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ACADEMIC LITERATURE REVIEW

The role of exercise on the innate immunity of the elderly

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Abstract The increased life span in human population has shown that some diseases, as infections, cancer and autoimmune phenomena, occur more frequently in the elderly than in the younger. We describe the ageing process involving the innate immune system and the improvement given by moderate physical activity. In addition, we discuss the altered neutrophil granulocytes function, the role of macrophages and natural killer cells, besides the influence of cytokines and secretory IgA. The acquired information help us to explain how these changes could favor the onset of diseases in the elderly and how they may boost their immune function.

Keywords Immunosenescence · Neutrophil granulocytes · SIgA · Moderate exercise · Cytokines

Introduction

Ageing may be considered as a slow and progressive preparation of the organism for a morphological and functional involution, which takes part in the biological cycle [39]. Many changes, involving systems, apparatuses and organs, occur during this continuous process. The immune function is also involved, thereby contributing to the increased susceptibility to infections, cancer and autoimmunity diseases [31].

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The immune response consists of two interactive components, the innate (natural) and the acquired (adaptive) response, both of them providing the primary defence against pathogens. Many evidences have suggested that acquired immunity is primarily affected by changes in T-cell function, with B-cell function relatively locked. The modifications of the innate immune system include altered phagocytic capacity, decreased generation of radicals and dysfunctional cytokines production [37].

In the elderly, the proinflammatory phenotype [in particular, the elevation of plasma levels of tumour necrosis factor-α (TNF-α) and interleukin (IL)-6] is associated with an increased morbidity and mortality. In contrast, the anti-inflammatory phenotype, especially IL-10 levels, may be associated with longevity [8].

In the elderly often, a progressive increase in the natural killer (NK) cell phenotype has been noticed. In contrast, in the centenarians, the increase in the NK cells correlated with a good functionality that did not result in meaningful decrease in comparison to the young people [20].

Physical activity and immune function

Inflammatory state, cancer and autoimmune diseases are very common in the elderly. We know the role of immune function in the onset of these illnesses. A compromised function of innate immunity leads to higher susceptibility to upper respiratory tract infections (URTI) such as cold or influenza [56]. Growing evidence revealed that regular and moderate physical activity could promote increase in the innate immune functions (Table 1). It has been demonstrated that the incidence and mortality rates for certain types of cancer, particularly tumours of the colon and the female reproductive tract, are lower among active subjects [57].

Exercise programs also appear to have a beneficial influence on clinical course, at least in the early stages of the disease. The

Table 1 Variations of innate immunity in the elderly through physical activity

	Effect of ageing	Effect of moderate exercise
NK cell numbers	Increased	Increased
NKCA	Decreased	Increased or unchanged
Neutrophil numbers	Unchanged	Increased
Neutrophil function	Decreased	Increased
Monocyte/macrophage function	Decreased	Increased
Pro-inflammatory cytokines	Increased	Low decreased
Anti-inflammatory cytokines	Decreased	Low increased
SIgA secretion rate	Decreased	Increased

NK Natural killer, *NKCA* natural killer cell activity, *SIgA* secretory IgA

role of the immune system may be limited, however, depending on the sensitivity of the specific tumour to cytolysis, the stage of cancer, the type of exercise program and many other complex factors [43].

Regular moderate physical activity may reduce URTI symptoms; in contrast, heavy acute or chronic exercise may increase the risk of upper respiratory tract infection [30]. Many reports suggest that infection severity, relapse and myocarditis may result when patients exercise vigorously [21]. In response to acute exercise, it has been observed that a rapid interchange of immune cells between peripheral lymphoid tissues and the circulation occurs [45]. The response depends on the intensity, duration and mode of exercise, changes in body temperature, blood flow, hydration status and body position concentrations of hormones and cytokines. The cells showing more responsiveness to the effects of acute exercise, both in terms of numbers and function, are NK cells, neutrophils and macrophages [60]. Instead, helper T-cell counts and other immune measures are not enhanced significantly. In response to long-term exercise training, NK-cell activity shows a significant elevation. Some evidence indicates that neutrophil function is suppressed during periods of heavy training. It has been reported that acute exercise bouts of moderate duration (<60 min) and intensity [<60% oxygen uptake (VO2max)] are associated with fewer perturbations and less stress to the immune system than are prolonged, high-intensity sessions [62].

Neutrophil granulocytes

The most frequent infectious diseases in elderly people affect the upper respiratory tract, increasing the risk of mortality in the population with higher susceptibility because of the lowered immune defence.

The primary barrier to bacteria and fungi attack is represented by polymorphonuclear cells. Various studies, comparing the old and the young population, have shown that neutrophil numbers in blood and in bone marrow are still the same [4]. Moreover, chemotaxis and vascular adhesion did not show changes in old adults [3]. Therefore, the compromised function of neutrophil granulocytes could be due to altered phagocytosis and decreased bactericidal capacity, which deals with degranulation and superoxide generation [22]. An explanation for this inability has been given by studying the expression of such membrane markers, as CD16, CD32, CD64 and CD11b. In detail, Butcher et al. [6] have identified an Fc-gamma receptor, called CD16, which declines with age. They noticed neutrophilia during bacterial infection but lowered level of CD16. It has been suggested that the origin of alteration arises in the bone marrow [6]. These findings could contribute to give more information about the reduced production of superoxide anion in response to Gram-positive bacteria, as *Staphylococcus aureus*. Presumably, these types of microbes need Fc-receptor and complement bond.

Escherichia coli, rather, depends on CD14 binding, likely unaffected by ageing; thus the elderly are more susceptible to *S. aureus* and other Gram-positive infections.

In this last mechanism, the presence of ion calcium is not required; thereby, the reactive oxygen intermediates do not undergo any changes.

The calcium intracellular concentration influences the phagocytosis and ability of killing microbes. The increase in calcium levels leads to activation of neutrophils granulocytes; thus, Wenisch et al. [67] hypothesized that inability of neutrophils may be due to elevated resting ion calcium levels; moreover, with ageing, the extrusion of calcium is reduced after stimulation with f-Met-Leu-Phe [23].

Indeed, the same group found that a decreased transport of esoses, fuel for the neutrophils, might be responsible for reduced functionality of these cells [67].

Long-lasting and severe URTI in elderly could not be due to the reduced numbers of neutrophils but to lowered expression of some membrane markers, involving the transmembrane signalling and the production of reactive species, which intervene in the killing of microbes.

Exercise and neutrophils

Relatively few studies have been carried out on various athletes to study the role of neutrophils during exercise. Exercise promotes the release of neutrophils into the circulation, depending on the increase in both catecholamine and cortisol levels. Neutrophils mobilised after exercise have an enhanced capacity to generate some forms of reactive oxygen species (ROS) when stimulated in vitro [50].

ROS generated during intense exercise may lead to DNA damage in leukocytes, but it is unknown if this damage is the result of neutrophil activation.

Following intensive and prolonged exercise training, the function of neutrophils included seems to be impaired [46].

In elite swimmers undergoing strong training, the oxidative activity of neutrophils is markedly lower than controls [55]. Instead, elite female rowers did not show alterations in granulocyte and monocyte phagocytosis and oxidative burst activity before a World Championship [47]. Furthermore, after downhill running in well-trained runners, alterations were absent in degranulation and respiratory burst activity [52]. However, at present, variation in exercise-induced alterations in neutrophil function could be dependent on the differences in exercise protocols and training status.

Macrophages

The macrophages exert a considerable role in immune response and act through several mechanisms as by phagocytosis and elimination of microbes and by the release of mediators like interleukin 1 (IL-1) and TNF-α. Moreover, they play a fundamental role in repairing tissue damage.

With increasing age, the number of monocytes does not appear to change appreciably [38]. Increasing experimental evidence supports the premise that haematopoietic stem cells age and have a limited functional life span [25]. This could explain the hypocellularity in the macrophage precursors observed in the bone marrow of elderly people [48]. Early works suggested that macrophages produce similar levels of cytokines and that difference in function could be modulated through changes in T- and B-cell responses to such substances [40]. Some authors found increased production of IL-1, IL-6, IL-8 and TNF-α by human macrophages, while others reported a decreased synthesis [9, 17]. The decreased production of IL-6 and TNF-α by monocytes from aged subjects following lipopolysaccharide stimulation has been associated with the deficiencies in the activation of protein kinase C (PKC) α, PKC-β_1, PKC-β_{11}, mitogen-activated protein kinase and deficient expression of c-FOS and c-Jun [12]. Additionally, Gon et al. reported a decreased release of granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor and the chemokine macrophage inflammatory protein 1 α (MIP 1α) by human macrophages. Overall, these contradictory results could be explained by the differences in experimental conditions, the methods used to measure the levels of cytokines and the health status of subjects [27].

A cause of macrophage ageing is the acquisition of defects in genomic DNA by a combination of both DNA damage and impaired DNA repair capacity and, consequently, the loss of several functional activities.

Interestingly, a recent study showing the effect of a higher production of TNF-α in splenic macrophages incubated in vitro with autologous serum suggested that the age-specific external milieu exerts an effect on macrophage activation [26]. In fact, monocytes/macrophages are exposed to many agents, like hormones, cytokines and fatty acids, which can act on phenotype and function, responsible for the functional plasticity and adaptation to changing microenvironments. The circulating levels of these agents may change in the elderly and have effects on macrophages [63].

Physical activity and macrophages

Macrophages are involved in skeletal muscle repair through pro-inflammatory and alternative functions. It has been supposed that ageing alters the abundance and properties of skeletal muscle macrophages that will influence their functional response to acute resistance exercise. Pre-exercise, young muscle tended to possess a greater number of macrophages, whereas elderly muscle possessed higher levels of IL-1 beta, Interleukin 1 receptor antagonist (IL-1Ra) and IL-10. Post-exercise, total macrophages did not change in either group. The number of CD11b+ and CD163+ cells increased only in the young. Both subpopulations increased their activity post-exercise exclusively in the young. This finding suggested that ageing results in a defective regulation of muscle macrophage function, both at baseline and in response to resistance exercise, that may limit muscle hypertrophy in older adults [54]. In a recent study in murine model, it has been shown that acute restraint stress is associated with impaired function of macrophages. Whereas, moderate physical training attenuates the effects of acute stress by a mechanism that involves an increase in tolerance of macrophages [36].

Natural killer

The natural killer cells play a critical role in the innate immune response against infections and tumours. NK are cytotoxic cells that differ from cytotoxic T cells by their ability to lyse targets without the requirement of an antigen sensitisation. Early studies suggested no changes in the cytotoxic ability of NK cells with age [34], whereas recently, new evidences contradict these findings. The number of NK cells appears to increase with ageing, but NK activity decreases [16, 35]. The functional decline of the NK cells has been attributed to various factors such as decreased responses to interferon (IFN)-α, IL-2 and IL-12 [5] and increased responses to the negative modulating adenosine triphosphate (ATP) [33].

In some studies, Moccheggiani et al. [42] reported the remarkable role of neuroendocrine-immune pathway in immunosenescence. Hypothalamic, pituitary, gonadal and thyroid hormones' receptors are present on NK cells and on many other immune cells to stimulate cytokine production, thereby affecting adaptive immune responses. Additionally, hormone deficiency, a peculiarity of the elderly people, leads to impaired immune responses. Furthermore, the bioavail-

ability of the ion zinc is relevant, which is important to maintain the efficacy of the neuroendocrine-immune network in ageing [42].

In contrast to the general age-related decline in T and B reactivity, the NK cell system is highly active in the majority of healthy elderly (>80 years) [32]. High NK activity was especially demonstrated in the >80-year group, suggesting that the rate of increase in age-specific cancer incidence tends to be slow and in the same cancers may actually decline in incidence over the age of 80 [10].

Physical activity and NK

In the NK cells, the intensity of exercise influences both the number and the activity. A single bout of exercise for at least 1 h causes cell decrease and a decline of the function; thus, the capacity to lyse tumour target cells is inhibited [51].

The response to chronic stress of an intensive exercise, in athletes compared with non-athletes, leads to increased NK cell activity (NKCA) [51]. In the old adults, a single bout of moderate exercise does not have influence on NKCA. A training program gives beneficial effects on resting NKCA, followed by increase control of both viral infections and of malignant cell formation [66].

Flynn et al. [19] observed a transient increase in NK cell number immediately after exercise in elderly women who underwent 10 weeks of resistance training. Moreover, a comparative study examining the relationship between active in respect to inactive lifestyles and immunocompetence showed that the concentration of NK-cells (CD16+CD56+) significantly increased in the elderly exercisers, compared to that of the age-matched control subjects, or of the young group. The phagocytotic activity of neutrophils showed an age-associated decline but of lesser degree in the elderly exercisers than in the elderly controls. These results suggest that habitual and moderate training in later life is associated with a lesser age-related decline in certain aspects of circulating T-cell function and innate immunity [68].

Another study demonstrated that the natural killer cells response to a single exercise challenge is normal in older individuals, but immediately after exercise, the elderly subjects manifest less suppression of phytohemagglutinin-induced lymphocyte proliferation than younger individuals. In contrast, a strenuous exercise seems to induce a more sustained post-exercise suppression of cellular immunity in older individuals than in young subjects. A few cross-sectional comparisons of immune status between physically fit elderly individuals and young sedentary controls suggest that habitual physical activity may enhance NK cell activity [59]. More recently, elderly men, who were under training regularly for more than 16 years, exhibited a NK cell percentage remarkably greater than those of control group [7].

Overall, only moderate exercise is able to enhance oxidative burst activity, blood granulocytes and monocyte phagocytosis [49, 62].

Cytokines

In the elderly subjects, lymphocytic population mostly represented are $CD28^{-}CD8^{+}$ T lymphocytes. These cells are responsible for an increased production of type 1 cytokines, as IFN-γ and TNF-α, that own defence activity and, on the other side, support a chronic inflammatory status [69]. This status is called "inflamm-ageing" and is likely due to a chronic antigenic load. The latter leads to peculiar increase in inflammatory cytokines and of acute-phase protein production (Table 2).

The inflammatory cytokines are able to improve the expansion and the survival of $CD4^{+}$ T cell effectors [11], thereby improving responses to vaccine. This action is due to the overcoming of the reduced transcription factor activation in aged CD4 cells, thus enhancing IL-2 production, which in turn leads to enhanced CD4 effector generation [29].

Many studies reported a decreased IL-2 and an increased IL-4 production, which is an anti-inflammatory cytokine belonging to type 2 cytokines pattern. IL-4 is mostly produced by activated $CD4^{+}$ cells than the virgin cells. Likely, its increased levels need to offset elevated serum levels of TNF-α and IFN-γ. Furthermore, Alberti et al. [2] have noticed a decreased ratio of IFN-γ/IL-4 in the ageing, suggesting a shift towards an increased role of pattern 2 than pattern 1.

IL-6 is an inflammatory mediator and may be involved in the pathogenesis of numerous age-associated pathologies such as various lymphoproliferative disorders [64]. An increase in IL-6 serum levels appears to be necessary to stimulate the hypothalamus [65].

An interesting research conducted on IL-15 in ultra-longeval subjects showed that this interleukin stimulated the proliferation of memory T cells ($CD45RO^{+}$), both CD4 and CD8, which were the most represented in the elderly. Furthermore, IL-15 led to NK $CD56^{+}$ cell differentiations, which have a key role on defence against bacteria, fungi,

Table 2 Changes of cytokines in elderly

Cytokines	Changes
IL-2	Decreased
IL-2R	Decreased
IFN-γ	Increased
TNF-α	Increased
IL-6	Increased
IL-15	Increased
IL-4	Increased
IL-10	Increased

IL Interleukin; *IFN* Interferon; *TNF* tumour necrosis factor

viruses and protozoa [18]. The enhanced levels seen in the centenarians may explain how the old subjects may protect themselves from infections [24].

Physical activity and cytokines

Some studies carried out on runners and marathoners have demonstrated increased blood concentrations of cytokines, both inflammatory and anti-inflammatory type. In contrast, moderate exercise for no more than 1 h did not seem to have appreciable effects in cytokines levels [61]. The highest level of a cytokine is that of IL-6, which increases after running for 6 h, reaching threefold the baseline level [14], and immediately after 2.5 h of running, IL-6 increased 5.5-fold [44]; besides, a rise of 100-fold has been detected on marathoners [51].

After 2 h by the end of exercise, it has been observed that there are increased levels of IL-1Ra, that is an inhibitor of IL-1, which intervenes to limit the harmful effect of IL-1. The up-regulation of IL-1Ra is due to several cytokines, including IL-6.

IL-1Ra rises 1.5 h post-run, while IL-6 increases during the run [44].

The transforming growth factor TGF-β has shown no enhanced levels, rather than TNF-α, which is increased about threefold in strenuous exercise.

Very interesting is the inhibitor role of IL-6, released in response to exercise-induced muscle damage, on TNF-α [52]. This inhibition may prevent some negative effects, leading to a better lipid profile, elevated insulin sensitivity, a lower blood pressure and anti-inflammatory activity [52]. Mostly, this anti-inflammatory effect may be due to regularly performed exercise [53].

Although it is an unexplored pathway, it could be hypothesized that there is a beneficial effect of exercise on the anti-inflammatory state of elderly people, if they maintain the capacity to release IL-6 during exercise. Resistance exercise, performed by old adults, have shown a decrease in TNF-α levels [28].

Even the intensity of the exercise has some influences on cytokine expression. That has been shown by a Polish study, which examined elderly women undergoing moderate-intensity exercise. The results demonstrated that the percentage of lymphocytes expressing intracellular IL-2 was higher than sedentary control women, and it was the same for young women [13]. The intracellular IL-4-expressing lymphocytes have been decreased, thus contributing to control higher levels of memory cells than naïve cells [13].

Secretory immunoglobulin-A

The secretory immunoglobulin-A (SIgA) are prevalent in saliva, mother's milk, tears, intestinal and bronchoalveolar secretions and in other mucosal fluids. They play a fundamental role against pathogens, which get in through the mucosas. The immunoglobulins bind bacteria and virus, avoiding adhesion and colonization of pathogens. Thus, they prevent infections of upper respiratory tract, as cold or influenza, which are very frequent in old adults. Therefore, decreased levels of SIgA contribute to higher susceptibility of elderly to this kind of infections. Studies carried out in elderly people reported lower SIgA secretion rates at rest both in women and in men [41, 15].

Physical activity and immunoglobulins

Furthermore, surface immune defence could get some beneficial effects by physical activity, performed at low-intensity; thus the SIgA secretion rate, reduced as a consequence of immunosenescence, may enhance.

The SIgA secretion rate depends on IgA concentration and saliva flow rate.

Increased value in SIgA secretion rate was given by an enhancement of SIgA concentration in old adults after an endurance exercise program for 12 months [1].

Sakamoto et al. [56], instead, found a rise of saliva flow rate after exercise; likely, the parasympathetic nervous system is activated after exercise.

The enhancement of saliva flow and SIgA secretion rate is just temporary after low-intensity exercise [56]; instead, another study reported high salivary IgA levels after 12 months of training, although the mechanism is unknown [1].

Recently, it has been demonstrated that a moderate physical activity, as 7,000 steps per day, may improve mucosal immune function in the elderly [58].

Conclusions

A large evidence suggests that the immune changes represent one of the most important phenomena for understanding the pathogenesis of the age-associated diseases. The innate immune system is affected by the ageing process.

Following these data, it may be considered extremely useful for elderly people to have a moderate exercise program to reverse physiological changes in immune function which occur with ageing, increasing their life quality.

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