tissue is still unclear. But in the mouse model studies, induced inflammatory responses of peritoneal macrophages were induced by exercise training, indicating a possible different effect of exercise on circular blood monocytes and tissue macrophages [44–46]. In obese mice studies, regular exercise training reduced systemic inflammation in high fat diet-fed mice [47, 48]. The macrophage infiltration into other sites of chronic inflammation has also been reported to be reduced by regular exercise training [49]. All these animal studies showed more evidence to demonstrate the anti-inflammatory effect of regular exercise.

After a single, acute bout of intense exercise, there was a transient increase in the number of inflammatory monocytes, which then returned to the baseline number during recovery [50]. This transient (~2 h) increase in monocytes most likely represents a migration of monocytes from the margins to the circulating pool [51]. In response to acute exercise, the preferential mobilization of $CD14^+CD16^+$ monocytes exhibited an inflammatory phenotype relative to $CD14^+CD16^-$ monocytes [52, 53]. Then the percentage of these $CD14^+CD16^+$ monocytes reduced in recovery, practically due to tissue recruitment or remarginalization [50]. These cells had a more inflammatory function to entry into tissues and were knocked off the endothelium in response to exercise. The cytokine production of monocytes was also influenced after acute exercise. Although spontaneous cytokine levels of $CD14^+$ monocytes did not change so much, the interleukin-6 (IL-6), IL1-α, and tumor necrosis factor-α (TNF-α) were significantly reduced post acute exercise, perhaps due to the reduced expression of LTR on the surface of monocytes [54–57]. In resistance exercise studies, an acute bout of resistance exercise also induced an acute increase in the number of circulation monocytes. The monocyte values returned to baseline between 15 and 30 min after high-dose resistance exercise or peaked at 120 min after the exercise cessation, due to different exercise doses [21, 22, 28].

Macrophages can be divided into two separate states: M1 and M2 macrophages. M1 macrophages always produce IL-6, nitric oxide, and TNF, which is an inflammatory state, whereas M2 macrophages produce anti-inflammatory cytokines and arginase [58]. Because there are little macrophages in circulation blood and most of them are matured in tissue, the study of acute exercise and macrophages in human are limited. In animal studies, prolonged exercise could reduce the antigen presentation ability of macrophages and the surface MHC II expression [59–61]. Acute exercise was reported to have potent stimulatory effects on M1 and M2 macrophages phagocytosis, nitrogen metabolism, chemotaxis, antitumor activity, and reactive oxygen [51, 62, 63].

27.2.3 Exercise and Dendric Cells

In human exercise studies, a single bout of dynamic exercise by healthy adults enhanced the generation of monocyte-derived DCs, but the functional consequences of this observation remained poorly understood [64]. The circulating number of DCs was detected to be increased after exercise, and this mobilization of DCs may be less prone to drive inflammatory processes [65, 66]. In animal models, the mixed leukocyte reaction, surface MHC II expression, and IL-12 production were significantly increased in DCs from regular exercise training; however, the costimulatory molecule of these DCs such as CD80 and CD86 showed no difference after training [67, 68]. During aerobic exercise, there is a preferential mobilization of plasmacytoid DCs. Due to the functional repertoire of plasmacytoid DCs, which includes production of interferons against viral and bacterial pathogens, exercise may improve immune-surveillance through preferentially mobilizing these DC effector cells [69]. However, there is very little information on the effects of exercise on DCs, which needs more investigation.

27.2.4 Exercise and Natural Killer Cells

Since NK cells are easy to study and exhibit a large magnitude change in response to exercise, they have received significant attention in the exercise immunology literature [11]. There existed much controversy on the effects of exercise training on NK cells, despite the fact that many results demonstrated the effects of exercise on NK cell function and number. Like other circulation leukocytes, through increased catecholamine-induced downregulation of adhesion molecule expression and shear stress, NK cells were immediately mobilized into the circulation in response to acute exercise [70, 71]. But after prolonged exercise, the number of NK cells in peripheral blood circulation was decreased, partially due to the tissue migration or remarginalization [71]. In a high-dose resistance exer-

cise (60–100%-1 RM at different volumes), the number of NK cells can be increased and sustained 15-min post exercise [21, 22]. Additionally, $CD16^+/CD56^+$ NK cell number was reported to reestablish to baseline values by 3-h post the prolonged aerobic exercise [20]. The varied count of $CD16^+/CD56^+$ NK cells was associated with the intensities and volumes of exercise. However, in contrast to other lymphocytes, there was no change in $CD16^+/CD56^+$ NK cell count under a low-dose bout of resistance exercise [72].

The key function of NK cells is innate cytotoxicity; NK cells are primarily known to characteristically secrete interferon gamma (IFN-γ) and induce cell death of infected cells. NK cell cytotoxicity was an well-known major functional measure of NK activity [73]. Early intervention or cross-sectional studies detected modest increases in NK cell cytotoxicity after moderate exercise training [74–76]. Beside this, A single bout of exercise could cause an increase in NK cell cytotoxicity, then quickly followed by a delayed suppression during exercise recovery [77]. The changes in the cytotoxic activity of NK cells was mostly driven by the changes in the proportion of NK cells among the peripheral blood mononuclear cell (PBMC) fraction. Indeed, both high- and moderate-intensity exercise were associated with significant shifts in circulating proportions of NK cells which significantly influence the interpretation of NK cell cytotoxicity [77]. However, the studies by other groups challenged this concept by using a wide range of tumor target cells (e.g., K562) in the detection of the effects of exercise on NK cell cytotoxicity [78]. They proposed that exercise evokes a preferential redeployment of NK cell subsets with a high differentiation phenotype and augments cytotoxicity against HLA-expressing target cells [78, 79]. Thus, till now it remains unclear if changes in NK cell function simply reflect exercise-induced alterations in the count of NK cells and NK cell subset distribution, or whether exercise affects the functional capability of NK cells at the individual cell level.

27.2.5 Exercise and Other Innate Immune Cells

The studies on effects of exercise on other innate immune cells such as basophils and eosinophils was collected and presented in Table 27.1.

27.3 The Effects of Exercise on Adaptive Immune Cells

Adaptive immunity is also known as acquired immunity or specific immunity, which is designed to protect our bodies by destroying invading microorganisms and preventing colonization [90]. The immunological memory that is created by adaptive immunity after an initial response to a specific pathogen leads to an future intensive response to subsequent encounters with that pathogen [19]. The main cells that are involved in the adaptive immunity are T and B lymphocytes, which are a subset of leukocyte. T cells play a large role in cell-mediated immune responses, whereas B cells are intimately involved in the humoral immune response [19]. It is widely accepted that proportional to exercise duration and intensity, there exists a lymphocytosis during and immediately after exercise. In this part, we will focus on exercise and the main adaptive immune cell function.

27.3.1 Exercise and B Cells

After immune activation, B cells undergo proliferation and differentiation and mature into memory and plasma cell. As the major cells involved in the creation of blood plasma and lymph antibodies, plasma cells produce IgA, IgD, IgE, IgM, and IgG immunoglobulin (Ig), each of which recognizes a unique antigen in the humoral immunity [91]. The effect of exercise on humoral Ig function has been evaluated through measurements of mucosal and serum Ig concentration. Brief or prolonged exercise studies reported that

Table 27.1 Effects of exercise on immune cells

Gender	Type	Exercise protocol	Rest periods	Key findings	References
Male	Lower body	Leg press	1 min/3 min	LE ↑	1996 [29]
Female	Upper and lower body	Leg press, leg extension, bench press, overhead press, leg curls, seated rows, biceps curls	3 min	LE ↑ at 90 min and 180 min post (untrained only)	2001 [80]
Female	Full body	Squat	2 min	$CD16^+/CD56^+$ NK and T cells ↑ by 0 min in all the group; B cells ↑ by 0 min post in high-strength group only (which performed more total work than low strength)	2001 [81]
Female	Full body	Squat	2 min	In control and training status, all tested LE ↑ by 0 min post	2003 [82]
Male	Circuit	Bench press, latissimus dorsi pull, leg press, shoulder press, leg extension, crunch, pull-up, biceps curls, leg extension, triceps exercise	1 min	All tested LE ↑ by 0 min post control and training status; NK ($CD16^+/CD56^+$) cells ↑ approx. 250% then ↓ blow BL by 30 min post; T ($CD4^+$) cells ↑ approx. 20% then ↓ blow BL by 30 min post; T ($CD8^+$) cells ↑ then ↓ blow BL by 30 min post; NE and MO remained ↑ and peaked at 2 h post (final time-point)	2003 [22]
Male	Circuit	Shoulder press, seated rows, lag press, leg extensions, leg curls, latissimus dorsi pull-downs, abdominal crunches, chest press	1:2 (work:rest) ratio	MO, NE, LY, NK cells, $CD8^+$ and $CD4^+$ T cells ↑ by 0 min post, then ↓; $CD8^+$ T cells ↓ to baseline by 15 min post; MO, LY, NK, and $CD8^+$ T cells except NE ↓ to baseline by 30 min post	2004 [21]
Male	Upper and lower body	Bench press and leg press, hamstring curl, knee station, biceps curls	Not provided	LY and LE (NE and MO accounted for the majority) ↑ post and remained ↑ at 3 h post; $CD8^+$ T and $CD16^+/CD56^+$ NK cells ↑ by 0 min post and ↓ to baseline by 3 h post; B cells ↑ by 3 h post	2003 [20]
Male	Circuit	Bench press, leg press, leg extension, shoulder press, pull-up, biceps curls, triceps exercise, crunch, latissimus dorsi pull, vertical row	1 min	NE ↑ by 0 min post (untrained or resistance trained)	2004 [83]
Male	Lower body	Leg press	1 min/3 min	LE, LY, MO, NE ↑ by 0 min post; The change of MO and LY was greatest in 1 min rest group	2005 [84]
Male	Upper limb eccentric	Eccentric contractions of the elbow flexors	1 min/3 min; 2 s rest between reps	LE and NE ↑ by 3 h post; MO and LY no change	2006 [85]
Female	Circuit	Arm curl, dead lift, triceps extension, back extension, bench press, seated row, squat, overhead press, leg curl	1 min between rounds	LE, LY, and NE ↑ by 0 min post in all exercise groups	2010 [86]

(continued)

Table 27.1 (continued)

Gender	Type	Exercise protocol	Rest periods	Key findings	References
Male	Circuit	Leg curl, biceps curls, leg press, shoulder press, latissimus pulldowns, bench press, seated row	2 min rest between exercise and 3 min rest between rounds	LE, LY, and NE ↑ by 3 h post and returned to baseline by 24 h post	2012 [23]
Male	Circuit	Biceps with barbell, triceps with barbell, trunk extension, sit-up, squat, knee flexion, standing shoulder flexion, dead lift, sitting paddle lift with device, supine bench press	1 min rest between rounds	No change was detected	2012 [87]
Male	Lower body	Leg press	3 min/2 min	LE remained ↑ by 0 min post, then ↓ to baseline; NE, LY ↑ by 0 min post then ↓ to baseline by 30 min post	2014 [28]
Male	Upper limb: isometric	Thumb exertion: lateral pinch	1 min	LE and LY ↑ by 0 min post; MO ↑ by 60 min post (resistance trained/untrained); T and B cells ↑ by 20 min post, then ↓ to baseline by 60 min post	2015 [88, 89]

Abbreviations: *BA* basophils, *EO* eosinophils, *LE* total leukocytes, *MO* monocytes, *NE* neutrophils, *LY* total lymphocytes, *post* post exercise

serum Ig concentration appears to remain either slightly increased, or unchanged [92–94]. The mucosal immune system protects the mucosal surfaces of the nasal passages, intestines, and the respiratory tract. The secretory IgA (SIgA) that is produced by plasma cells is the major effector function of the mucosal immune system providing the pathogens [95, 96]. The effect of exercise on the changes of the secretion of SIgA in saliva has been widely studied [97]. Training status, intensity of the exercise bout, and duration of the exercise could influence the response of SIgA [11]. High levels of saliva SIgA was important to enhance basic immune capacity and was associated with low incidence of URTI in athletes. Substantial transient falls in saliva SIgA could increase the risk of URTI [98, 99]. Although some early studies indicated falls in saliva SIgA concentration in endurance athletes or during intensive periods of training [99–102], the majority of studies reported that the saliva SIgA concentration in athletes was the same as non-athletes except when athletes are engaged in heavy training [103, 104]. This decreased saliva SIgA in athletes after high-intensity exercise is partly due to a withdrawal of the inhibitory effects of the parasympathetic nervous system [11]. Thus, acute bouts of moderate exercise showed little impact on plasma cell Ig expression, but prolonged heavy exercise and intensified training could evoke decreases in saliva SIgA secretion.

Except their Ig antibody secretion role in humoral and mucosal immunity, B cells were also engaged in initiating T cell-mediated immune responses and played a key role [105]. B cell number was mildly increased during and immediately after exercise and was proportional to exercise duration and intensity. But this enhanced number of B cells falling below pre-exercise levels during the early stages of recovery and returning to basal level within 24 h [25, 106]. Besides that, a consistent elevated circulation B cell number was detected either during or after high-dose resistance exercise (evident after 3 h rest, 60–100%-1 RM at different volumes) [20, 81, 82]. The elevated circulation B cell count was also detected even in low-dose resistance exercise [107]. Well, except the high- and low-dose exercise, bouts of different dose exercise could be admitted that induced an acute lymphocytosis

with occurs either during or immediately after exercise. Furthermore, higher exercise doses should be augmented to measure the effect of different types of exercise on the circulation B cell count, and further research is needed to clarify the effects of exercise training on immunological function of B cells.

27.3.2 Exercise and T Cells

After antigen challenge, T cells proliferate and differentiate into multiple effector T cell clones. These expanded T cells can be divided into several subsets of cells, each with a distinct function [108]. Some of them are able to recognize the antigen that causes the initial response and regulated the immunological events in both humoral and cell-mediated immunity. The cell surface cluster of differentiation (CD) markers and the cytokines profiles that T cell produced can be used to classify different T cell phenotypes. $CD4^+$ helper/inducer T cells can be divided into type 1 (Th2), type 2 (Th2), Th17, and T follicular helper cells [109]. Th1 cells function to eliminate intracellular pathogens and are associated with organ-specific autoimmunity. Conversely, Th2 cells mount responses to extracellular parasites and indirectly regulate inflammatory activity through secretion of cytokine IL-4, IL-5, IL-6, and IL-13 [110]. Through the secretion of the regulator cytokine IL-10, Th2 cells could also negatively regulate inflammation. The cytokines that are released from Th2 cells could activate B cells, leading B cells to proliferate and differentiate into memory and plasma cells [111]. Like $CD4^+$ T cells, $CD8^+$ T cells are classified into type 1 (Tc1) and type 2 (Tc2) cells according to their cytokine profiles. These $CD8^+$ T cells are also known as cytotoxic T cells, which are central to resistance against intracellular pathogens [112]. Different types of T cells in adaptive immunity play different roles; hence, differential analysis of T cell subtypes is necessary.

Several studies have uncovered a decreased T cells proliferation both during and after exercise [11]. The function of T cells appears to be sensitive to increases in training load in well-trained athletes undertaking a period of intensified training, together with a decreased circulating Th1 T cell counts, which suggested that a long period of intensified training exhibits decreases in T cell functionality. However, a lymphocytosis is observed during and immediately after exercise, with numbers of cells falling below pre-exercise levels during the early stages of recovery [113]. These variations of T cells number in different exercises might be proportional to exercise intensity and duration [55, 114]. In resistance exercise studies, the responses of $CD4^+$ T cells to resistance exercise were different based on the different study groups. It was reported that $CD4^+$ lymphocytosis existed immediately after high-dose resistance exercise [21, 22, 82], or increased during 0–60 min following very low-dose resistance exercise [89]. Then the counts of $CD4^+$ T cells returned to baseline within 30 min following the high-dose exertion [21], or remained elevated at 60 min succeeding a low-dose exertion [89]. In contrast to exercise induced T cell number, following a body resistance exercise protocol (60–70%-1 RM at different volumes), there was no detected change in $CD4^+$ T cell count (despite an increase in total lymphocytes) [20]. Actually, in the resting stage (more than 24 h resting after the last training session) of athletes, the circulating lymphocyte (include all type of T cells) and functions appeared to be broadly similar to those of non-athletes [115].

As in the case of $CD4^+$ T cells, a $CD8^+$ T cell lymphocytosis has been detected to exist immediately following high-dose resistance exercise (60–70%-1 RM), which reportedly returned to baseline levels by 15 min succeeding exercise or decreased below pre-exercise levels by 30 min of rest, and then returned to baseline values by 3 h post exercise [20, 21, 82]. During the very low-dose resistance exercise, the count of $CD8^+$ T cells increased from 0 to 60 min post exercise training and returned to baseline between 20 and 60 min post exercise [89]. Slight variances in exercise volume or differences in the timing of blood collections after exercise might be related to the number of non-consistent CD8+ T cells that were reported in different papers.

Till now, it has been accepted that exercise is somehow correlated with T cell function. However, it is debated whether T cell proliferation is truly impaired during or after exercise. Thus, further research is necessary to clarify the relationship of T cell count and function in different exercise training programs.

27.4 Perspective

During exercise, no matter acute or chronic, there exists a marked difference in the circulating levels of immune cells and other factors that have immunomodulatory effects by influencing leukocyte trafficking and functions. The effects of exercise on the normal functioning of the immune system have been widely agreed to be profound [116–118]. It is already known that the single exercise bouts only induce a transient immune response. However, these effects cumulated over time and formed the immunological adaptations to chronic exercise training. Based on exercise dose, prolonged periods of intensive exercise training could depress immunity [119, 120], while there was no doubt that regular exercise training may reduce the risk of disease such as the URTI due to its anti-inflammatory, thymic-activity reinvigorated, and boost-immunity effects. However, more rigorous standardization of studies is required to reveal reliable data which could assist in improving the safety of exercise and health status.

Data accumulated from preclinical experiments have demonstrated that exercise can directly regulate the immune system and has the potential to indirectly affect cancer, asthma, chronic disease, and cardiovascular disease through the regulation of immune response [121–126]. Essentially, this points to a new direction for exercise immunology studies, which may aim to exploit exercise training as one of the new compound therapy strategies. To this end, the molecular mechanisms of immune cell infiltration and functional regulation and inflammatory cytokines occurring during exercise need much broader and deeper investigations.

Acknowledgments This work was supported by the grants from National Natural Science Foundation of China (81722008, 91639101, and 81570362 to JJ Xiao), Innovation Program of Shanghai Municipal Education Commission (2017-01-07-00-09-E00042 to JJ Xiao), the grant from Science and Technology Commission of Shanghai Municipality (17010500100, 18410722200 to JJ Xiao), the development fund for Shanghai talents (to JJ Xiao), and the Sailing Program from Science and Technology Commission of Shanghai (19YF1415400 to J Wang).

Competing Financial Interests The authors declare no competing financial interests.

References

1. Iwasaki A, Medzhitov R (2015) Control of adaptive immunity by the innate immune system. Nat Immunol 16(4):343–353
2. Gasteiger G, Rudensky AY (2014) Interactions between innate and adaptive lymphocytes. Nat Rev Immunol 14(9):631–639
3. Sattler S (2017) The role of the immune system beyond the fight against infection. Adv Exp Med Biol 1003:3–14
4. Pan W, Zhu Y, Meng X, Zhang C, Yang Y, Bei Y (2018) Immunomodulation by exosomes in myocardial infarction. J Cardiovasc Transl Res 12(1):28–36
5. Bei Y, Shi C, Zhang Z, Xiao J (2019) Advance for cardiovascular health in China. J Cardiovasc Transl Res 12(3):165–170
6. Peake J (2013) Interrelations between acute and chronic exercise stress and the immune and endocrine systems. In: Constantini N, Hackney A (eds) Endocrinology of physical activity and sport. Contemporary Endocrinology Humana Press, Totowa, NJ, pp 258–280
7. Nieman DC, Henson DA, Gusewitch G, Warren BJ, Dotson RC, Butterworth DE, Nehlsen-Cannarella SL (1993) Physical activity and immune function in elderly women. Med Sci Sports Exerc 25(7):823–831
8. Nieman DC, Johanssen LM, Lee JW (1989) Infectious episodes in runners before and after a roadrace. J Sports Med Phys Fitness 29(3):289–296
9. Nieman DC, Johanssen LM, Lee JW, Arabatzis K (1990) Infectious episodes in runners before and after the Los Angeles Marathon. J Sports Med Phys Fitness 30(3):316–328
10. Gleeson M (2007) Immune function in sport and exercise. J Appl Physiol (1985) 103(2):693–699
11. Walsh NP, Gleeson M, Shephard RJ, Gleeson M, Woods JA, Bishop NC, Fleshner M, Green C, Pedersen BK, Hoffman-Goetz L, Rogers CJ, Northoff H, Abbasi A, Simon P (2011) Position

statement. Part one: immune function and exercise. Exerc Immunol Rev 17:6–63
12. Asimakos A, Toumpanakis D, Karatza MH, Vasileiou S, Katsaounou P, Mastora Z, Vassilakopoulos T (2018) Immune cell response to strenuous resistive breathing: comparison with whole body exercise and the effects of antioxidants. Int J Chron Obstruct Pulmon Dis 13:529–545
13. Wang L, Lv Y, Li G, Xiao J (2018) MicroRNAs in heart and circulation during physical exercise. J Sport Health Sci 7(4):433–441
14. Freidenreich DJ, Volek JS (2012) Immune responses to resistance exercise. Exerc Immunol Rev 18:8–41
15. Bigley AB, Simpson RJ (2015) NK cells and exercise: implications for cancer immunotherapy and survivorship. Discov Med 19(107):433–445
16. Robson PJ, Blannin AK, Walsh NP, Castell LM, Gleeson M (1999) Effects of exercise intensity, duration and recovery on in vitro neutrophil function in male athletes. Int J Sports Med 20(2):128–135
17. Shek PN, Sabiston BH, Buguet A, Radomski MW (1995) Strenuous exercise and immunological changes: a multiple-time-point analysis of leukocyte subsets, CD4/CD8 ratio, immunoglobulin production and NK cell response. Int J Sports Med 16(7):466–474
18. Riera Romo M, Perez-Martinez D, Castillo Ferrer C (2016) Innate immunity in vertebrates: an overview. Immunology 148(2):125–139
19. Myrphy K, Travers P, Walport M, Janeway CA (2012) Janeway's Immunobiology, 8th edn. Garland Science, New York
20. Natale VM, Brenner IK, Moldoveanu AI, Vasiliou P, Shek P, Shephard RJ (2003) Effects of three different types of exercise on blood leukocyte count during and following exercise. Sao Paulo Med J 121(1):9–14
21. Simonson SR, Jackson CG (2004) Leukocytosis occurs in response to resistance exercise in men. J Strength Cond Res 18(2):266–271
22. Ramel A, Wagner KH, Elmadfa I (2003) Acute impact of submaximal resistance exercise on immunological and hormonal parameters in young men. J Sports Sci 21(12):1001–1008
23. Mooren FC, Volker K, Klocke R, Nikol S, Waltenberger J, Kruger K (2012) Exercise delays neutrophil apoptosis by a G-CSF-dependent mechanism. J Appl Physiol (1985) 113(7):1082–1090
24. Hulmi JJ, Myllymaki T, Tenhumaki M, Mutanen N, Puurtinen R, Paulsen G, Mero AA (2010) Effects of resistance exercise and protein ingestion on blood leukocytes and platelets in young and older men. Eur J Appl Physiol 109(2):343–353
25. Peake JM, Neubauer O, Walsh NP, Simpson RJ (2017) Recovery of the immune system after exercise. J Appl Physiol (1985) 122(5):1077–1087
26. Gleeson M, Bishop NC (2005) The T cell and NK cell immune response to exercise. Ann Transplant 10(4):43–48
27. Michishita R, Shono N, Inoue T, Tsuruta T, Node K (2010) Effect of exercise therapy on monocyte and neutrophil counts in overweight women. Am J Med Sci 339(2):152–156
28. Ihalainen J, Walker S, Paulsen G, Hakkinen K, Kraemer WJ, Hamalainen M, Vuolteenaho K, Moilanen E, Mero AA (2014) Acute leukocyte, cytokine and adipocytokine responses to maximal and hypertrophic resistance exercise bouts. Eur J Appl Physiol 114(12):2607–2616
29. Kraemer WJ, Clemson A, Triplett NT, Bush JA, Newton RU, Lynch JM (1996) The effects of plasma cortisol elevation on total and differential leukocyte counts in response to heavy-resistance exercise. Eur J Appl Physiol Occup Physiol 73(1–2):93–97
30. Peake JM (2002) Exercise-induced alterations in neutrophil degranulation and respiratory burst activity: possible mechanisms of action. Exerc Immunol Rev 8:49–100
31. McCarthy DA, Macdonald I, Grant M, Marbut M, Watling M, Nicholson S, Deeks JJ, Wade AJ, Perry JD (1992) Studies on the immediate and delayed leucocytosis elicited by brief (30-min) strenuous exercise. Eur J Appl Physiol Occup Physiol 64(6):513–517
32. Ortega E, Collazos ME, Maynar M, Barriga C, De la Fuente M (1993) Stimulation of the phagocytic function of neutrophils in sedentary men after acute moderate exercise. Eur J Appl Physiol Occup Physiol 66(1):60–64
33. Ortega E (2003) Neuroendocrine mediators in the modulation of phagocytosis by exercise: physiological implications. Exerc Immunol Rev 9:70–93
34. Peake J, Suzuki K (2004) Neutrophil activation, antioxidant supplements and exercise-induced oxidative stress. Exerc Immunol Rev 10:129–141
35. Bishop NC, Gleeson M, Nicholas CW, Ali A (2002) Influence of carbohydrate supplementation on plasma cytokine and neutrophil degranulation responses to high intensity intermittent exercise. Int J Sport Nutr Exerc Metab 12(2):145–156
36. Swirski FK, Nahrendorf M, Etzrodt M, Wildgruber M, Cortez-Retamozo V, Panizzi P, Figueiredo JL, Kohler RH, Chudnovskiy A, Waterman P, Aikawa E, Mempel TR, Libby P, Weissleder R, Pittet MJ (2009) Identification of splenic reservoir monocytes and their deployment to inflammatory sites. Science 325(5940):612–616
37. Skinner NA, MacIsaac CM, Hamilton JA, Visvanathan K (2005) Regulation of Toll-like receptor (TLR)2 and TLR4 on CD14dimCD16+ monocytes in response to sepsis-related antigens. Clin Exp Immunol 141(2):270–278
38. Flynn MG, McFarlin BK, Phillips MD, Stewart LK, Timmerman KL (2003) Toll-like receptor 4 and CD14 mRNA expression are lower in resistive exercise-trained elderly women. J Appl Physiol (1985) 95(5):1833–1842
39. McFarlin BK, Flynn MG, Campbell WW, Craig BA, Robinson JP, Stewart LK, Timmerman KL,

Coen PM (2006) Physical activity status, but not age, influences inflammatory biomarkers and toll-like receptor 4. J Gerontol Ser A Biol Sci Med Sci 61(4):388–393
40. McFarlin BK, Flynn MG, Campbell WW, Stewart LK, Timmerman KL (2004) TLR4 is lower in resistance-trained older women and related to inflammatory cytokines. Med Sci Sports Exerc 36(11):1876–1883
41. Sloan RP, Shapiro PA, Demeersman RE, McKinley PS, Tracey KJ, Slavov I, Fang Y, Flood PD (2007) Aerobic exercise attenuates inducible TNF production in humans. J Appl Physiol (1985) 103(3):1007–1011
42. Stewart LK, Flynn MG, Campbell WW, Craig BA, Robinson JP, McFarlin BK, Timmerman KL, Coen PM, Felker J, Talbert E (2005) Influence of exercise training and age on CD14+ cell-surface expression of toll-like receptor 2 and 4. Brain Behav Immun 19(5):389–397
43. Timmerman KL, Flynn MG, Coen PM, Markofski MM, Pence BD (2008) Exercise training-induced lowering of inflammatory (CD14+CD16+) monocytes: a role in the anti-inflammatory influence of exercise? J Leukoc Biol 84(5):1271–1278
44. Kizaki T, Takemasa T, Sakurai T, Izawa T, Hanawa T, Kamiya S, Haga S, Imaizumi K, Ohno H (2008) Adaptation of macrophages to exercise training improves innate immunity. Biochem Biophys Res Commun 372(1):152–156
45. Lu Q, Ceddia MA, Price EA, Ye SM, Woods JA (1999) Chronic exercise increases macrophage-mediated tumor cytolysis in young and old mice. Am J Physiol 276(2 Pt 2):R482–R489
46. Sugiura H, Nishida H, Sugiura H, Mirbod SM (2002) Immunomodulatory action of chronic exercise on macrophage and lymphocyte cytokine production in mice. Acta Physiol Scand 174(3):247–256
47. Vieira VJ, Valentine RJ, Wilund KR, Antao N, Baynard T, Woods JA (2009) Effects of exercise and low-fat diet on adipose tissue inflammation and metabolic complications in obese mice. Am J Physiol Endocrinol Metab 296(5):E1164–E1171
48. Vieira VJ, Valentine RJ, Wilund KR, Woods JA (2009) Effects of diet and exercise on metabolic disturbances in high-fat diet-fed mice. Cytokine 46(3):339–345
49. Zielinski MR, Muenchow M, Wallig MA, Horn PL, Woods JA (2004) Exercise delays allogeneic tumor growth and reduces intratumoral inflammation and vascularization. J Applied Physiol (1985) 96(6):2249–2256
50. Simpson RJ, McFarlin BK, McSporran C, Spielmann G, o Hartaigh B, Guy K (2009) Toll-like receptor expression on classic and pro-inflammatory blood monocytes after acute exercise in humans. Brain Behav Immun 23(2):232–239
51. Okutsu M, Suzuki K, Ishijima T, Peake J, Higuchi M (2008) The effects of acute exercise-induced cortisol on CCR2 expression on human monocytes. Brain Behav Immun 22(7):1066–1071
52. Hong S, Mills PJ (2008) Effects of an exercise challenge on mobilization and surface marker expression of monocyte subsets in individuals with normal vs. elevated blood pressure. Brain Behav Immun 22(4):590–599
53. Steppich B, Dayyani F, Gruber R, Lorenz R, Mack M, Ziegler-Heitbrock HW (2000) Selective mobilization of CD14(+)CD16(+) monocytes by exercise. Am J Physiol Cell Physiol 279(3):C578–C586
54. Rivier A, Pene J, Chanez P, Anselme F, Caillaud C, Prefaut C, Godard P, Bousquet J (1994) Release of cytokines by blood monocytes during strenuous exercise. Int J Sports Med 15(4):192–198
55. Starkie RL, Angus DJ, Rolland J, Hargreaves M, Febbraio MA (2000) Effect of prolonged, submaximal exercise and carbohydrate ingestion on monocyte intracellular cytokine production in humans. J Physiol 528(Pt 3):647–655
56. Lancaster GI, Khan Q, Drysdale P, Wallace F, Jeukendrup AE, Drayson MT, Gleeson M (2005) The physiological regulation of toll-like receptor expression and function in humans. J Physiol 563(Pt 3):945–955
57. Starkie RL, Rolland J, Angus DJ, Anderson MJ, Febbraio MA (2001) Circulating monocytes are not the source of elevations in plasma IL-6 and TNF-alpha levels after prolonged running. Am J Physiol Cell Physiol 280(4):C769–C774
58. Mills CD, Ley K (2014) M1 and M2 macrophages: the chicken and the egg of immunity. J Innate Immun 6(6):716–726
59. Ceddia MA, Voss EW Jr, Woods JA (2000) Intracellular mechanisms responsible for exercise-induced suppression of macrophage antigen presentation. J Appl Physiol (1985) 88(2):804–810
60. Ceddia MA, Woods JA (1999) Exercise suppresses macrophage antigen presentation. J Appl Physiol (1985) 87(6):2253–2258
61. Woods JA, Ceddia MA, Kozak C, Wolters BW (1997) Effects of exercise on the macrophage MHC II response to inflammation. Int J Sports Med 18(6):483–488
62. Ortega E, Forner MA, Barriga C (1997) Exercise-induced stimulation of murine macrophage chemotaxis: role of corticosterone and prolactin as mediators. J Physiol 498(Pt 3):729–734
63. Woods JA, Davis JM (1994) Exercise, monocyte/macrophage function, and cancer. Med Sci Sports Exerc 26(2):147–156
64. LaVoy EC, Bollard CM, Hanley PJ, O'Connor DP, Lowder TW, Bosch JA, Simpson RJ (2015) A single bout of dynamic exercise by healthy adults enhances the generation of monocyte-derived-dendritic cells. Cell Immunol 295(1):52–59
65. Ho CS, Lopez JA, Vuckovic S, Pyke CM, Hockey RL, Hart DN (2001) Surgical and physical stress increases circulating blood dendritic cell

counts independently of monocyte counts. Blood 98(1):140–145
66. Deckx N, Wens I, Nuyts AH, Lee WP, Hens N, Koppen G, Goossens H, Van Damme P, Berneman ZN, Eijnde BO, Cools N (2015) Rapid exercise-induced mobilization of dendritic cells is potentially mediated by a Flt3L- and MMP-9-dependent process in multiple sclerosis. Mediat Inflamm 2015:158956
67. Chiang LM, Chen YJ, Chiang J, Lai LY, Chen YY, Liao HF (2007) Modulation of dendritic cells by endurance training. Int J Sports Med 28(9):798–803
68. Liao HF, Chiang LM, Yen CC, Chen YY, Zhuang RR, Lai LY, Chiang J, Chen YJ (2006) Effect of a periodized exercise training and active recovery program on antitumor activity and development of dendritic cells. J Sports Med Phys Fitness 46(2):307–314
69. Brown FF, Campbell JP, Wadley AJ, Fisher JP, Aldred S, Turner JE (2018) Acute aerobic exercise induces a preferential mobilisation of plasmacytoid dendritic cells into the peripheral blood in man. Physiol Behav 194:191–198
70. Benschop RJ, Oostveen FG, Heijnen CJ, Ballieux RE (1993) Beta 2-adrenergic stimulation causes detachment of natural killer cells from cultured endothelium. Eur J Immunol 23(12):3242–3247
71. Timmons BW, Cieslak T (2008) Human natural killer cell subsets and acute exercise: a brief review. Exerc Immunol Rev 14:8–23
72. Dorneles GP, Colato AS, Galvao SL, Ramis TR, Ribeiro JL, Romao PR, Peres A (2016) Acute response of peripheral CCr5 chemoreceptor and NK cells in individuals submitted to a single session of low-intensity strength exercise with blood flow restriction. Clin Physiol Funct Imaging 36(4):311–317
73. Bjorkstrom NK, Ljunggren HG, Michaelsson J (2016) Emerging insights into natural killer cells in human peripheral tissues. Nat Rev Immunol 16(5):310–320
74. McFarlin BK, Flynn MG, Phillips MD, Stewart LK, Timmerman KL (2005) Chronic resistance exercise training improves natural killer cell activity in older women. J Gerontol Ser A Biol Sci Med Sci 60(10):1315–1318
75. Nieman DC, Nehlsen-Cannarella SL, Markoff PA, Balk-Lamberton AJ, Yang H, Chritton DB, Lee JW, Arabatzis K (1990) The effects of moderate exercise training on natural killer cells and acute upper respiratory tract infections. Int J Sports Med 11(6):467–473
76. Shephard RJ, Shek PN (1999) Effects of exercise and training on natural killer cell counts and cytolytic activity: a meta-analysis. Sports Med 28(3):177–195
77. Nieman DC, Miller AR, Henson DA, Warren BJ, Gusewitch G, Johnson RL, Davis JM, Butterworth DE, Nehlsen-Cannarella SL (1993) Effects of high-vs moderate-intensity exercise on natural killer cell activity. Med Sci Sports Exerc 25(10):1126–1134
78. Bigley AB, Rezvani K, Chew C, Sekine T, Pistillo M, Crucian B, Bollard CM, Simpson RJ (2014) Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells. Brain Behav Immun 39:160–171
79. Bigley AB, Rezvani K, Pistillo M, Reed J, Agha N, Kunz H, O'Connor DP, Sekine T, Bollard CM, Simpson RJ (2015) Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells. Part II: impact of latent cytomegalovirus infection and catecholamine sensitivity. Brain Behav Immun 49:59–65
80. Potteiger JA, Chan MA, Haff GG, Mathew S, Schroeder CA, Haub MD, Chirathaworn C, Tibbetts SA, McDonald J, Omoike O, Benedict SH (2001) Training status influences T-cell responses in women following acute resistance exercise. J Strength Cond Res 15(2):185–191
81. Dohi K, Mastro AM, Miles MP, Bush JA, Grove DS, Leach SK, Volek JS, Nindl BC, Marx JO, Gotshalk LA, Putukian M, Sebastianelli WJ, Kraemer WJ (2001) Lymphocyte proliferation in response to acute heavy resistance exercise in women: influence of muscle strength and total work. Eur J Appl Physiol 85(3–4):367–373
82. Miles MP, Kraemer WJ, Nindl BC, Grove DS, Leach SK, Dohi K, Marx JO, Volek JS, Mastro AM (2003) Strength, workload, anaerobic intensity and the immune response to resistance exercise in women. Acta Physiol Scand 178(2):155–163
83. Ramel A, Wagner KH, Elmadfa I (2004) Correlations between plasma noradrenaline concentrations, antioxidants, and neutrophil counts after submaximal resistance exercise in men. Br J Sports Med 38(5):E22
84. Mayhew DL, Thyfault JP, Koch AJ (2005) Rest-interval length affects leukocyte levels during heavy resistance exercise. J Strength Cond Res 19(1):16–22
85. Peake JM, Nosaka K, Muthalib M, Suzuki K (2006) Systemic inflammatory responses to maximal versus submaximal lengthening contractions of the elbow flexors. Exerc Immunol Rev 12:72–85
86. Ghanbari-Niaki A, Saghebjoo M, Rashid-Lamir A, Fathi R, Kraemer RR (2010) Acute circuit-resistance exercise increases expression of lymphocyte agouti-related protein in young women. Exp Biol Med (Maywood, NJ) 235(3):326–334
87. Mukaimoto T, Ohno M (2012) Effects of circuit low-intensity resistance exercise with slow movement on oxygen consumption during and after exercise. J Sports Sci 30(1):79–90
88. Szlezak AM, Tajouri L, Keane J, Szlezak SL, Minahan C (2015) Micro-Dose of Resistance-Exercise: Effects of Sub-Maximal Thumb Exertion on Leukocyte Redistribution and Fatigue in Trained Male Weightlifters. JPES 15:365–377

89. Szlezak AM, Tajouri L, Keane J, Szlezak SL, Minahan C (2016) Isometric thumb exertion induces B cell and T cell lymphocytosis in trained and untrained males: physical aptitude determines response profiles. IJKSS 4:55–66
90. Bonilla FA, Oettgen HC (2010) Adaptive immunity. J Allergy Clin Immunol 125(2 Suppl 2):S33–S40
91. Mauri C, Bosma A (2012) Immune regulatory function of B cells. Annu Rev Immunol 30:221–241
92. Nehlsen-Cannarella SL, Nieman DC, Jessen J, Chang L, Gusewitch G, Blix GG, Ashley E (1991) The effects of acute moderate exercise on lymphocyte function and serum immunoglobulin levels. Int J Sports Med 12(4):391–398
93. Nieman DC, Tan SA, Lee JW, Berk LS (1989) Complement and immunoglobulin levels in athletes and sedentary controls. Int J Sports Med 10(2):124–128
94. Petersen AM, Pedersen BK (2005) The anti-inflammatory effect of exercise. J Appl Physiol (1985) 98(4):1154–1162
95. Svendsen IS, Hem E, Gleeson M (2016) Effect of acute exercise and hypoxia on markers of systemic and mucosal immunity. Eur J Appl Physiol 116(6):1219–1229
96. Gleeson M, Pyne DB, Callister R (2004) The missing links in exercise effects on mucosal immunity. Exerc Immunol Rev 10:107–128
97. Bishop NC, Gleeson M (2009) Acute and chronic effects of exercise on markers of mucosal immunity. Front Biosci (Landmark Ed) 14:4444–4456
98. Gleeson M, McDonald WA, Pyne DB, Cripps AW, Francis JL, Fricker PA, Clancy RL (1999) Salivary IgA levels and infection risk in elite swimmers. Med Sci Sports Exerc 31(1):67–73
99. Neville V, Gleeson M, Folland JP (2008) Salivary IgA as a risk factor for upper respiratory infections in elite professional athletes. Med Sci Sports Exerc 40(7):1228–1236
100. Rutherfurd-Markwick K, Starck C, Dulson DK, Ali A (2017) Salivary diagnostic markers in males and females during rest and exercise. J Int Soc of Sports Nutr 14:27
101. Carins J, Booth C (2002) Salivary immunoglobulin-A as a marker of stress during strenuous physical training. Aviat Space Environ Med 73(12):1203–1207
102. Fahlman MM, Engels HJ (2005) Mucosal IgA and URTI in American college football players: a year longitudinal study. Med Sci Sports Exerc 37(3):374–380
103. Tiollier E, Gomez-Merino D, Burnat P, Jouanin JC, Bourrilhon C, Filaire E, Guezennec CY, Chennaoui M (2005) Intense training: mucosal immunity and incidence of respiratory infections. Eur J Appl Physiol 93(4):421–428
104. Whitham M, Laing SJ, Dorrington M, Walters R, Dunklin S, Bland D, Bilzon JL, Walsh NP (2006) The influence of an arduous military training program on immune function and upper respiratory tract infection incidence. Mil Med 171(8):703–709
105. LeBien TW, Tedder TF (2008) B lymphocytes: how they develop and function. Blood 112(5):1570–1580
106. Ronsen O, Pedersen BK, Oritsland TR, Bahr R, Kjeldsen-Kragh J (2001) Leukocyte counts and lymphocyte responsiveness associated with repeated bouts of strenuous endurance exercise. J Appl Physiol (1985) 91(1):425–434
107. Szlezak AM, Szlezak SL, Keane J, Tajouri L, Minahan C (2016) Establishing a dose-response relationship between acute resistance-exercise and the immune system: Protocol for a systematic review. Immunol Lett 180:54–65
108. Zuniga-Pflucker JC (2004) T-cell development made simple. Nat Rev Immunol 4(1):67–72
109. Luckheeram RV, Zhou R, Verma AD, Xia B (2012) CD4(+)T cells: differentiation and functions. Clin Dev Immunol 2012:925135
110. Doucet C, Brouty-Boye D, Pottin-Clemenceau C, Jasmin C, Canonica GW, Azzarone B (1998) IL-4 and IL-13 specifically increase adhesion molecule and inflammatory cytokine expression in human lung fibroblasts. Int Immunol 10(10):1421–1433
111. Couper KN, Blount DG, Riley EM (2008) IL-10: the master regulator of immunity to infection. J Immunol 180(9):5771–5777
112. Harty JT, Tvinnereim AR, White DW (2000) CD8+ T cell effector mechanisms in resistance to infection. Annu Rev Immunol 18:275–308
113. Lancaster GI, Halson SL, Khan Q, Drysdale P, Wallace F, Jeukendrup AE, Drayson MT, Gleeson M (2004) Effects of acute exhaustive exercise and chronic exercise training on type 1 and type 2 T lymphocytes. Exerc Immunol Rev 10:91–106
114. McCarthy DA, Dale MM (1988) The leucocytosis of exercise. A review and model. Sports Med 6(6):333–363
115. Nieman DC (2000) Is infection risk linked to exercise workload? Med Sci Sports Exerc 32(7 Suppl):S406–S411
116. Simpson RJ, Kunz H, Agha N, Graff R (2015) Exercise and the Regulation of Immune Functions. Prog Mol Biol Transl Sci 135:355–380
117. Xiao W, Liu Y, Luo B, Zhao L, Liu X, Zeng Z, Chen P (2016) Time-dependent gene expression analysis after mouse skeletal muscle contusion. J Sport Health Sci 5(1):101–108
118. Nieman DC, Wentz LM (2019) The compelling link between physical activity and the body's defense system. J Sport Health Sci 8(3):201–217
119. Yuan X, Xu S, Huang H, Liang J, Wu Y, Li C, Yuan H, Zhao X, Lai X, Hou S (2018) Influence of excessive exercise on immunity, metabolism, and gut microbial diversity in an overtraining mice model. Scand J Med Sci Sports 28(5):1541–1551
120. Cipryan L (2018) The effect of fitness level on cardiac autonomic regulation, IL-6, total antioxidant

capacity, and muscle damage responses to a single bout of high-intensity interval training. J Sport Health Sci 7(3):363–371
121. Hojman P (2017) Exercise protects from cancer through regulation of immune function and inflammation. Biochem Soc Trans 45(4):905–911
122. Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW (2017) Exercise-dependent regulation of the tumour microenvironment. Nat Rev Cancer 17(10):620–632
123. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA (2011) The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol 11(9):607–615
124. Lancaster GI, Febbraio MA (2014) The immunomodulating role of exercise in metabolic disease. Trends Immunol 35(6):262–269
125. Apostolopoulos V, Borkoles E, Polman R, Stojanovska L (2014) Physical and immunological aspects of exercise in chronic diseases. Immunotherapy 6(10):1145–1157
126. Mach N, Fuster-Botella D (2017) Endurance exercise and gut microbiota: a review. J Sport Health Sci 6(2):179–197