EXERCISE AND SPORTS SCIENCES

EFFECT OF EXERCISE ON THE IMMUNE SYSTEM: RESPONSE, ADAPTATION AND CELL SIGNALING

Artigo de Revisão

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ABSTRACT

Introduction: Over the last century, people have become less active, adopting more sedentary habits. This scenario has increased the incidence of chronic diseases such as cardiovascular diseases, type 2 diabetes and metabolic syndrome. The practice of physical activities can influence healthiness by altering the metabolic state and also the immune system. Objective: To review the literature for studies that address the effects promoted by physical exercise on the development of immune responses and the possible signal transduction pathways. Methods: The SciELO and PubMed data bases were consulted. Results: The available literature shows that during the practice of exercise, various subpopulations of leukocytes are altered in accordance with the intensity and duration of the activity performed. Exercise of moderate intensity stimulates a pro-inflammatory response, while those of high intensity tend to promote anti-inflammatory responses that could decrease damage to skeletal muscle. Such alterations are observed in cells that present antigens (such as macrophages and dendritic cells), neutrophils, natural killer cells (NK) and in surface molecules like Toll-like receptors (TLR) and major histocompatibility complex class II, as well as the entire repertoire of cytokines. Conclusion: The current state of knowledge suggests that the alterations in the immune system are dependent on parameters inherent to exercise and that in order to have all these alterations occurring, some cell signaling cascades are activated, giving rise to a complex process of phosphorylation/dephosphorylation that culminates in the activation of transcription factors, translation of mRNA's, protein synthesis and cell proliferation.

Keywords: physical activity, cytokines, effector cells, cell signaling.

INTRODUCTION

During the last century, the population of developed and developing countries has become less physically active, either by the alteration in the kind of work, or by adoption of new habits attributable in part to changes in the demands of work and the adoption of new habits that are increasingly sedentary. This alteration has led to remarkable increases in the incidence of chronic diseases, such as cardiovascular diseases and type 2 diabetes, highlighted words obesity, musculoskeletal disorders, pulmonary diseases, certain types of cancer and neurological disorders. Regardless of the health status, sedentarism has also been affecting both the quality and life expectancy of these populations[1].

The responses promoted by exercise, both acutely and chronically, affect many components of the immune system. Exercise of moderate intensity may stimulate parameters related to cellular immunity and hence decrease the risk of infection, while high-intensity exercise may promote a decrease of these same parameters, increasing the risk of infectious diseases [2-4].

According to the American College of Sports Medicine (ACSM), aerobic activities ranging from 40 to 59% of VO_{2max}, 55 to 69% of maximal heart rate and 12-13 on the Borg's subjective perceived exertion scale are considered moderate intensity, while aerobic activities ranging between 60 and 84% of VO_{2max}, 70 and 89% of maximal heart rate and 14-16 on the Borg's subjective perceived exertion scale are considered high intensity[5,6]. The International Society of Exercise and Immunology (ISEI), in its official guideline, states that the immune dysfunction observed after exercise is more remarkable when the exercise is continuous, prolonged (> 1.5h) and performed at an intensity ranging from moderate to high (55 and 75% of VO_{2max})[7]. Despite these recommendations, not all articles refered to in this review used these parameters for the exercise control (VO_{2max}, HR, subjective perceived exertion) and the evaluated individuals present great diversity (athletes, non-athletes). More complicating was the fact that many studies were performed with experimental animals. These studies were classified with regards for exercise intensity (moderate and intense) according to their description in the original article.

The present study aimed to systematically review the documented effects of exercise on the behavior of cells in the immune system and identify possible signal transduction pathways affected, which guide immune responses.

Basic considerations for the immune response

Immunological response can be understood in two forms: innate response and adaptive response. The innate response includes physical barriers (e.g. skin), chemical barriers (e.g. tears, complement system) and the participation of cells such as macrophages, neutrophils, dendritic cells, natural killer cells

(NK) and microbicide molecules such as the nitric oxide (NO) and the superoxide anion (O_2^-). The adaptive immune response mainly involves T lymphocytes T (CD4+ and CD8+), B lymphocytes and their products, cytokines and antibodies, respectively. It can be divided into a humoral immune response (mediated by antibodies) and a cellular immune response (cell mediated, such as T lymphocytes and macrophages). The CD4+ lymphocytes (auxiliary/*helper*-Th0) may be different in many subpopulations among which we can mention the Th1 cells (type 1 T helper) and the Th2 cells (type 2 T helper), which produce different patterns of cytokines[8,9]. The differentiation of CD4+ lymphocytes into Th1 cells is stimulated by interleukin 12 (IL-12), produced by cells that present antigens (macrophages and dendritic cells), while the differentiation into Th2 cells is induced by the autocrine action of IL-4 produced by CD4+ lymphocytes. The function of Th1 cells relates to the cellular immune response for the control of infections caused by intracellular microorganisms by predominantly producing interferon-gamma (IFN-). Th2 cells mostly continue producing IL-4 and their existence correlates with the humoral immune response for the control of extracellular infections. Many factors guide an immunological response such as the cytokines and co-stimulating molecules predominantly present in the activation microenvironment, the kind of antigen and other early events, which involve dendritic cells and NK cells during the innate immune response. Together, these factors determine whether an infection is controlled, or not. Many of these can be modulated by exercise[9,10].

Cytokines

Cytokines are low molecular weight (5,000 - 30,000 Da) glycoproteins that play a central role in the mediation and regulation of immunological responses[12]. They act as messengers between the cells of the immune, hematopoietic and neuroendocrine systems[13].

The cytokines have been classified as pro- or anti-inflammatory, according to the roles performed. The main anti-inflammatory cytokines are IL-10 and TGF-β (transformation growth factor-beta) that may, among other factors, inhibit the production of pro-inflammatory cytokines[14]. Among the pro-inflammatory cytokines, we can mention IL-1, IL-2, IL-12, IL-18, IFN-γ and TNF-α. Some competitive antagonists are said to be anti-inflammatory, such as the antagonist of the IL-1 receptor (IL-1ra), which prevents IL-1 from binding to its receptor[15]. IL-12, which is recognized as a pro-inflammatory cytokine[14], presents as a subunit called p40 that when free can inhibit IL-12 activity, which indirectly has an anti-inflammatory property[16]. Chemokine, a chemotactic protein of monocytes (MCP-1), can also indirectly act as an anti-inflammatory by inhibition of the production of IL-12[17]. The production of anti-inflammatory cytokines is regulated by a variety of factors[14]. Catecholamines and glucocorticoids stimulate the production of IL-4, IL-10 and IL-13 in vitro[18-21], as does prostaglandin E2 (PGE2), which also increases the production of IL-10, IL-12, (p40) and IL-13[22,23]. While ***in vivo***, catecholamines promote increases in the synthesis of the IL-10 and IL-1ra [24,25].

IL-6, also known as "cytokine gp130", is a cytokine which participates in the inflammatory process, being considered an interleukin responsive to inflammation[26]. However, it presents an indirect anti-inflammatory action by the stimulation of the synthesis of IL-1ra and IL-10[27,28]. This cytokine has been named myocin, since the contraction of skeletal muscles during prolonged exercises releases large concentrations of it into the circulation[28-35]. The IL-8 and IL-15 have also been described by some studies as myocins[28,32,36,37] (table1).

Physical exercise effect on cells of the immune system

Neutrophils

Neutrophils are phagocytes that play an important role in the innate immune response, usually being the first cell type recruited to the infection site. Thus, they are involved in many of the inflammatory processes, including those in muscular tissue, promoted by the exercise. The sequence of events which occurs during the neutrophil

Table 1. Main cytokines involved in the inflammatory process.

Cytokine/ chemokine	Receptor	Main effects	Main producing cells	References
IL-1-α and β	IL-1RI and IL-1RII	Pro-inflammatory, activates and releases of TNF-alpha and IL-6, promotes the acute phase of the inflammation.	Monocyte, macrophage, neutrophil	95.100
IL-1ra	IL-1 RI	Anti-inflammatory, antagonist competitor of the IL-1	Monocyte, macrophage, neutrophil	25.100
IL-2	IL-2Rα,β,γ	Pro-inflammatory, proliferation of T and B lymphocytes, induces IFN-γ production	Th0, Th1	100
IL-12	IL-12R	Pro-inflammatory, increases production of IFN-g and induces differentiation Th0-Th1	Macrophage, dendritic cell and NK	100
IL-18 (superfamily IL-1)	IL-18Rα,β	Pro-inflammatory, induces Th1	Macrophage, dendritic cell	100
IL-17	IL-17R	Pro-inflammatory, induces IL-6 and IL-8	Th17	100
IFN-γ	IFN-γR	Pro-inflammatory, activates macrophage to produce toxic radicals, TNF-α production	Th1, NK and muscle cells	46.100
TNF-α	Members of the superfamily TNF-R	Pro-inflammatory, induces shock proteins, IL-1, apoptosis	Monocyte, macrophage	95.96.100
IL-4	IL-4R	Anti-inflammatory, inhibits production of IL-1 α/β, TNF- α and IL-6; induces differentiation of Th0-Th2, proliferation and differentiation of B lymphocytes.	Th2, mastocyte and basophil	100
IL-10	IL-10R	Anti-inflammatory, inhibits IL-1, IL-6 and TNF- α	Treg, Th2 and macrophage	25.100
IL-13	IL-13R	Anti-inflammatory, inhibits production of IL-1, IL-6, TNF-α	Th2	100
TGF-β	TGF-βRI, TGF-βRII complex	Anti-inflammatory, inhibits IFN-γ	Treg, macrophage	99.100
IL-6	IL-6R	Pro/anti-inflammatory, activates respiratory explosion in neutrophils, production of proteins of acute phase; inhibits IL-1 and TNF-α; glucose uptake in the skeletal muscle; lipolysis in the muscle and adipose tissue; hepatic glyconeogenesis	Monocyte, macrophage and muscle cell	28.29.30.37.100
IL-8 (CXCL8)	IL-8R (CXCR1)	Pro-inflammatory, chemotactic factor for neutrophil and basophil; induces degranulation and respiratory explosion in neutrophil; angiogenesis	Monocyte, macrophage, neutrophil and muscle cell	28.37.100
IL-15	IL-15Rα and IL-2Rβ, γ	Pro-inflammatory, chemotactic for T lymphocyte and NK, induces IFN-g and TNF-α; muscle hypertrophy	Monocyte, fibroblast and muscle cell	37.100

response includes adherence, chemiotaxis, phagocytosis, oxidative burst, degranulation and elimination of the microorganism[38].

Many elements are involved in the behavior of neutrophils and in the immune response to exercise, which influence neuroendocrine mediators, steroids release, production of cytokines and oxi-reduction processes that are associated to the production of free radicals[39]. The activation of the muscle fiber increases the release of calcium (Ca^2+), leading to the synthesis of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α) and IL-1β, which regulate the expression of selections by the endothelial cells that attract circulating neutrophils to the region. IL-6 and IL-8 cytokines, which are secreted after tissue damage, stimulate the signaling pathway that activates NADPH-oxidase causing the release of reactive oxygen species[40].

Wolach et al.[41] examined the effect of anaerobic exercise (Wingate test) and aerobic exercise (performed at 70-80% of HRmax) on the function of neutrophil in female judo athletes compared to sedentary women. There was a significant decrease in the chemotaxis of neutrophils 24h after aerobic exercise in both groups, but there was no difference in the bactericide activity or superoxide release. The authors also did not observe significant changes in the neutrophil function after anaerobic exercise in the groups. The decrease in the chemotactic chain, only observed in aerobic exercise, suggested that it was altered due to the existing interdependence between volume and intensity and not by the intensity per se. Although the effect in the neutrophils chemotactic activity decrease was transitory and reverted within 48h after exercise, it is possible to generate a "window of opportunity" in which the increased risk of infection should be considered[42].

Intense physical exercise promotes degranulation of neutrophils increasing the concentration of enzymes such as the myeloperoxidase (MPO), which acts as a marker of neutrophil migration into the muscle and of the degranulation of these in the serum[43].

The infiltration of neutrophils within rats submitted to five weeks of swimming exercise was more remarkable in oxidative fibers (red) than in glycolytic fibers (white). Significant differences have not been observed in the concentration of protein markers for neutrophil activity (MPO) between rats trained, untrained or at rest. However, a single session of exhaustive exercise produced significant MPO increases in untrained animals compared to the trained group suggesting a possible protective effect from training in the muscle tissue[44].

Antigen-presenting cells

T lymphocytes recognize antigens only when presenting cells (dendritic cells, macrophages and B lymphocytes) expose those antigens on their surface in association with molecules of the major histocompatibility complex (MHC). Prolonged and extenuating aerobic exercises decrease the expression of Toll-like receptors (TLRs) in macrophages and compromise the presentation of antigens to T lymphocytes, especially for the Th1 inflammatory response. This anti-inflammatory effect avoids the usual tissue damage caused by inflammatory mediators and reduces the risk of chronic inflammatory diseases, but increases the susceptibility to infections by intracellular microorganisms[45].

Macrophages of mice submitted to aerobic training at moderate intensity performed on treadmill increased their microbiocidal capacity and the production of IFN-γ, TNF-α and NO resulting in a diminished infection by *Listeria monocytogenes*. Decreases in the IL-10 production was also observed. Still, in these cells, training promoted a decrease of the β 2-adrenergic receptors (β 2AR)[46], as previously reported for lymphocytes after resistance training[47]. The β 2AR is a member of the G-protein coupled receptors and functions to link regulation of the immune system via the sympathetic nervous system[48]. This receptor also is involved with the inhibition of the induction of NO sintase enzyme (iNOS). Decreases in the levels of ß 2AR is a contributing factor that contributes to the rise in the microbiocide activity of macrophages promoted by moderate training[46].

Dendritic cells internalize antigens and express a large number of co-stimulatory molecules that are important for presenting antigens to T cells, stimulating their clone expansion[49]. Chiang et al.[50] observed in rodents an increase in the number of dendritic cells, together with their expression of class II MHC and production of IL-12, after five weeks of treadmill training that increased in velocity and inclination over time suggesting an induction of the capacity of the immune cell response.

NK cells

The NK cells are lymphocytes with natural cytotoxicity for cells infected by virus and tumor cells, discarding primary sensibilization and independent from presentation via MHC. These cells present the receptor III as surface markers for the constant region (Fc) of IgG, the Fcg (CD16) and a neural cell adhesion molecule (CD56)[51], which is responsible for homotypic adhesion[52]. Based on the CD56 expression, these cells may be divided in two subpopulations: CD56dim, which present high levels of CD16, are more cytotoxic and correspond to 90% of the NK cells present in the peripheral circulation; and CD56bright, whose CD16 levels are lower or non-existing and correspond to about 10% of the total circulating NK cells[53,54]. The CD56bright phenotype is able to produce a variety of cytokines including IFN-γ and TNF-α., which are involved in the interface between the innate and adaptive immune response, especially by the production of IFN-γ, which induces the polarization of TCD4+ in Th1[53-56]. Once activated, the CD56bright cells become equally cytotoxic as the CD56dim [57] subpopulation suggesting that the CD56bright cells are immediate precursors of CD56dim[52]. The repertoire of adhesion molecules and chemokines receptors expressed by these subpopulations are unique, which causes migration to different sites. CD56dim preferably migrate to acute inflammatory sites, while CD56bright to the secondary lymphoid organs[52,58].

NK cells present remarkable sensitivity to the stress induced by physical exercise, which promotes their redistribution from the peripheral blood to other tissues. This suggests that the NK cells may be a potential link between regular physical activity and general health status[59]. Mobilization of peripheral circulation may occur via mechanisms that include stress caused by a substantial increase in the peripheral blood flow and decreased expression of adhesion molecules induced by catecholamine[60], whose production is stimulated by the physical exercise[61]. However, during excessive prolonged exercise (>3h), the concentration of circulating NK cells may return to the pre-exercise level, or even become lower[62]. It is hypothesized that this decrease is due to the migration of these cells to sites of muscular injury[63]. Some studies demonstrate that the two subgroups, CD56bright and CD56dim, increase during exercise; however, there is a differential mobilization between them. The CD56bright:CD56dim ratio ranges between the resting period, during exercise and in the recovery period, being lower in the two first moments and increased in the third. This observation demonstrates that this balance during reco-

very from the physiological stress favors the subgroup CD56bright [64-66]. It is during this period when the recovery from the homeostasis and tissue adaptation[67] occurs, suggesting that this subgroup may play an important role in the process[59]. Although the NK CD56bright cells are mainly found in secondary lymphoid organs[52,58], these cells are also found in inflammatory sites[58,68], which may be explained by their great capacity for cytokine production and expression of adhesion molecules targeting them to the injured tissue[58]. In addition to cytokine production, CD56bright cells release many angiogenic growth factors in the uterine circulation[69], suggesting that, summed to other factors, they can contribute to the angiogenesis, which is a physiological adaptation to regular exercise[59].

Despite these facts, the role of the NK cells associated to exercise should be further investigated.

Subpopulations of lymphocytes

The concentration of all lymphocyte subpopulations increases in the vascular compartment during exercise and decreases to levels lower than those presented in the pre-exercise period after long duration physical work[70,71]. During exercise, the CD4+ :CD8+ ratio decreases, reflecting a more remarkable increase in the TCD8+ cells in comparison to the TCD4+ [26]. Although the concentration of all lymphocyte subpopulations increases, the percentage of TCD4+ cells decreases due to the fact that the NK cells increase more than any other subpopulation[26,59].

The decrease in the lymphocyte concentration in the post exercise period may be, at least partly, a consequence of an apoptosis mechanism[72]. Higher lymphocytes apoptosis percentage in humans has been described immediately after the performance of high-intensity exercises[72-74].

The level of lymphocytes apoptosis when the exercise was performed at 38% VO_{2max} (6.9 ± 0.5%) was similar to the basal levels (6.2 ± 0.2%) and significantly increased when the exercise intensity reached 61% VO_{2max} (10.4 ± 0.6%). Significant increases in the exercise-induced apoptosis indices were observed with a gradual load increase, reaching the maximum peak after an exhaustive exercise (100% VO_{2max}), reaching an apoptosis percentage of 22.4 ± 0.4%. After 20 minutes of recovery, the apoptotic index was significantly lower, dropping even more after 40 min, and reaching to the basal levels after 60 min post-exercise[72]. Intense exercise was also able to decrease the glutathione concentration (GSH) of lymphocytes, inducing oxidative stress, while the 8, 9 and 3 active caspases content and the DNA fragmentation appeared to increase[75]. Some authors tend to associate intense exercise to apoptosis due to the activity of the high levels of catecholamine produced[72], while others associate it to the increase of oxidative stress[75,76].

Kruger et al.[77] showed that the leukocytes redistribution, a crucial mechanism for hematopoiesis regulation, was active during the alteration in the lymphocytes concentration promoted by the exercise. The catecholamine increase promoted by exercise may be associated to this redistribution, since the lymphocytes present α and β adrenergic receptors at the surface, suggesting a neurohormonal regulation.

T helper lymphocytes (Th)

The virgin TCD4+ lymphocyte expresses the CD28 co-stimulatory molecule on its surface, which interacts with its ligand, the B7 molecule, on the surface of the antigen-presenting cell. The CD28-B7 interaction triggers the cell signaling events for the synthesis of IL-2 and the expression of its receptor (IL-2R) by the T cell leading to its proliferation and differentiation[78,79]. As an individual ages, the absolute number of T lymphocytes decreases, as well as the expression of CD28 molecules and the production of a Th1 pattern of cytokines (IL-2 and IFN-γ) with a concomitant increase in type Th2 cytokines (IL-4). This alteration in the Th1/Th2 balance may contribute to the higher vulnerability of elderly individuals to certain infections[80].

A study conducted with 28 elderly individuals demonstrated that after six months of training with moderate-intensity exercise the absolute number of TCD4+ lymphocytes (CD28+ CD4+) increased, as well as the number of IFN-γ-producing cells (Th1). The IL-4-producing T cells (Th2) did not display significant alterations in levels[81]. Other studies corroborated this observation demonstrating that the absolute number of T lymphocytes and TCD4+[82] cells, along with IL--2R expression in T cells[83], increased in elderly subjects submitted to combined moderate-intensity exercises (resistive and strength) or resistance training program[81]. Therefore, this increased expression would favor a Th1 response, preventing infections, especially those caused by intracellular microorganisms.

Effect of physical exercise in the cytokine production

Cytokine production may be modulated by a set of stimuli, including hormonal stress, oxidative stress and extenuating exercise[15]. The first study suggesting that physical exercise induced an increase of the plasma concentrations of cytokines was published in 1983 and showed that the plasma obtained from humans after exercise practice, when intraperitoneally injected in rats, promoted an increase in the rectal temperature of those animals[84].

Many authors have reported an increase in the serum concentration of anti-inflammatory cytokines after different types of exercise. IL-6 increase has been associated with extenuating exercise in one marathon runner[85], as well as in response to other exercise types, in which increase of approximately 100 fold was observed in the plasma concentration[26,28-33]. IL-6 increase is closely connected to exercise intensity[27,28], which indirectly represents the muscle mass involved in the contractile activity[28]. Exercises that involve limited muscle mass, such as muscles of the upper extremities, may be insufficient to increase the IL-6 plasma concentrations above the pre-exercise levels. On the other hand, running, which involves a greater quantity of muscle groups, is the exercise modality in which the most remarkable IL-6 increase was observed[28]. The serum level peak of this cytokine was observed at the end of the exercise performance or in a short period of time after it, followed by a rapid decrease that returned to the pre--exercise period levels[35]. Thus, the combination between modality, intensity and duration of physical activity determine the magnitude of the plasma concentration of exercise-induced IL-6[28]. Besides the immune modulator effect, this cytokine also has important metabolic effects, such as increases in the uptake of glucose and fatty acids by skeletal muscle, increases in hepatic gluconeogenesis and lipolysis in adipose tissue (figure 1). In the same flow of thinking, IL-8 appears to have angiogenic effects[28,36,37] and IL-15, also produced by muscle contraction, seems to have anabolic effects and in the reduction of adiposity[36,37,86]. Although some studies do not show significant increases in the plasma IL-15 after exercise[87,88], Tamura et al.[89] observed this increase in individuals submitted to 30 minutes of exercise on a treadmill with an intensity of 70% of HRmax predicted by age (HRmax = 220 – age). The authors attribute the lack of consensus in the literature to the different experimental parameters and especially to the timing of the IL-15 measurement after exercise.

Increases in the IL-1ra, IL-4, IL-10, IL-12p40 and MCP-1 concentrations were observed after maximal exercise performance[90], resisted exercise[91,92], downhill running[63], intense cycling[93], endurance running and cycling[92].

In a study performed in male individuals, runners and triathletes, an increase of 60% in the plasma concentration of IL-1ra was observed immediately after a performance of moderate intensity exercise (MIE) (1h of running on treadmill, 60% VO_{2max}), while the downhill running (DR) (45min [–10% of gradient], 60% VO_{2max}) promoted an increase of 100% in the concentration and a high-intensity run (HIR) (1h of treadmill running, 85% VO_{2max}) promoted an increase of 120%. These values were even higher one hour after the end of the physical activity, being 1.3 times higher than the pre-exercise plasma concentration, in the MIE; 2.4 times higher in the DR and five times higher in the HIE. The IL-10 concentration increased only immediately after the HIE (6.3 times) and one hour after this activity (seven times), remaining unchanged in the two other types of training, MIE and DR. The IL-12p40 plasma levels were 30% higher immediately after performance of HIE, while 1h after performance of the three types of exercise, increased only 10%, in the MIE; 15% in the DR and 25% in HIE12.

Increases of the anti-inflammatory cytokines produced during exercise possibly occurs to restrict the post-inflammatory reactions that are a response to the damage to the skeletal musculature caused by the exercise [93], and can also inhibit the production of pro-inflammatory cytokines associated with the development of pathological states, such as type 2 diabetes, cardiovascular diseases and metabolic syndrome[94]. On the other hand, the production of anti-inflammatory cytokines during exercise may result in an increase to the susceptibility to infections[90]. However, many investigations have shown that the practice of moderate exercises induces a Th1 response, with production of pro-inflammatory cytokines[48,59,81]. Resistance exercises of moderate intensity induced a light systemic inflammatory response, which is characterized, at least partly, by increases in the serum levels of inflammatory cytokines, such as IL1β and TNF-α[95,96].

Keller et al.[97] reported that the TNF-α super-expression returned to normal concentrations after 1h of acute swimming exercise in mice whose TNF-α (TNFR) gene receptor was deleted. Additionally, chronic exercise appeared to suppress pro-inflammatory cytokines, such as TNF-α and IL-6, and increasd anti-inflammatory cytokines including IL-4, IL-10 and TGF-β[98,99].

The effect of physical exercise in the signaling pathways involved in the immune response.

The molecular interactions that occur on the cell surface, such as ligand-receptor interactions, trigger a cascade of cytoplasmic biochemical signaling involving numerous signaling transduction pathways. These signals may result in the production of proteins, cytokines, receptors expression and proliferation. During the antigen/receptor ligation in lymphocytes, the antigen receptor aggregation leads to an activation of tyrosine kinase proteins associated with the receptors in the cytoplasmic portion of the cellular membrane. It initiates intracellular signaling by the phosphorylation of a tyrosine residue in the cytoplasmic tails of the aggregated receptors. Other tyrosine kinases may be activated to phosphorylate other targets, until transcription factors are activated and act in the nucleus, inducing to transcription of some genes[100].

The IL-6 signaling is similar to the leptin's due to the leptin receptor (LRb) and the gp130Rβ share high level of homology in their sequences and both activate the signaling pathway of the Janusactivated kinase (JAK) – signal transducer and activator of transcription (STAT) protein complex. When the IL-6 ligates to the IL-6Rα /gp130Rβ homodimerized receptor, it results in a cascade of signaling, which is initiated by JAK self-phosphorylation and activation, followed by SH2 domain recruiting, which contains the tyrosine phosphate protein SHP2, which leads to activation of the Ras-ERK1/2 signaling cascade[28]. The IL-6 may play functions in the immunological system, stimulating the IL-1ra and IL-10 synthesis[27,28], as well as interfere in many metabolic processes via AMPK and PI3K-AKT signaling[28] (figure 1).

The mTOR protein (mammalian target of papamycin – immunosuppressive drug) is a serine/threonine kinase involved in many cellular processes, which include metabolism, growth (hypertrophy and hyperplasia), survival, aging, synaptic plasticity and memory[103]. The signaling pathway of this enzyme may be activated by: 1) physical exercise practice; 2) low levels of cellular energy, via AMPK (AMP--activated kinase protein); 3) growth factors such as insulin and IGF-1; 4) amino acids, via Rag GTPases; 5) Wnt family signals via glycogen sintase kinase 3 (GSK3)[104]. In the immunological system, signaling involving mTOR is triggered by the antigens ligation to their specific receptors in T and B cells or to TLR and by the ligation of interleukins to their receptors[104,105].

This kinase enzyme may be presented in two different complexes: mTORC1 and mTORC2. The mTOR and the LST8 (also called GβL), with the regulating associated protein mTOR (RAPTOR) constitute the mTORC1 complex. RAPTOR is essential to the mTORC1 activity. The mTORC2 complex also presents LST8, but, rather than to RAPTOR, it is associated with RICTOR (a structure insensitive to the rapamicine immunosupressive drug) and possibly to a MAPKAP1 (mitogen-activated protein kinase associated to protein 1, also known as SIN1)[105].

The mTORC1 complex stimulates protein synthesis and cellular proliferation, while the mTORC2 complex alters the cytoskeleton organization. The tuberous sclerosis complex 1 (TSC1) and 2 (TSC2) together constitute the functional complex that acts as an inhibitor

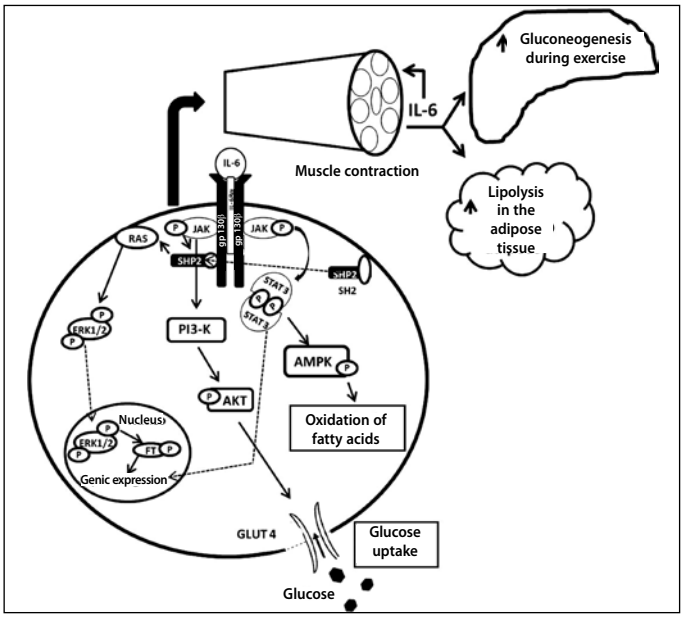
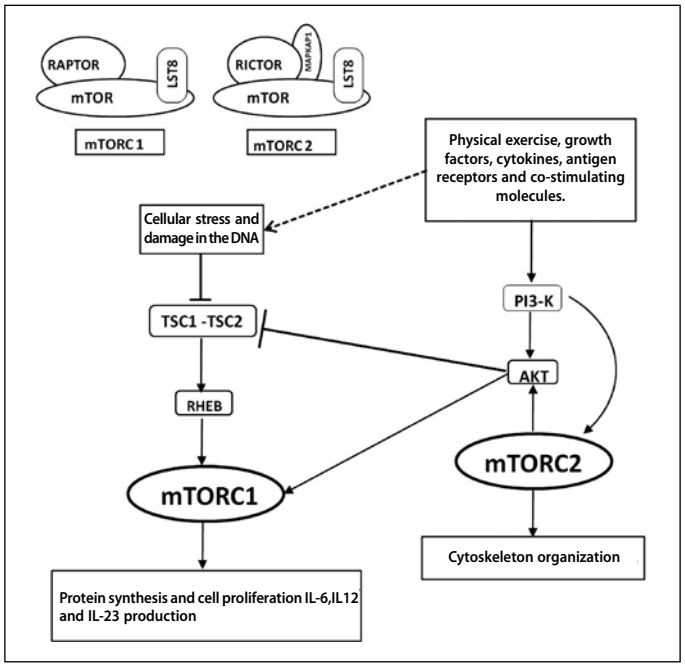


Figure 2. mTORC1 and mTORC2 signaling pathways. A) mTORC1 and mTORC2 complexes. B) Signaling pathway. The tuberous sclerosis 1 complex (TSC1) + TSC2 complex (TSC1-TSC2) is the main negative regulator of mTOR. PI3-K – AKT activation results in inhibitory phosphorylation of TSC2 and removes the RHEB repression (Ras homologous), which is a stimulator of mTORC1. Low levels of nutrients and energy and hypoxia conditions (promoted by physical exercise) increase the mTORC1 inhibition mediated by TSC1-TSC2. mTORC2, activated by PI3K, directly phosphorylates AKT and also regulates the dynamics of the actin 105 cytoskeleton.

of mTORC1. Exercise may cause the production of growth factors and cytokines; the latter, with co-stimulating molecules and antigen receptors activate PI3K, which subsequently activates AKT (PKB). This completely activated enzyme inhibits TSC2 by phosphorylation, allowing mTORC1 activation. Alternatively, cellular stress and DNA damage, which can also be promoted by physical activity, may inhibit mTORC1 activity for promoting the TSC1-TSC2 regulating capacity. This complex acts via RHEB inhibition (a GTPase homologous to Ras, abundant in the brain), which is an mTORC1 stimulator (figure 2)[105].



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mTORC1 inhibition leads to a pro-inflammatory effect in phagocytic cells, increasing their capacity to produce cytokines, such as IL-6, IL-12 and IL-23, and decreasing the production of anti-inflammatory cytokines such as IL-10. This inhibition is also able to stimulate Th1 and Th17 responses, which are typically inflammatory[106]. The mTORC1 pathway can be activated in phagocytes in response to the bacterial infection or after exposure to lipopolysaccharides (LPS), or even during practice physical exercise[107].

CONCLUSION

Regular practice of physical exercise should be positive to health; however, parameters such as volume and intensity need to be considered for the prescribed programs to obtain the best results. Generally speaking, exercise of moderate intensity promotes protection against infections caused by intracellular microorganisms, since it guides the immune response to a predominance of Th1 cells. Conversely, high-intensity activities cause increases the concentrations of anti-inflammatory cytokines (Th2 pattern), presumably to decrease damage in muscular tissue resulting from inflammation, although it may result in an increase of susceptibility to infections. Figure 3 summarizes the main effects of physical exercise in the immunological system.

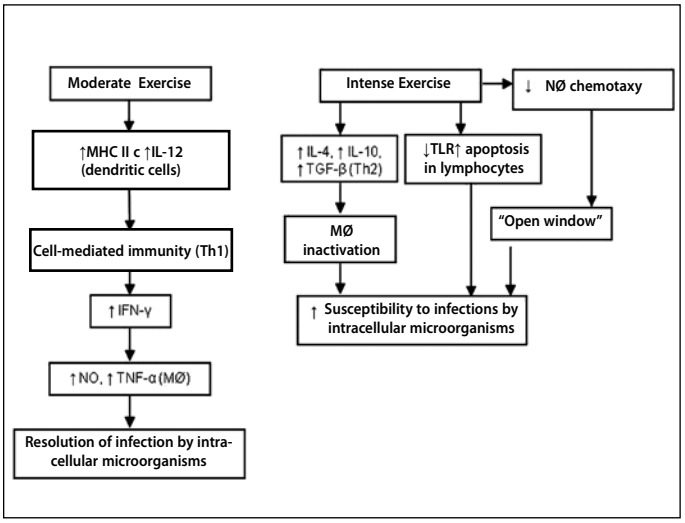

Figure 3. Sum of the effects of physical exercise of moderate and intense intensity in the immunological response. Moderate exercise promotes alterations in parameters of the immunological system, resulting in better resolution of infections by intracellular microorganisms, while in intense exercise these alterations result in increase of susceptibility to infections by these microorganisms. MØ – macrophages, Nφ – neutrophils.

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