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Current Knowledge and New Challenges in Exercise Immunology

Aktueller Erkenntnisstand und zukünftige Herausforderungen in der Sportimmunologie

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Summary

› **Exercise has a significant effect** on the regulation of the immune system. Acute bouts of exercise induce an intensity-dependent leukocytosis, followed by redistribution of effector cells into peripheral tissues. These processes are a result of the activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, increased hemodynamics, and the release of stress hormones such as catecholamines and glucocorticoids.

› **During periods of intensive training,** athletes frequently report increased symptoms of upper respiratory tract infections (URTI) which may be a result of a stress overload associated with an impairment of mucosal immunity. In contrast, single bouts of short-term or moderate intensity as well as regular exercise training are mainly "immuno-enhancing".

› **In this regard,** exercise positively affects the composition of the T cell compartment and the function of various leukocyte subpopulations. Regular exercise of moderate intensity also exerts immune-regulating effects during inflammation-associated diseases, such as obesity, type 2 diabetes, or cardiovascular diseases, and counteracts hallmarks of immunosenescence.

› **Consequently,** exercise represents a powerful behavioral intervention that has the potential to improve both immune function and health outcomes in subjects of all ages in prevention and therapy. The present review summarizes the current knowledge, new challenges and future directions in the field of exercise immunology.

Zusammenfassung

› **Sport hat einen bedeutenden Einfluss** auf die Regulation des Immunsystems. Akute Belastungen induzieren eine intensitätsabhängige Leukozytose, gefolgt von einer Umverteilung von Effektorzellen in die peripheren Gewebe. Diese Prozesse resultieren aus der Aktivierung des sympathischen Nervensystems und der Hypothalamus-Hypophysen-Nebennieren-Achse sowie der damit verbundenen erhöhten Hämodynamik und Freisetzung von Stresshormonen wie Katecholaminen und Glukokortikoiden.

› **In Phasen intensiven Trainings** berichten Sportler häufig über vermehrte Symptome von Infekten der oberen Atemwege, die auf eine stress-induzierte Beeinträchtigung der mukosalen Immunabwehr zurückzuführen sein könnten. Demgegenüber wirken einzelne Belastungseinheiten in moderater Intensität sowie regelmäßiges Training mit ausreichender Regeneration hauptsächlich „immunstärkend".

› **In dieser Hinsicht** wirkt sich Sport positiv auf die Zusammensetzung des T-Zell-Kompartiments aus und verbessert die Funktion verschiedener Leukozyten-Subpopulationen über die gesamte Lebensspanne. Darüber hinaus vermittelt regelmäßiges Training mit moderater Intensität einen immunregulierenden Effekt bei entzündungsassoziierten Erkrankungen, wie Diabetes Typ 2, Adipositas und kardiovaskulären Erkrankungen. Über ähnliche Mechanismen wirkt ein aktiver Lebensstil zentralen Aspekten der Immunseneszenz entgegen und stärkt so das schwächer werdende Immunsystem im Alter.

› **Zusammenfassend** stellt körperliche Aktivität eine zentrale oder additive Verhaltensintervention dar, die das Potenzial hat, über eine Verbesserung der Immunfunktion und entzündungsregulierende Mechanismen zahlreiche positive Effekte in Prävention und Therapie zu vermitteln. Diese Übersichtarbeit fasst den aktuellen Erkenntnisstand zentraler sportimmunologischer Themen kompakt zusammen, diskutiert einzelne nicht eindeutig geklärte Fragestellungen und gibt einen Einblick in die zukünftigen Entwicklungen und Herausforderungen der Disziplin.

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Introduction

Exercise immunology is a dynamic developing sub-discipline of sports medicine. Although the knowledge about the diverse relationship between exercise and the immune system is profound, the complexity of immunity and its bidirectional interactions with other physiological systems continuously represents an enormous challenge. However, the present review summarizes the current knowledge, new challenges and future directions in the field of exercise immunology.

Effects of Exercise on Infection Risk

Since early reports on a higher incidence of infections of the upper respiratory tract (URTI) in endurance athletes after periods of intensified training and competitions and the development of the open window theory (37, 65), immunology research focused primarily on the acute and chronic effects of different types of exercise on immune system parameters and the identification of potential key risk factors. During the last years, there is increasing evidence, which challenges this theory as discussed later on in this chapter. On the other hand, it is generally accepted that regular and moderate physical exercise improves the hosts immunocompetence and protects against infectious diseases. Therefore, in this section a distinction is made between the athlete's population and a public health perspective.

The most frequent illnesses in athletes are URTI and these infections are more likely to occur during intense training cycles and after tapering or after competitions than having seasonal patterns. There are early reports showing a 2-6-fold increase in the reported symptoms of URTI for several weeks after running a marathon and an association with the individual running time (65). Most of the evidence initially originated from studies, which involved running disciplines, but a series of data has confirmed the association between heavy exercise and URTI in other sports (65). Subsequently, much effort has been spent to the identification of potential mechanisms and risk factors for the increased URTI susceptibility in athletes. However, it is challenging to interpret the clinical impact of changes in single immune system parameters because the immune system as a whole developed great redundancy. Nevertheless, a number of studies have shown that an acute bout of exercise, depending on mode, intensity and duration, is associated with a transient change in numerous immune system parameters such as peripheral leukocyte numbers and function or saliva immunoglobulin concentration (see section 5). A genetic basis for a higher susceptibility to URTI has been proposed by both exercise and non-exercise studies demonstrating that the regulation of several anti-inflammatory pro-inflammatory cytokines is characteristic for illness prone individuals (20). Findings from studies investigating mucosal immune system (MIS) integrity are more controversial, as some reported on associations between saliva Immunoglobulin A (sIgA) concentrations and URTI incidence while others did not (65).

However, since many studies from the past monitored URTI incidence by self-reports but neither verified an infectious cause by a laboratory identification of pathogens nor by a physical examination, the open window theory has been called into question. It is still debatable whether the URTI symptoms, which particularly occur in high performance athletes, are actually caused by infectious agents (7, 65). Further, it has been shown that there is a discrepancy between the physician's URTI diagnosis frequency and verified infections by pathological tests (11). The latter demonstrate that bacterial and viral pathogens coincide URTI episodes in only 5% and 30-40% of cases of URTI episodes, respectively (11, 54). To date, there is increasing evidence that rather other exercise-induced inflammatory stimuli or a viral reactivation (7, 21) are the major cause of the upper respiratory symptoms (URS). Cox et al. (11) examined the effectiveness of a prophylactic administration of an antiviral agent for the control of Epstein Barr Virus (EBV) reactivation and URS in elite distance runners. They showed that the treatment resulted in a significant (-82%) reduction in the detectable EBV load in saliva without any difference in the URS incidence compared to the control group. A series of studies demonstrated that URS might be caused by a local airway inflammation instead. It has been speculated that the latter could be mediated by various mechanisms such as physico-chemical strains, asthmatic reactions and the migration of inflammatory cytokines, e.g. originating from the damaged skeletal muscle to the respiratory system (65, 66). Taken together, these data raise reasonable doubt on the validity of the open windows theory and suggest other non-infectious causes for URS in elite athletes. Apart from that, even if opportunistic infections are causative for URS in athletes, it is believed that additional/or other internal and external factors which precede or parallel episodes of intensified training or competition, such as mental stress and anxiety, sleep disruption, traveling, nutritional deficiencies, and exposure to climatic changes etc. likely play a key role in the impaired immune competence (7, 66). Additionally, endurance competitions per se increase the risk of acquiring novel infections due to the exposure to human crowds (7).

Apart from the detrimental effects of exhaustive exercise periods, there is limited evidence that master athletes are predisposed to have rather a more efficacious immune defense as they suffer from fewer URTI episodes, which allows them to realize higher training volumes and thereby to compete more successfully (66). It is speculated that beside genetic factors (62) this population is characterized by behavioral factors such as a more effective hygiene routine, diet, sleep and stress management (66). Nevertheless, illness frequencies in athletic populations do not appear to be higher than in the general population (7) but they do not show such a typical relationship of symptom episodes to seasonal patterns (11).

Beside from athletic populations and competitive sports, regular exercise training is a major protective factor as it ameliorates immune function, whereas a sedentary lifestyle depresses immunity (43, 44). Both experimental and epidemiological research studies indicate a negative relationship between activity level and both, URTI incidence (43, 44) and the severity of URTI symptoms (43). In a 12-month observational study Matthews et al. (37) evaluated the activity level of 547 healthy adults (age 20-70 years). After adjustment for a number of potential confounders including age, education, psychosocial measures and dietary factors, they showed that moderate levels of physical activity reduce the risk of URTI about 20%. Nonetheless, due to methodological limitations in the majority of research studies, a Cochrane review from 2015 declares that it is impossible to determine the effectiveness of exercise in altering the occurrence, severity, or duration of URS to date (22).

Effects of Acute Exercise on Leukocyte Numbers and Function

Acute bouts of exercise are well-known to modulate the innate as well as adaptive immune response by affecting immune cell numbers and functions (29, 65). Basically, the innate immune response represents the first line of defense against harmful pathogens and consists of cellular components such as granulocytes, macrophages, natural killer cells (NK), dendritic cells (DC) as well as soluble factors such as ›

complement proteins among others (13). As an essential part of the innate immune response, granulocyte neutrophils represent a type of granula-secreting phagocytes that migrate to the inflamed tissue as first-responders to inflammatory cells (60). Acute exercise induces a first rapid neutrophilia, followed by a second delayed rise of blood neutrophil count a few hours later, depending on the duration and intensity of exercise (65). Novel findings let assume that the priming of neutrophils may be implicated in skeletal muscle inflammation after high-intensity exercise (45). On a functional level, unstimulated neutrophils respond to acute exercise stress with increased degranulation, oxidative burst and phagocytosis (65).

Additionally, after endurance exercise, the concentration of some complement proteins, such as C5a, is increased in the peripheral blood, promoting the chemotaxis of neutrophils (57). Monocytes are the largest type of blood leukocytes that can differentiate into macrophages or DCs after migration into damaged tissues and serve phagocytosis, antigen-presentation and cytokine production (72). With regard to monocytes, acute exercise induces a transient monocytosis of approximately two hours which is most likely due to a shift of monocytes from the marginalized to the circulating pool (65). Preferentially, acute exercise stimulates the mobilization of the proinflammatory CD14+/CD16+ monocyte subtype relative to classical CD14+/CD16- monocytes (29). To date, there is still a lack of studies investigating the exercise-induced mobilization of DCs, which act in the initiation of immune response by antigen presentation (24).

Interestingly, a recent study demonstrated a near fourfold increase of the number of monocyte-derived DCs (mo-DCs) after dynamic running exercise until volitional exhaustion without comprise of functional parameters (34). Since DCs are characterized by their unique ability to cross-present viral and tumor antigens, repetitive bouts of acute exercise might promote beneficial effects for health (24). NK cells are a minor subpopulation of lymphocytes which exhibit cytotoxicity and secrete cytokines promoting defense mechanisms against tumor- and virus-infected cells (70). Similarly to other blood leukocytes, NK-cells show a rapid mobilization in response to an acute bout of exercise (29). Preferentially, the cytotoxic CD56dim NK cell subset rather than the INF-Y producing CD56bright subtype appears to be mobilized by exercise (65). Moreover, functional changes in NK cell cytotoxicity depend on the intensity and duration of exercise. While short bouts of low- to moderate intensity exercise induce an increase, NK cell cytotoxicity expressed on a per cell basis can be reduced for hours after exhausting and prolonged exercise, probably favoring an increased susceptibility to infectious diseases (29, 65).

Contrary to the innate immune response, the adaptive immunity is characterized by antigenic specificity and immunological memory and is composed of two main types of lymphocytes termed T cells and B cells (13). T cells are derived from the bone marrow and migrate to the thymus, where MHC-receptors are formed on their surface, allowing them to identify specifically foreign antigens. Furthermore, the differentiation process includes the maturation into diverse subpopulations such as CD4+ T-helper, CD8+ cytotoxic and regulatory T cells (Treg) (46). B cells are the carriers of the humoral immune response and are the only cells capable of producing antibodies after differentiation into plasma cells (3). Acute exercise results in transient biphasic changes in the numbers of circulating lymphocytes marked by

lymphocytosis during and immediately after exercise, while numbers of cells sinking below basal levels during the early recovery period (26).

Studies indicate that the initial increase of lymphocytes may be the result of mobilization from the marginal pool, the spleen as well as other lymphoid tissues, while the exercise-induced lymphopenia in the post-exercise period seems to be due to redistribution in lymphoid- and non-lymphoid organs and apoptosis (27, 28). Particularly, exercise-induced mobilization of T cells seems to be affected by differentiation stage. Accordingly, highly differentiated T cells show a more frequent mobilization response to acute exercise compared to low differentiated T cells (51, 53). Unlike T cells, B cell mobilization does not seem to be triggered by effector status. In response to acute exercise, the immature B cell subpopulation displays the largest increase, followed by memory B cells and naïve B cells (63).

However, recent studies reveal that the behavior of the exercise-induced mobilization of differentiated T cells is highly dependent on exercise intensity, training status, and individual predispositions such as CMV serostatus and age (12, 33, 51). Thus, high-intensity loads induce greater apoptosis in highly differentiated T cells than moderate intensity exercise (27). Moreover, high physical fitness individuals show a greater decrease of mobilized highly differentiated effector memory T cells (mTeff) in the early post-exercise period, possibly indicating more efficient clearance mechanisms (12). Independently of exercise intensity CMV-seronegative athletes mobilize more low- and medium differentiated T cells than CMV-seropositive (33). Further, the amount of CD34+ hematopoietic progenitor cells and angiogenic T cells (TANG) is inversely correlated with age and older adults display attenuated exercise-induced mobilization of these cell types (51).

To date, only a limited number of studies are available investigating the effects of acute exercise on Treg cells. Tregs are a specialized subgroup of T cells that modulate the activation of the immune system by suppressing the activation and proliferation of effector T-cells as well as maintaining tolerance to self-antigens (6, 7). Novel studies demonstrated that Treg cells are mobilized in response to high-intensity exercise stress (12, 27). In this context, a higher level of physical fitness appears to promote a stronger mobilization (12). On the one hand, Treg mobilization amplifies exercise-induced immunosuppression, but on the other hand, it may also have immune regulatory effects (67).

Effects of Regular Activity on Immune Cell Numbers and Function

Novel studies suggest that chronic exercise has the potential to modulate both the number and function of cells of the innate immunity (1, 8, 50, 59). Although exercise training seems to reduce the neutrophil count only under conditions of chronic inflammation, regular exercise has a significant impact on neutrophil function (65). Recently it was reported that four weeks of hypoxic exercise training in sedentary healthy men increased the expression of adhesion molecules and opsonic receptors, and also enhanced the bactericidal capacity and apoptosis of neutrophils at basal conditions and after acute exhausting exercise (8).

However, exercise modalities seem to have powerful impact on markers of neutrophil function, as normoxic exercise training did not show any effect (8). In response to

chronic exercise training, it was demonstrated that physically active individuals show a lower percentage of the pro-inflammatory CD14+CD16+ monocyte subtype (29, 56). It seems likely that this reduction contributes to the anti-inflammatory effects of chronic exercise. The evidence for the effects of exercise training on DCs is weak, as to date only results from animal models are available. In rat model, DC numbers increased after chronic exercise. Moreover, regular exercise amplified major histocompatibility complex II (MHC II) expression on rat DCs and increased their production of IL-12, a cytokine that modulates the differentiation of naïve T cells and stimulates T cell growth and function (9, 35). Indeed, exercise-induced increases in DC number may protect against cancer and virus infections because of their ability to present viral and tumoral antigens supporting balanced regulation of immune function.

Nevertheless, future human studies that verify the behavior

Figure 1

Chronic exercise training: Effects of moderate and intense training cycles on immune cell numbers and function. During the season moderate and intense training cycles alternate. Moderate training increases the number of naive T cells, reduces TEMRA cells, and improves neutrophil function. In contrast, intensive training reduces the number of circulating naive T cells, increases the number of TEMRA cells, and decreases neutrophil function. This could possibly increase the susceptibility of athletes to infections in intense training cycles. However, athletes show an increased Treg cell frequency. With regard to NK cell cytotoxicity, study results are controversial.

of DCs in response to chronic exercise are essential. With regard to the effects of exercise training on the frequency and cytotoxicity of NK cells, the results of many studies are controversial due to methodological discrepancies and different exercise regimens (type, duration, intensity) (71). While some studies indicated an increased NK cell frequency and higher NK cell cytotoxicity in athletes compared to sedentary controls, others reported no effects (43). In contrast to studies with healthy young subjects, most studies including healthy older subjects have shown no effects of chronic exercise on the cytotoxicity of NK cells (71). Regarding the impact of chronic exercise on peripheral lymphocyte numbers, most longitudinal studies have failed to demonstrate any major changes (65).

Though, current cross-sectional studies reported a VO_2max dependent decrease of the proportion of total peripheral lymphocytes as physiological adaptation to high-volume endurance exercise training (2, 41). Consistently, T and B cell function appears to be modulated by regular exercise. Especially, well-trained athletes undertaking high-intensive training regimens showed decreased numbers of cytotoxic CD8+ T cells, decreased T cell proliferation and a decline in stimulated B cell immunoglobulin (Ig) synthesis (2, 32, 64). Therefore, athletes who train for long periods of time in high- volume and high-intensity exercise loads may be more prone to infectious diseases through reductions in T cell functionality.

However, recent studies demonstrated an increased Treg cell frequency in athletes (67). Due to their anti-inflammatory properties, Tregs could at least partially compensate impaired immune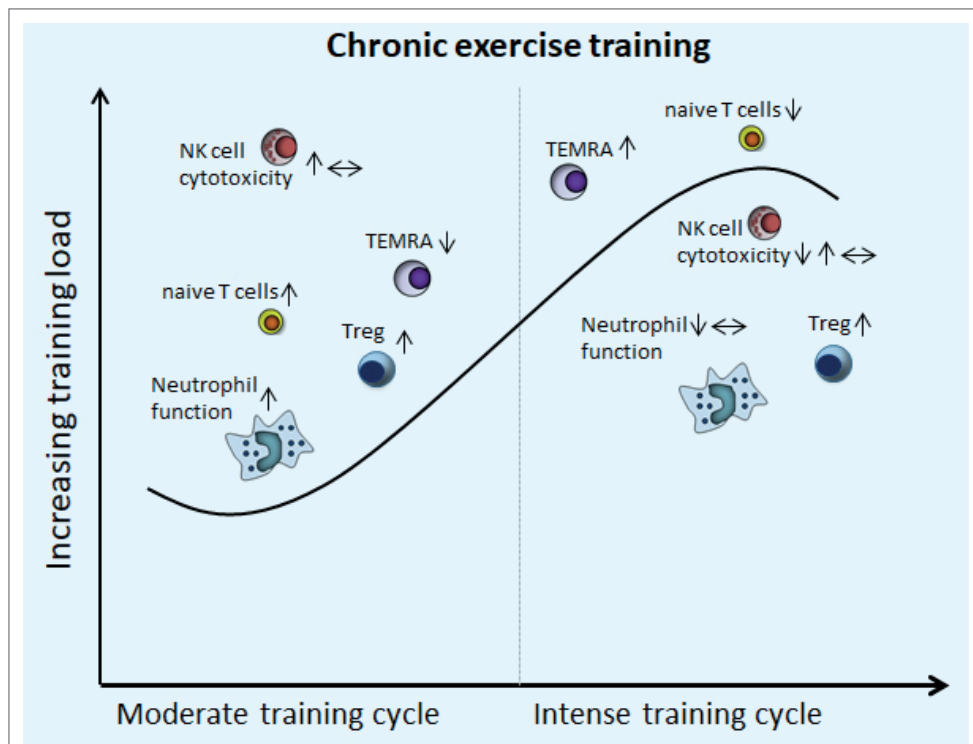 function during periods of heavy exercise loads. Moreover, lymphocyte apoptosis sensitivity is associated with aerobic endurance training status (2, 26). After ex vivo cultivation, lymphocytes of athletes showed reduced sensitivity to specific apoptosis inducers such as PHA-L. Although lymphocyte apoptosis was similar under basal conditions between athletes and non-athletes, molecular signatures differed in lymphocytes of highly endurance trained athletes characterized by a balanced modulation of pro- and anti-apoptotic apoptosis proteins and micro-RNAs such as XIAP, BAK1, miR-23a and miR-27a in athletes (2).

Hence, it is suggested that lymphocytes adapt to exercise training by increasing their resistance to apoptosis and facilitating lymphocyte homeostasis. By this, lymphocytes of athletes may be better prepared to combat the transient immune suppression post-exercise (2). Accordingly, it has been reported that lymphocytes adapt to chronic exercise by up-regulation of cellular defense systems such as heatshock protein 72 (HSP72) (16). In addition, recent studies show that the proportions of low differentiated and highly differentiated T cell subpopulations are also modulated by regular exercise (12, 59). Thus, at baseline, the proportions of mTeff were lower, while memory regulatory T cells (mTreg) were higher in high physical fitness subjects (12). Considerably, a study discovered changes in naïve and memory T cells in elite swimmers even during season (59). During the initial training period characterized by a gradually increasing load, CD4+ naïve, CD8+ naïve, gamma-delta effector-memory (γδ EM) and central-memory (CM) T cells increased in peripheral blood, while γδ terminal effector (TEMRA) T cells decreased. Though, there was an increase in CD8+ TEMRA, ❯

γδ TEMRA and EM T cells alongside a decrease in naïve T cell subpopulations during the subsequent intense training cycle (59). Results indicate that athletes may be more prone to infections in response to increased heavy training loads during season, while moderate exercise training in pre-season appears to promote immune function (Figure 1). Additionally, it has been reported that exercise training mobilizes naïve T cells and decreases TEMRA cells under pathophysiological pre-diabetic conditions (50). The results propose that chronic exercise by increasing naïve T cells repertoire might be beneficial for patients suffering from autoimmune diseases who are at increased risk of reactivating latent viruses and novel infections.

Effects of Exercise on Mucosal Immunity

The MIS represents a network of mechanical, cellular and humoral factors which are integrative regulated to exert protection against invading antigens. MIS can be mainly found at the nasal passages, the respiratory tract, and the intestines. It offers a protective role at all mucosal surfaces, and the effectiveness of its immunity is based on mucosal epithelial cells (ECs) covered by mucus and antimicrobial products and fortified by both innate and adaptive components of host defense (39, 40, 46).

High rates of infections in athletes have led to an increasing focus on the mechanisms of mucosal homeostasis in the respiratory tract during exercise. It is well-known that neuronal signals and stress responses are important regulators of the immunity at mucosal sites. These include psychological stress, various environmental stressors, and exercise. The majority of studies in the field of exercise and mucosal immunity have focused on the respiratory tract. Most studies presented changes in the secretion of SIgA in saliva after exercise and training (65). These results are partly inconsistent, because methods of saliva collection and diurnal variations importantly affect the results. However, after acute intensive endurance exercise most studies observed a reduction of SIgA which seems to be associated with an increased risk of URTI in athletes. In contrast, exercise and training of moderate intensities can increase IgA levels and might be associated with a reduced incidence of infections (20). Accordingly, SIgA has shown moderate diagnostic value, while its utility is limited due to large intra- and inter-individual variation (65). Since SIgA is affected by vegetative nerve stimulation, it is speculated that exercise of long duration and high intensity induces the activation of the sympathetic nervous system followed by an inhibition of salivary IgA synthesis, exocytosis and transcytosis (20). Saliva concentrations of α-amylase and lysozyme increase after intensive exercise, but no association to athletes' infection rates have been found so far (65).

Regarding the effect of exercise on intestinal mucosal surfaces there are less data available. While some recent data provide evidence for health promoting effects of exercise on microbiota and gut barrier function, some human studies demonstrated perturbations of the mucosal immune homeostasis and an increased intestinal permeability especially after exercise of long duration in hot environment (73). In these subjects a modest circulatory endotoxaemia was observed which was accompanied by a pro-inflammatory cytokinaemia. However, the underlying mechanisms and the clinical relevance is still discussed (18).

Molecular Mechanisms of Exercise-Induced Immune Changes

Various molecular mechanisms have been identified which mediate acute and chronic exercise effects on the adaptive and innate immune function. These mechanisms are versatile, but also integrative and contiguous. An important process seems to be the increased hemodynamics during exercises, including an increase in cardiac output, vascular vasodilation, and blood flow. The greater mechanical forces on the endothelium induce leukocytes demargination and redistribution throughout the body. An important driver of this process is the individuals stress response mediated by the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal axis (HPA axis). The activation of both axes produce signals for receptors on a variety of immune cell subtypes (14). Norepinephrine and epinephrine represent ligands for adrenergic receptors which can be found on T cells, monocytes, and NK cells. After stimulation, important cellular functions, such as proliferation, differentiation, cytokine production, migration properties and trafficking, antibody production, or cytotoxicity are affected, implicating a major role for adrenergic mechanisms for regulating central immune cell functions (14). Mobilization of hematopoietic progenitor cells seems to depend on β2-adrenergic mechanisms as well (1).

Moreover, the action of catecholamines seems to have immune-regulating effects, since adrenoceptor activation downregulates the lipopolysaccharide (LPS)-induced production of inflammatory cytokines. The release of cortisol from the adrenal cortex affects leukocyte mobilization, redistribution, and exhibits anti-inflammatory effects by inhibiting various immune cell functions (40). Recent data provide evidence that cytokines, such as IL-6 and IL-7, and proteases are also important factors for immune cell activation, proliferation and survival. However, their particular role on the immune cell function during exercise is not quite clear (58). An important role for IL-6 and matrix metalloproteinases (MMPs) was proved for leukocyte redistribution during pathological conditions, such as cancer (49). Similarly, epigenetic mechanisms gained progressively interest in exercise immunology.

Accordingly, exercise affects epigenetic regulation of gene expression by various mechanisms, such as DNA methylation, histone modification and alterations in microRNA profiles. Some recent data showed immunological health benefits due to exercise training through epigenetic mechanisms. However, actually this research is a growing field and has to be integrated in the current knowledge in exercise immunology (17, 52). Regarding intracellular signaling, the exercise-induced stress stimulus has been shown to affect various intracellular signaling mechanisms, such as an altered Ca2+ signaling, changes in metabolic intermediates such as the NAD+/NADH and AMP/ATP ratio, phosphorylation of kinases, cellular repair and recycling processes, and oxidative balance (58).

With regard to oxidative stress, regular exercise training increases the body's antioxidant defense system followed by the prevention of oxidative damage to cellular structures. Due to the close bi-directional relationship between oxidative stress and inflammation an exercise-induced increase of anti-oxidative enzymes, such as superoxide dismutase (SOD), might be a favorable immune-regulating adaptation in response to training (58).

Exercise Effects on Immunosenescence

The term immunosenescence describes the process of progressive dysfunction during aging. Age-decline of various immunological processes contributes to the increased susceptibility of elderly persons to acute and chronic infections, autoimmune diseases, systemic inflammatory diseases, and cancer. Central functions of both the innate as well as the adaptive immune system decline in older people, and the adaptive response seems to be more affected (46, 48).

While T cell number remains constant during aging, the quality of the T cell compartment undergoes an important remodeling process. Accordingly, aging is associated with a slight and progressive decline of the CD4/CD8 T-cell ratio alongside a diminution in numbers of naïve T cells. Instead, more differentiated memory cells accumulate, which can be most profoundly observed within the CD8+ T cell compartment (48). Here, an increased percentage of T cells lacking expression of the lymphoid homing receptor CCR7 and the costimulatory molecules CD27 and CD28 alongside re-expressing CD45RA, can be found. These cells, termed T effector memory cells re-expressing CD45RA (TEMRA) cells, have a reduced ability to proliferate upon antigen contact, but produce large amounts of pro-inflammatory cytokines allowing them to potentially participate in immune pathology (48, 50).

Cellular changes are accompanied by profound modifications of the systemic cytokine network. While levels of IL-2 slightly decrease, aging is accompanied by a two- to four-fold increase in circulating cytokines, chemokines, and proteases, collectively termed 'gerokines'. The progressive increase in gerokines, such as TNF-α, IL-6 and C-reactive protein (CRP) (48) reflects a generally increased basal activity of the entire inflammatory network that has recently been termed 'inflamm-aging' (48). Inflamm-aging is amplified by the existence of other immunological risk factors, such as obesity or smoking, and the blood stream represents an important distributor of inflammatory signals throughout the body.

Consequently, systemic inflammatory signals affect local, age-associated cellular changes to a senescence-associated secretory phenotype (SASP) that can have deleterious effects on the tissue microenvironment (5, 30, 31). Increased systemic inflammation seems to be inversely associated with a decline of immune function which mainly affects the T cell compartment (30, 31) (Figure 2). During exercise, older subjects were reported to mobilize substantially fewer naïve CD8+ T cells compared to younger people. These changes are attributed to a reduction in thymic output
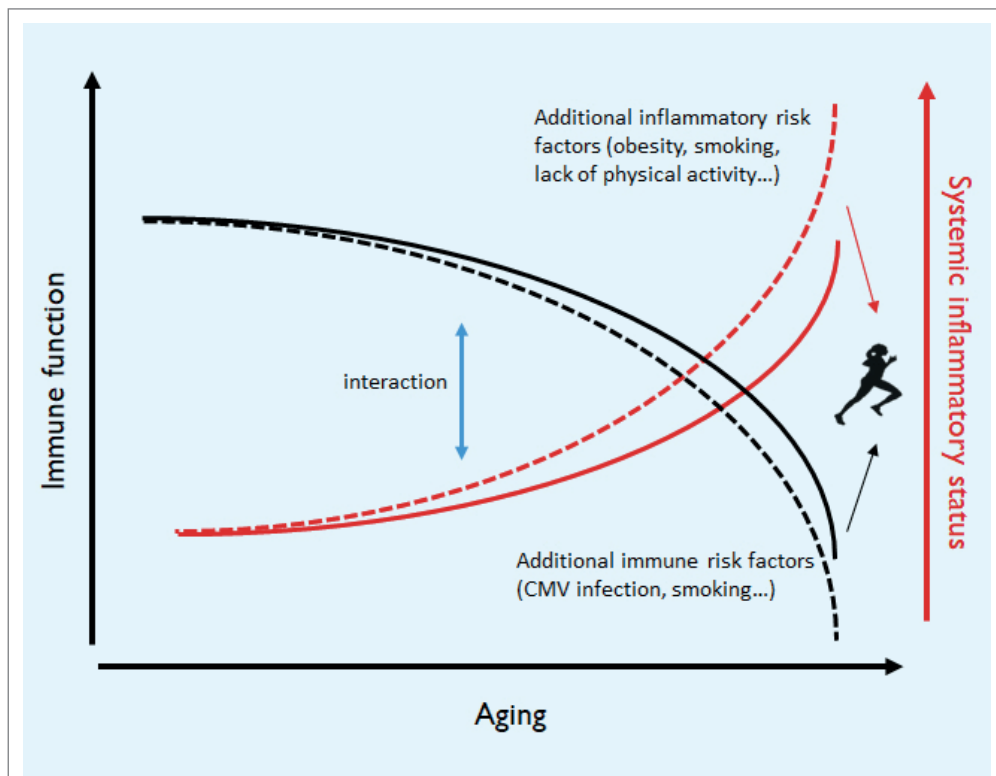

Figure 2

Interaction of progressive systemic inflammation and a decline of immune function during aging and by additional immune risk factors (CMV=Cytomegalovirus).

and to a reduced sensitivity of β2-ARs during aging, which negatively affects catecholamine-induced immune cell redeployment (28).

Recent studies proved that exercise is able to reverse hallmarks of immune senescence, specifically with regard to T cells. It is widely accepted, that regular endurance exercise such as running or walking, increases CD4+/CD8+ ratio in older adults (65). Our own group demonstrated that regular endurance training is followed by proportional increases of naïve and central memory T cells, while proportions of CD8+-TEMRA cells decreased in older pre-diabetic subjects (50). Acute and chronic exercise are followed by an increase of circulating haematopoietic progenitor cells (HPCs) which have been shown to decline during aging (27, 29). The mobilization of cells might reflect an increased production of myeloid lineage cells and a higher lymphoid potential. Animal studies showed that regular treadmill running exerts direct effects on the microenvironment of the bone marrow niche. Pro-inflammatory signals were down regulated and phenotype and function of HPCs were improved (15). Finally, not just younger, but older active individuals (>65 years) benefit from exercising by an increasing T cell proliferation, NK cell cytotoxicity, and neutrophil phagocytic activity (65) (Figure 3).

Some remarkable clinical benefits of exercise, such as a decreased risk of infection and an improved immunological response to vaccination, have been also proved in older adults (25, 67). Accordingly, active elderly women reveal a higher induction of antibodies against Flu B in their 18-month second vaccination follow-up (69). Similarly, regular exercising of moderate intensity for 25-30 minutes at three days per week for a period of ten months induced a significant increase in antibody titer to influenza vaccination (25).
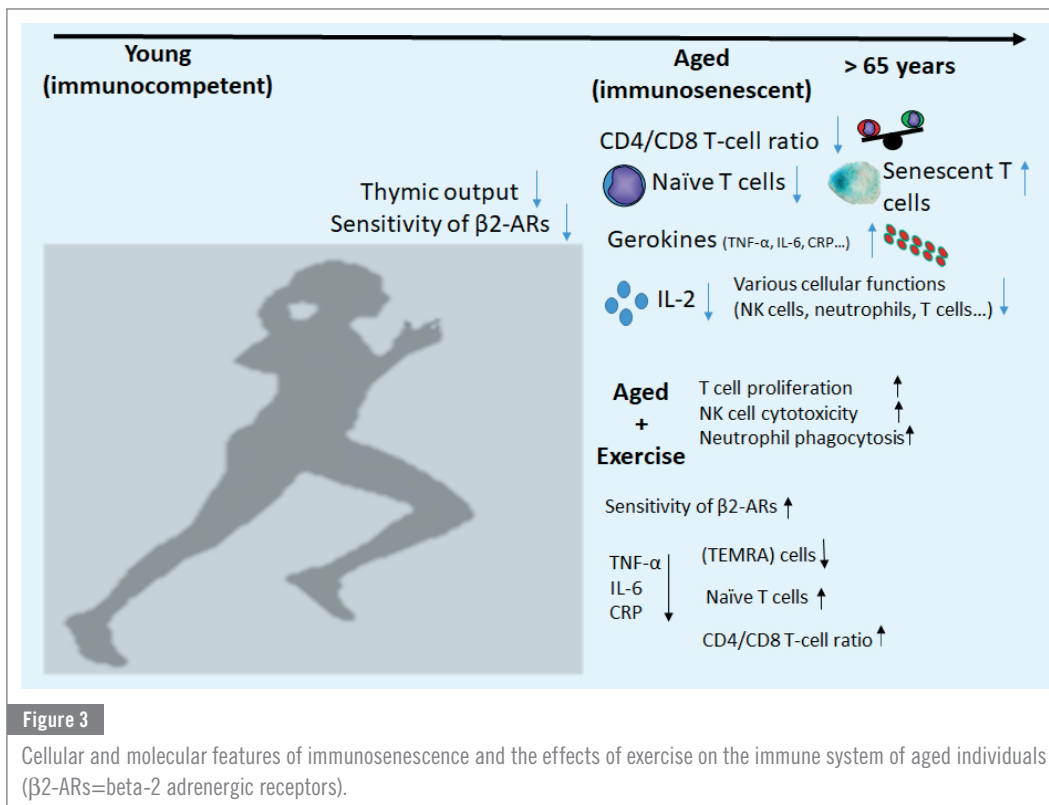
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Figure 3
Cellular and molecular features of immunosenescence and the effects of exercise on the immune system of aged individuals (β2-ARs=beta-2 adrenergic receptors).

Regulatory Effects of Exercise on Inflammatory Status

The prevalence of obesity and chronic diseases rises worldwide. There is a huge body of evidence that a chronic low-grade inflammation is etiologically linked to the pathogenesis of many of these chronic diseases such as type 2 diabetes, specific types of cancer, dementia, cardiovascular diseases (19, 31, 65). This state is characterized by a 2- to 3-fold elevation in plasma concentrations of several inflammatory cytokines (IL-1beta, TNF-alpha) and acute phase proteins like CRP. During the last 2 decades many additional mediators of inflammation have been proposed (e.g. Adiponectin, leptin, resistin, visfatin, specific microRNA, autoantibodies, inflammasome & DAMPS) raising the question about the origin of these inflammatory signal molecules. Overweight and obesity are independent risk factors in developing a series of non-communicable diseases and there is growing evidence that malfunctioning adipocytes, especially those constituting to visceral fat mass, are the inducers of a chronic inflammatory state. Since adipose tissue (AT) is composed of various cell types, such as fibroblasts, endothelial cells, and leukocytes, the relative amounts of inflammatory so-called adipokines produced by adipocytes themselves remain often unknown.

In lean AT, the number of immune cells is low and mainly restricted to anti-inflammatory cell types such as M2 type macrophages and Tregs. During the progression of obesity, there is an excessive fat energy storage which leads to an enlargement of fully differentiated adipocytes and pathologic expansion of AT. These processes are accompanied by both changes in the phenotype of various AT resident immune cells and the invasion of additionally recruited immune cells from the blood. This metabolically orchestrated inflammation, also known as metaflammation, is characterized by a spillover of pro-inflammatory mediators from AT resident leukocytes to the blood (23, 31).

For instance, the progressive infiltration of M1 macrophages enhances the secretion rate of pro-inflammatory mediators resulting in an increase of these cytokines in plasma. Besides, NK cells and T cells increase in AT during obesity while the number of inflammation regulating cells like M2 macrophages and Tregs decreases (23, 31, 45).

Epidemiological cross-sectional studies demonstrate both an association between physical inactivity and low-grade systemic inflammation and that self-reported physical activity and physical fitness is negatively associated with the presence of inflammatory biomarkers (47). Moreover, some longitudinal studies demonstrate that exercise training interventions may suppress systemic low-grade inflammation (38), most human RCTs are inconclusive or failed to show a decrease in the inflammatory level due to methodological limitations though (10). Multiple pathways by which exercise acts as an anti-inflammatory intervention have been discussed. First of all, regular exercise induces a negative energy balance and alters body composition in terms of a reduced fat mass (19). Second, exercise reduces the pro-inflammatory state of AT by means of a reduced recruitment of leukocytes to AT (19) and inducing a switch to an anti-inflammatory phenotype of many immune cells (macrophages, monocytes, T-cells) (19, 45).

Third, upon work skeletal muscle produces many cytokines and other peptides with anti-inflammatory properties. In this regard, IL-6 and other myokines act in a hormone-like fashion and execute endocrine effects in other organs and tissues than the skeletal muscle. IL-6 induces the production of anti-inflammatory cytokines such as IL-1ra and IL-10 (55), soluble TNF-alpha receptors (29), and inhibits the endotoxin-induced TNF-alpha production (55). Fourth, exercise stimulates the release of stress hormones with anti-inflammatory properties such as cortisol and adrenaline by activating both the SNS and the HPA axes (19). Last, recent evidence shows a close relationship between the integrity of gut microbiota and immune function and overall health. Since there is emerging research data which indicates that exercise and physical fitness ameliorates the gut microbiota (in terms of a higher diversity and balanced composition of microorganisms, see 4) limited evidence indicates that exercise-induced alterations of the gut microbiota account for a better immune function (4, 36). Taken together, it is believed that the direct and indirect anti-inflammatory effects of each bout of exercise, which accumulate over time, mediate a high proportion of both the preventive and therapeutic efficacy of exercise.

Perspectives

Most of the available data indicate that exercise is a powerful behavioral intervention to improve immune and overall health outcomes in subjects at all ages. Given that the global burden of chronic diseases is steadily rising, the development and promotion of strategies to a long-term increase of daily physical activity levels at the societal level are necessary. In parallel, scientists are tasked with deepening their understanding of molecular mechanisms in exercise immunology, optimize exercise regimes, and to investigate the effects of combined lifestyle modifications including exercise, nutritional, pharmacological, and other behavioral strategies. Thus, there is a need of well-controlled, randomized interventional training studies using different exercise regimens with multiple end points in order to develop guidelines for immune-enhancing training strategies. In parallel, exercise immunology should make use of innovative biomedical techniques to connect applied research questions more efficiently with basic science being the next step to translational science. ■

Conflict of Interest
The authors have no conflict of interest.

References

(1) **AGHA NH, BAKER FL, KUNZ HE, GRAFF R, AZADAN R, DOLAN C, LAUGHLIN MS, HOSING C, MARKOFSKI MM, BOND RA, BOLLARD CM, SIMPSON RJ.** Vigorous exercise mobilizes CD34+ hematopoietic stem cells to peripheral blood via the β2-adrenergic receptor. Brain Behav Immun. 2018; 68: 66-75. doi:10.1016/j.bbi.2017.10.001

(2) **ALACK K, KRÜGER K, WEISS A, SCHERMULY R, FRECH T, EGGERT M, MOOREN FC.** Aerobic endurance training status affects lymphocyte apoptosis sensitivity by induction of molecular genetic adaptations. Brain Behav Immun. 2019; 75: 251-257. doi:10.1016/j.bbi.2018.10.001

(3) **BAO Y, CAO X.** The immune potential and immunopathology of cytokine-producing B cell subsets: A comprehensive review. J Autoimmun. 2014; 55: 10-23. doi:10.1016/j.jaut.2014.04.001

(4) **BARTON W, PENNEY NC, CRONIN O, GARCIA-PEREZ I, MOLLOY MG, HOLMES E, SHANAHAN F, COTTER PD, O'SULLIVAN O.** The microbiome of professional athletes differs from that of more sedentary subjects in composition and particularly at the functional metabolic level. Gut. 2018; 67: 625-633. doi:10.1136/gutjnl-2016-313627

(5) **BATATINHA HAP, ROSA NETO JC, KRÜGER K.** Inflammatory features of obesity and smoke exposure and the immunologic effects of exercise. Exerc Immunol Rev. 2019; 25: 96-111.

(6) **BETTELLI E, CARRIER Y, GAO W, KORN T, STROM TB, OUKKA M, WEINER HL, KUCHROO VK.** Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature. 2006; 441: 235-238. doi:10.1038/nature04753

(7) **CAMPBELL JP, TURNER JE.** Debunking the Myth of Exercise-Induced Immune Suppression: Redefining the Impact of Exercise on Immunological Health Across the Lifespan. Front Immunol 2018; 16; 9: 648.

(8) **CHEN YC, CHOU WY, FU TC, WANG JS.** Effects of normoxic and hypoxic exercise training on the bactericidal capacity and subsequent apoptosis of neutrophils in sedentary men. Eur J Appl Physiol. 2018; 118: 1985-1995. doi:10.1007/s00421-018-3935-7

(9) **CHIANG LM, CHEN YJ, CHIANG J, LAI LY, CHEN YY, LIAO HF.** Modulation of dendritic cells by endurance training. Int J Sports Med. 2007; 28: 798-803. doi:10.1055/s-2007-964914

(10) **CHURCH TS, EARNEST CP, THOMPSON AM, PRIEST EL, RODARTE RQ, SAUNDERS T, ROSS R, BLAIR SN.** Exercise without weight loss does not reduce C-reactive protein: the INFLAME study. Med Sci Sports Exerc. 2010; 42: 708-716. doi:10.1249/MSS.0b013e3181c03a43

(11) **COX AJ, GLEESON M, PYNE DB, CALLISTER R, HOPKINS WG, FRICKER PA.** Clinical and laboratory evaluation of upper respiratory symptoms in elite athletes. Clin J Sport Med. 2008; 18: 438-445. doi:10.1097/JSM.0b013e318181e501

(12) **DORNELES GP, DA SILVA IM, PERES A, ROMÃO PRT.** Physical fitness modulates the expression of CD39 and CD73 on CD4+ CD25- and CD4+ CD25+ T cells following high intensity interval exercise. J Cell Biochem. 2019; 120: 10726-10736. doi:10.1002/jcb.28364

(13) **DRANOFF G.** Cytokines in cancer pathogenesis and cancer therapy. Nat Rev Cancer. 2004; 4: 11-22. doi:10.1038/nrc1252

(14) **ELENKOV IJ, WILDER RL, CHROUSOS GP, VIZI L.** The sympathetic nerve–an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev. 2000; 52: 595-638.

(15) **EMMONS R, NIEMIRO GM, DE LISIO M.** Hematopoiesis with Obesity and Exercise: Role of the Bone Marrow Niche. Exerc Immunol Rev. 2017; 23: 82-95.

(16) **FEHRENBACH E, NIESS AM, VOELKER K, NORTHOFF H, MOOREN FC.** Exercise intensity and duration affect blood soluble HSP72. Int J Sports Med. 2005; 26: 552-557. doi:10.1055/s-2004-830334

(17) **FERIOLI M, ZAULI G, MAIORANO P, MILANI D, MIRANDOLA P, NERI LM.** Role of physical exercise in the regulation of epigenetic mechanisms in inflammation, cancer, neurodegenerative diseases, and aging process. J Cell Physiol. 2019; 234: 14852-14864. doi:10.1002/jcp.28304

(18) GILL SK, TEIXEIRA A, RAMA L, PRESTES J, ROSADO F, HANKEY J, SCHEER V, HEMMINGS K, ANSLEY-ROBSON P, COSTA RJ. Circulatory endotoxin concentration and cytokine profile in response to exertional-heat stress during a multi-stage ultra-marathon competition. Exerc Immunol Rev. 2015; 21: 114-128.

(19) GLEESON M, BISHOP NC, STENSEL DJ, LINDLEY MR, MASTANA SS, NIMMO MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol. 2011; 11: 607-615. doi:10.1038/nri3041

(20) GLEESON M, PYNE DB, ELKINGTON LJ, HALL ST, ATTIA JR, OLDMEADOW C, WOOD LG, CALLISTER R. Developing a multi-component immune model for evaluating the risk of respiratory illness in athletes. Exerc Immunol Rev. 2017; 23: 52-64.

(21) GLEESON M, PYNE DB, AUSTIN JP, LYNN FRANCIS J, CLANCY RL, MCDONALD WA, FRICKER PA. Epstein-Barr virus reactivation and upper-respiratory illness in elite swimmers. Med Sci Sports Exerc. 2002; 34: 411-417. doi:10.1097/00005768-200203000-00005

(22) GRANDE AJ, KEOGH J, HOFFMANN TC, BELLER EM, DEL MAR CB. Exercise versus no exercise for the occurrence, severity and duration of acute respiratory infections. Cochrane Database Syst Rev. 2015; 16: CD010596. doi:10.1002/14651858.CD010596.pub2

(23) HUH JY, PARK YJ, HAM M, KIM JB. Crosstalk between adipocytes and immune cells in adipose tissue inflammation and metabolic dysregulation in obesity. Mol Cells. 2014; 37: 365-371. doi:10.14348/molcells.2014.0074

(24) JOFFRE OP, SEGURA E, SAVINA A, AMIGORENA S. Cross-presentation by dendritic cells. Nat Rev Immunol. 2012; 12: 557-569. doi:10.1038/nri3254

(25) KOHUT ML, ARNTSON BA, LEE W, ROZEBOOM K, YOON KJ, CUNNICK JE, MCELHANEY J. Moderate exercise improves antibody response to influenza immunization in older adults. Vaccine. 2004; 22: 2298-2306. doi:10.1016/j.vaccine.2003.11.023

(26) KRÜGER K, MOOREN FC. Exercise-induced leukocyte apoptosis. Exerc Immunol Rev. 2014; 20: 117-134.

(27) KRÜGER K, ALACK K, RINGSEIS R, MINK L, PFEIFER E, SCHINLE M, GINDLER K, KIMMELMANN L, WALSCHEID R, MUDERS K, FRECH T, EDER K, MOOREN F-C. Apoptosis of T-Cell Subsets after Acute High-Intensity Interval Exercise. Med Sci Sports Exerc. 2016a; 48: 2021-2029. doi:10.1249/MSS.0000000000000979

(28) KRÜGER K, LECHTERMANN A, FOBKER M, VÖLKER K, MOOREN FC. Exercise-induced redistribution of T lymphocytes is regulated by adrenergic mechanisms. Brain Behav Immun. 2008; 22: 324-338. doi:10.1016/j.bbi.2007.08.008

(29) KRÜGER K, MOOREN FC, PILAT C. The Immunomodulatory Effects of Physical Activity. Curr Pharm Des. 2016; 22: 3730-3748. doi:10.2174/1381612822666160322145107

(30) KRÜGER K. Die wachsende Bedeutung immunregulatorischer Effekte von körperlicher Aktivität. Dtsch Z Sportmed. 2017; 68: 277-279. doi:10.5960/dzsm.2017.308

(31) KRÜGER K. Inflammation during Obesity – Pathophysiological Concepts and Effects of Physical Activity. Dtsch Z Sportmed. 2017; 68: 163-169. doi:10.5960/dzsm.2017.285

(32) LANCASTER GI, FEBBRAIO MA. The immunomodulating role of exercise in metabolic disease. Trends Immunol. 2014; 35: 262-269. doi:10.1016/j.it.2014.02.008

(33) LAVOY EC, HUSSAIN M, REED J, KUNZ H, PISTILLO M, BIGLEY AB, SIMPSON RJ. T-cell redeployment and intracellular cytokine expression following exercise: Effects of exercise intensity and cytomegalovirus infection. Physiol Rep. 2017; 5: e13070. doi:10.14814/phy2.13070

(34) LAVOY ECP, BOLLARD CM, HANLEY PJ, O'CONNOR DP, LOWDER TW, BOSCH JA, SIMPSON RJ. A single bout of dynamic exercise by healthy adults enhances the generation of monocyte-derived-dendritic cells. Cell Immunol. 2015; 295: 52-59. doi:10.1016/j.cellimm.2015.02.007

(35) LIAO HF, CHIANG LM, YEN CC, CHEN YY, ZHUANG RR, LAI LY, CHIANG J, CHEN YJ. Effect of a periodized exercise training and active recovery program on antitumor activity and development of dendritic cells. J Sports Med Phys Fitness. 2006; 46: 307-314.

(36) MAILING LJ, ALLEN JM, BUFORD TW, FIELDS CJ, WOODS JA. Exercise and the Gut Microbiome: A Review of the Evidence, Potential Mechanisms, and Implications for Human Health. Exerc Sport Sci Rev. 2019; 47: 75-85. doi:10.1249/JES.0000000000000183

(37) MATTHEWS CE, OCKENE IS, FREEDSON PS, ROSAL MC, MERRIAM PA, HEBERT JR. Moderate to vigorous physical activity and risk of upper-respiratory tract infection. Med Sci Sports Exerc. 2002; 34: 1242-1248. doi:10.1097/00005768-200208000-00003

(38) MATTUSCH F, DUFAUX B, HEINE O, MERTENS I, ROST R. Reduction of the plasma concentration of C-reactive protein following nine months of endurance training. Int J Sports Med. 2000; 21: 21-24. doi:10.1055/s-2000-8852

(39) MCGHEE JR, FUJIHASHI K. Inside the mucosal immune system. PLoS Biol. 2012; 10: e1001397. doi:10.1371/journal.pbio.1001397

(40) MCGREGOR BA, MURPHY KM, ALBANO DL, CEBALLOS RM. Stress, cortisol, and B lymphocytes: a novel approach to understanding academic stress and immune function. Stress. 2016; 19: 185-191. doi:10.3109/10253890.2015.1127913

(41) MINUZZI LG, RAMA L, CHUPEL MU, ROSADO F, DOS SANTOS JV, SIMPSON R, MARTINHO A, PAIVA A, TEIXEIRA AM. Effects of lifelong training on senescence and mobilization of T lymphocytes in response to acute exercise. Exerc Immunol Rev. 2018; 24: 72-84.

(42) MORO-GARCÍA MA, FERNÁNDEZ-GARCÍA B, ECHEVERRÍA A, RODRÍGUEZ-ALONSO M, SUÁREZ-GARCÍA FM, SOLANO-JAURRIETA JJ, LÓPEZ-LARREA C, ALONSO-ARIAS R. Frequent participation in high volume exercise throughout life is associated with a more differentiated adaptive immune response. Brain Behav Immun. 2014; 39: 61-74. doi:10.1016/j.bbi.2013.12.014

(43) NIEMAN DC, HENSON DA, AUSTIN MD, SHA W. Upper respiratory tract infection is reduced in physically fit and active adults. Br J Sports Med. 2011; 45: 987-992. doi:10.1136/bjsm.2010.077875

(44) NIEMAN DC, HENSON DA, GUSEWITCH G, WARREN BJ, DOTSON RC, BUTTERWORTH DE, NEHLSEN-CANNARELLA SL. Physical activity and immune function in elderly women. Med Sci Sports Exerc. 1993; 25: 823-831. doi:10.1249/00005768-199307000-00011

(45) OLIVEIRA AG, ARAUJO TG, CARVALHO BM, GUADAGNINI D, ROCHA GZ, BAGAROLLI RA, CARVALHEIRA JB, SAAD MJ. Acute exercise induces a phenotypic switch in adipose tissue macrophage polarization in diet-induced obese rats. Obesity (Silver Spring). 2013; 21: 2545-2556. doi:10.1002/oby.20402

(46) PARKIN J, COHEN B. An overview of the immune system. Lancet. 2001; 357: 1777-1789. doi:10.1016/S0140-6736(00)04904-7

(47) PARSONS TJ, SARTINI C, WELSH P, SATTAR N, ASH S, LENNON LT, WANNAMETHEE SG, LEE IM, WHINCUP PH, JEFFERIS BJ. Physical Activity, Sedentary Behavior, and Inflammatory and Hemostatic Markers in Men. Med Sci Sports Exerc. 2017; 49: 459-465. doi:10.1249/MSS.0000000000001113

(48) PAWELEC G, DERHOVANESSIAN E, LARBI A, STRINDHALL J, WIKBY A. Cytomegalovirus and human immunosenescence. Rev Med Virol. 2009; 19: 47-56. doi:10.1002/rmv.598

(49) PEDERSEN L, IDORN M, OLOFSSON GH, LAUENBORG B, NOOKAEW I, HANSEN RH, JOHANNESEN HH, BECKER JC, PEDERSEN KS, DETHLEFSEN C, NIELSEN J, GEHL J, PEDERSEN BK, THOR STRATEN P, HOJMAN P. Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. Cell Metab. 2016; 23: 554-562. doi:10.1016/j.cmet.2016.01.011

(50) PHILIPPE M, GATTERER H, BURTSCHER M, WEINBERGER B, KELLER M, GRUBECK-LOEBENSTEIN B, FLECKENSTEIN J, ALACK K, KRÜGER K. Concentric and Eccentric Endurance Exercise Reverse Hallmarks of T-Cell Senescence in Pre-diabetic Subjects. Front Physiol. 2019; 10: 684. doi:10.3389/fphys.2019.00684

(51) ROSS MD, MALONE EM, SIMPSON R, CRANSTON I, INGRAM L, WRIGHT GP, CHAMBERS G, FLORIDA-JAMES G. Lower resting and exercise-induced circulating angiogenic progenitors and angiogenic T cells in older men. Am J Physiol Heart Circ Physiol. 2018; 314: H392-H402. doi:10.1152/ajpheart.00592.2017

(52) SCHENK A, KOLIAMITRA C, BAUER CJ, SCHIER R, SCHWEIGER MR, BLOCH W, ZIMMER P. Impact of Acute Aerobic Exercise on Genome-Wide DNA-Methylation in Natural Killer Cells-A Pilot Study. Genes (Basel). 2019; 10: E380. doi:10.3390/genes10050380

(53) SIMPSON RJ, FLORIDA-JAMES GD, COSGROVE C, WHYTE GP, MACRAE S, PIRCHER H, GUY K. High-intensity exercise elicits the mobilization of senescent T lymphocytes into the peripheral blood compartment in human subjects. J Appl Physiol (1985). 2007; 103: 396-401. doi:10.1152/japplphysiol.00007.2007

(54) **SPENCE L, BROWN WJ, PYNE DB, NISSEN MD, SLOOTS TP, MCCORMACK JG, LOCKE AS, FRICKER PA.** Incidence, etiology, and symptomatology of upper respiratory illness in elite athletes. Med Sci Sports Exerc. 2007; 39: 577-586. doi:10.1249/mss.0b013e31802e851a

(55) **STEENSBERG A, FISCHER CP, KELLER C, MØLLER K, PEDERSEN BK.** IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. Am J Physiol Endocrinol Metab. 2003; 285: E433-E437. doi:10.1152/ajpendo.00074.2003

(56) **STEPPICH B, DAYYANI F, GRUBER R, LORENZ R, MACK M, ZIEGLER-HEITBROCK HW.** Selective mobilization of CD14(+)CD16(+) monocytes by exercise. Am J Physiol Cell Physiol. 2000; 279: C578-C586. doi:10.1152/ajpcell.2000.279.3.C578

(57) **SUGAMA K, SUZUKI K, YOSHITANI K, SHIRAISHI K, MIURA S, YOSHIOKA H, MORI Y, KOMETANI T.** Changes of thioredoxin, oxidative stress markers, inflammation and muscle/renal damage following intensive endurance exercise. Exerc Immunol Rev. 2015; 21: 130-142.

(58) **TARNOPOLSKY M.** Exercise Metabolism-Exerkines Are Medicine. Cell Metab. 2015; 25: 978-984.

(59) **TEIXEIRA AM, RAMA L, CARVALHO HM, BORGES G, CARVALHEIRO T, GLEESON M, ALVES F, TRINDADE H, PAIVA A.** Changes in naïve and memory T-cells in elite swimmers during a winter training season. Brain Behav Immun. 2014; 39: 186-193. doi:10.1016/j.bbi.2014.01.002

(60) **TENG T-S, JI A-L, JI X-Y, LI Y-Z.** Neutrophils and Immunity: From Bactericidal Action to Being Conquered. J Immunol Res. 2017; 9671604. doi:10.1155/2017/9671604

(61) **TICINESI A, LAURETANI F, TANA C, NOUVENNE A, RIDOLO E, MESCHI T.** Exercise and immune system as modulators of intestinal microbiome: implications for the gut-muscle axis hypothesis. Exerc Immunol Rev. 2019; 25: 84-95.

(62) **TRAMMELL RA, TOTH LA.** Genetic susceptibility and resistance to influenza infection and disease in humans and mice. Expert Rev Mol Diagn. 2008; 8: 515-529. doi:10.1586/14737159.8.4.515

(63) **TURNER JE, SPIELMANN G, WADLEY AJ, ALDRED S, SIMPSON RJ, CAMPBELL JP.** Exercise-induced B cell mobilisation: Preliminary evidence for an influx of immature cells into the bloodstream. Physiol Behav. 2016; 164: 376-382. doi:10.1016/j.physbeh.2016.06.023

(64) **VERDE T, THOMAS S, SHEPHARD RJ.** Potential markers of heavy training in highly trained distance runners. Br J Sports Med. 1992; 26: 167-175. doi:10.1136/bjsm.26.3.167

(65) **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.** Position statement. Part one: Immune function and exercise. Exerc Immunol Rev. 2011; 17: 6-63.

(66) **WALSH NP.** Recommendations to maintain immune health in athletes. Eur J Sport Sci. 2018; 18: 820-831. doi:10.1080/17461391.2018.1449895

(67) **WEINHOLD M, SHIMABUKURO-VORNHAGEN A, FRANKE A, THEURICH S, WAHL P, HALLEK M, SCHMIDT A, SCHINKÖTHE T, MESTER J, VON BERGWELT-BAILDON M, BLOCH W.** Physical exercise modulates the homeostasis of human regulatory T cells. J Allergy Clin Immunol. 2016; 137: 1607-1610.e8. doi:10.1016/j.jaci.2015.10.035

(68) **WEISBERG SP, MCCANN D, DESAI M, ROSENBAUM M, LEIBEL RL, FERRANTE AW JR.** Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003; 112: 1796-1808. doi:10.1172/JCI200319246

(69) **WONG GCL, NARANG V, LU Y, CAMOUS X, NYUNT MSZ, CARRE C, TAN C, XIAN CH, CHONG J, CHUA M, HOW W, MOK E, TAMBYAH P, POIDINGER M, ABEL B, BURDIN N, QUEMENEUR L, BOSCO N, NG TP, LARBI A.** Hallmarks of improved immunological responses in the vaccination of more physically active elderly females. Exerc Immunol Rev. 2019; 25: 20-33.

(70) **ZHANG C, TIAN Z.** NK cell subsets in autoimmune diseases. J Autoimmun. 2017; 83: 22-30. doi:10.1016/j.jaut.2017.02.005

(71) **ZIMMER P, SCHENK A, KIEVEN M, HOLTHAUS M, LEHMANN J, LÖVENICH L, BLOCH W.** Exercise induced alterations in NK-cell cytotoxicity - methodological issues and future perspectives. Exerc Immunol Rev. 2017; 23: 66-81.

(72) **ZIEGLER-HEITBROCK L.** The CD14+ CD16+ blood monocytes: Their role in infection and inflammation. J Leukoc Biol. 2007; 81: 584-592. doi:10.1189/jlb.0806510

(73) **ZUHL M, SCHNEIDER S, LANPHERE K, CONN C, DOKLADNY K, MOSELEY P.** Exercise regulation of intestinal tight junction proteins. Br J Sports Med. 2014; 48: 980-986. doi:10.1136/bjsports-2012-091585