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Review article

Resistance training and innate immunosenescence of the innate immune system

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ABSTRACT

Phagocytic cells constitute the first defense line against the diversity of infectious agents. The effects of aging on the immune function – immunosenescence – affect the phagocytic capacity of neutrophils and monocytes/macrophages and result in increased risk to cancer and other diseases. The aim of this review was to assess the functional aspects of the innate system cells in aging. Evidence brought about by this review suggests that resistance training is a useful therapy to mitigate the adverse effects of the innate immune system aging process. Resistance training is consistently recommended as assistent strategy for prevention of the inflamaging and associated chronic diseases, but establishing adequate program is still in demand. In addition, future studies are needed to improve our understanding of the resistance training-induced mechanisms underlying changes in phagocytic activity in the elderly.
Key words: Resistance training; Monocytes; Macrophages; Neutrophils; Elderly.

Entrenamiento de resistencia e inmunosenescencia del sistema inmune innato

RESUMEN

Las células fagocíticas constituyen la primera línea de defensa contra los agentes infecciosos. Los efectos del envejecimiento sobre la función inmune – inmunosenescencia – afectan la capacidad fagocítica de neutrófilos y monocitos/macrófagos y resultan en riesgo aumentado para el cáncer y otras enfermedades. El objetivo de esta revisión fue evaluar los aspectos funcionales de las células del sistema innato en el envejecimiento. Las evidencias revisadas sugieren que el entrenamiento de resistencia es una terapia útil para atenuar los efectos adversos del proceso de envejecimiento del sistema inmune innato. Se recomienda el entrenamiento de resistencia continuamente como estrategia complementaria para la prevención de la inflamación y de las enfermedades crónicas asociadas, pero hay que establecer el programa adecuado. Además, se necesitan más investigaciones para mejorar nuestra comprensión de los mecanismos modulados por el entrenamiento de resistencia que inducen a los cambios en la actividad fagocítica en las personas mayores.
Palabras clave: Entrenamiento de resistencia; Monocitos; Macrófagos; Neutrófilos; Anciano.

Treinamento resistido e imunossenescência do sistema imune inato

RESUMO

As células fagocitárias constituem a primeira linha de defesa contra agentes infecciosos. Os efeitos do envelhecimento sobre a função imune – imunossenescência – afetam a capacidade fagocítica de neutrófilos e monócitos/macrófagos e resultam em aumento do risco para câncer e outras doenças. O objetivo desta revisão foi avaliar os aspectos funcionais das células do sistema inato durante o envelhecimento. Os estudos revisados sugerem que o treinamento resistido é uma terapia útil para atenuar os efeitos adversos do processo de envelhecimento do sistema imune inato. Recomenda-se que o treinamento resistido seja aplicado continuamente como estratégia complementar para a prevenção da inflamação e doenças crônicas associadas, porém deve-se estabelecer o programa adequado. Ressalta-se ainda que, são necessários mais estudos para melhorar a compreensão sobre os mecanismos modulados pelo treinamento resistido que induzem a alterações na atividade fagocítica em idosos.
Palavras chave: Treinamento resistido; Monócitos; Macrófagos; Neutrófilos; Idosos.

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Introduction

The elderly people represent the fastest growing age group in the world. In absolute terms, the estimated contingent of elderly individuals should reach 2 billion by 2050 worldwide.[1] Increase in the elderly population is a great challenge for public health, since this population is more susceptible to several diseases related to immune system impairment, or immunosenescence. The conceptual definition of immunosenescence encompasses the decline in efficiency of innate and adaptive immune responses against common pathogens.[2]

The biological cascade in the body's natural defenses against injuries or diseases is a vital part of the immune system. Typically, this process is characterized by an acute response triggered by rapid increase of inflammatory signaling in the circulation.[2-4] However, the immunosenescence phenomenon is paradoxally characterized by an exacerbated systemic inflammatory status that modifyes the basal profile of pro-inflammatory cytokines, known as inflammaging.[3] This scenario is more evident after the fourth or fifth decades of life when there is greater susceptibility to diseases such as cancers and infections. [2-4]

Although the effects of aging on the innate immune system are not completely elucidated,[1] it is presumed that part of the subclinical inflammatory processes associated with immunosenescence is due to the chronic activation of this system due to the decline of the phagocytic capacity of neutrophils and monocytes/macrophages (M/Mø).[4] The phagocytic capacity of neutrophils has proved to be an important predictor of morbidity and mortality in the geriatric people.[1] Therefore, it is very important to establish interventions to prevent or attenuate the imunesenescence.

In this perspective, it is well established that chronic effects of resistance training (RT) can result in health benefits and be especially valuable in elderly. When performed with appropriate intensity, RT can improve strength, muscle mass and oxygen consumption as well as reducing frailty and the risk of falls.[5] In line, many studies suggest that the benefits of RT extend to reducing the pro-inflammatory milieu of the elderly.[5-7] Nonetheless, there is lack of understanding about the influence of RT on the functional response of immune innate cells (that constitute the first line of defense during immunosenescence). Therefore, the purpose of this review was to be investigated the main physiological adaptations induced by RT on neutrophil and M/Mø functional responses, as well as to assess the power and limitations of these studies.

Methods

Search strategy

The data revised were found in scientific journals (until december 2016) in the following databases: PubMed, Scopus, SportDiscus, PsycINFO, PsycARTICLES and Medline, the following indexed terms were used: "imunossenescence", "innate immunity", "resistance training", in combination with the terms "aging" and / or "elderly" to be found anywhere in the articles.

Inclusion and exclusion criteria

Only studies published in English with observational descriptions or whose experimental tests showed effect of RT on innate immunity were included. The articles were examined by internal validity under the following criteria: (1) research with a resistance training only; (2) longitudinal studies; (3) studies using instruments with high reliability, and; (4) descriptive investigations with minimal experimental sample loss. Those that: (1) did not meet the criteria and (2) were duplicated studies, were excluded.

Results

From 57 identified papers, 26 related to resistance training and innate immunity, 21 were excluded because they did not meet the criteria established for this review. Thus, five were analyzed. Figure 1 presents the paper prism selection for the present study:

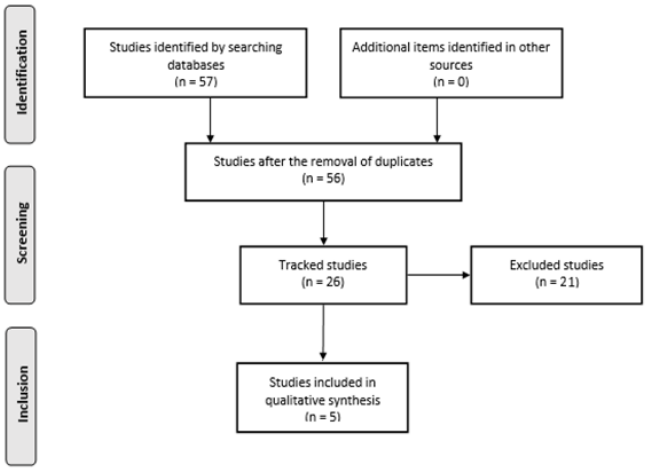

Figure 1. Prism of studies selection and criteria.

Imunosenescence

Immunosenescence is characterized by progressive functional alterations of the innate and adaptive immunity. Although several studies have associated this condition with an immunogical deterioration, it is more appropriate to interpret this phenomenon as a result of a complex state of functional dysregulation, with decay of some elements being somehow balanced by enhancements on other areas.[2] The main clinical outcomes include high susceptibility to infections, malignancies, autoimmune diseases, atherosclerosis, neurodegenerative diseases and reduced vaccine effectiveness.[8]

When we approach immunity aging and its impact on functional capacity, it is very important to emphasize that it is not an isolated act. The imunne system is regulated by plethora of steroid and non-steroid hormones, neurotransmitters and cytokines.[2] Thus, the etiology of immunosenescence is multifactorial and also reflects the continued exposure to pathogens as well as to persistent infectious processes that might contribute an immune exhaustion.[10] In this sense, inflammaging may arise as a complex remodeling due to the gradual and persistent production of pro-inflammatory systemic cytokines.[9,10] A higher and perpetuaded concentration of proinflammatory citokines are predictive markers of mortality, regardless of pre-existing morbidity.[10] Faced with the need for effective strategies to attenuate the impact of inflammaging, physical exercises are considered the most potent non-pharmacological treatment capable of controlling or reversing imbalances resulting from immunosenescence.[5,7,11]

Imunosenescence and innate imune system

The innate immune system is the first line of defense and acts quickly and unspecifically in response to the pathogens. The capacity of professional phagocytes (neutrophils and the M/Mø dual) to eliminate bacterias and other pathogens is an important indicator of proper cellular immunity. This system consists of successive stages of considerable complexity. For example, efficient phagocytic response includes microbicidal activity that begins with the production of different reactive oxygen species e.g.

superoxide anion (O^{2-}) and hydrogen peroxide (H_2O_2), action of cytoplasmatic granules, proteases, and oxidase electrons in the phagocytic vacuole.[12] Reactive oxygen species act as inflammatory signaling and perform an important role in defense against pathogens.[12,13]

Several aspects of the innate immune system are reduced during the aging, such as the ability to respond to pathogens and to activate the adaptive immunity.[2] The mechanisms underlying these changes included changes in the expression of receptors, signaling pathway elements, and total cell counts. The impact of a reduction in neutrophil and natural killer (NK) cell activities predicts higher mortality in the elderly[14] and a deregulation of Toll-Like receptor (TLR) expression affect the effectiveness of vaccines and hyperresponsiveness to viral infection.[15]

Neutrophils

Neutrophils are polymorphonuclear leukocytes and represent about 40-60% of leucocytes. This cell type is produced (≈$2X10^{11}$ daily) in the bone marrow from myeloid precursors, with an estimated half-life of 8 hours. Polymorphonuclear leukocytes eliminate pathogens by intracellular (phagocytosis) or Neutrophyl Extra Cellular Traps (through release of protein granules, histones and chromatin), which result in a lower cell damage.[15] After phagocytosis, the pathogens are exposed to reactive oxygen species (ROS) and antibacterial proteins. Figure 2 shows the phagocytic and microbicidal activity of neutrophils in routine assays carried out in our laboratory.

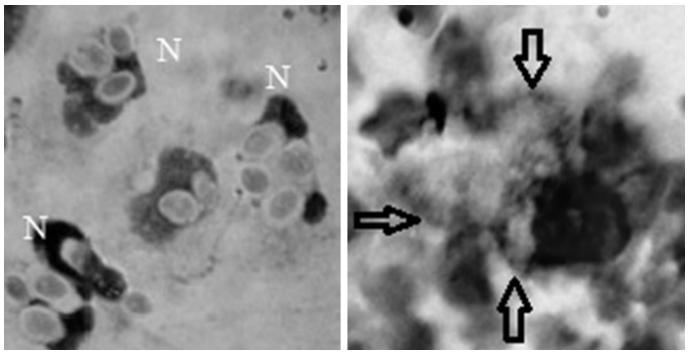

Figure 2. Neutrophils exerting phagocytic activity on Saccharomyces cerevisiae (Left panel) and microbicide activity by the nitro blue tetrazolium reduction test (Right panel). (N: neutrophils; Arrows: formazan production. Sample from a woman aged > 65 years-old).

Neutrophils depend on the ability of diapedesis to move to the target (tissues and organs). They are recruited to the site of infection by chemokines and products released by microorganisms.[16,17]

Typically, the steps that constitute the neutrophil response include: adhesion, chemotaxis, phagocytosis, oxidative reactions, degranulation, and microbial death.[16] In human studies, neutropenia (decline in neutrophil cells) exposes the organism to immunodeficiency and increases mortality risks. Failures in the chemotactic mechanisms in the elderly prolong the time for the phagocytic response and, consequently, favors bacterial proliferation and the chronic inflammatory state.[18] In this condition, elderly neutrophils exhibit attenuation of the phagocytic capacity and greater production of superoxides (O_2^-) and hydrogen peroxide (H_2O_2) when compared to younger adults, revealing an important predictor of morbidity and mortality in the geriatric people.[18,19] In opposition, Sauce et al.[19] suggest from normal to slightly elevated the production of these reactive species in apparently healthy elderly. It is likely that this inconsistency is partially explained by specificity of the stimulus[2,18] and the moment at which the analyzes were conducted.[2,10,18,19]

In recent papers, several neutrophil functions (adherence, chemotaxis, phagocytosis, microbicidal activity and antioxidant parameters) were measured in young, middle-aged, and centenarian individuals.[16,20] Surprisingly, middle age groups exhibited worse results in comparison by centenarians and young (lower chemotaxis and phagocytosis, as well as higher adherence and levels of superoxides). In centenarians, we observed a preserved antioxidant ability and a reduced production of superoxides in neutrophils,[20] probably due to a "survival effect" among these excepcionally sucessful individuals. Therefore, these characteristics should be better investigated, since they may be associated with the efficacy of organic defenses and longevity.[16,20,21]

Monocytes and macrophages

Monocytes represent a type of cellular component with high mobility and that respond to inflammatory processes through differentiation involving antigen-exhibiting cells. The absolute number of monocytes increases with aging and this change is associated to the condition of greater clinical fragility.[22] On the other hand, functional decline is observed, in the expression of TLR family receptors.[2-4] The TLR expression in monocytes decline inversely associated with the production cytokines in elderly. TLR are transmembrane proteins with important function for the recognition of pathogens and the mediation of inflammatory responses.[23] The decrease in RTL expression in the elderly contributes to higher exposure to diseases, since they delay clinical symptoms related to infection.[15] This point becomes worrisome because it is unknown if changes in TLR expression are characteristic of the aging process or nutritional, genetic and environmental factors.[24]

Macrophages are mature cells derived from the monocyte and with specific denominations according to the tissues; they host (skin, bones, brain, liver, spleen, among others). They exhibit phenotypic heterogeneity in view of the considerable capacity to functionally adapt to the tissue milieu.[4,24] It is established that macrophage-derived cytokines affect the adaptive immune response.[9] Renshaw et al.[25] showed that lipopolysaccharide-stimulated peritoneal macrophages of old mices exhibited lower secretion of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) compared to younger littermates. However, results in humans suggest that higher circulating levels of proinflammatory cytokines in the elderly act as compensatory mechanism to the decline in functional ability.[26,27]

Due to technical limitations, studies involving macrophages usually are performed in an animal model. However, findings with human samples suggest that the phagocytic capacity of macrophages of older people decline in parallel to the levels of chemokines derived from macrophages MIP-1α, MIP-1β, MIP-2 and eotaxin.[28] Together, the M/Mø functions changed with aging, which promote the chronic inflammation and associated diseases.[24] Figure 3 illustrates the phagocytic activity of circulating monocytes in the elderly obtained from a study conducted in our laboratory.

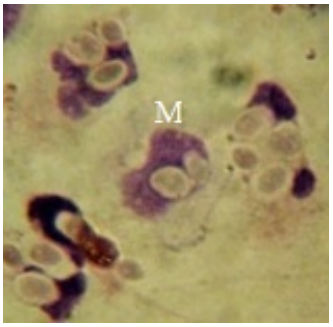

Figure 3. Circulating monocytes phagocyting two units of Saccharomyces cerevisiae in blood sample from woman > 65 years-old. M: monocytes.

Physical exercise and immunosenescence of the innate system

It is generally established that physically active individuals are prone to greater longevity because because of a lower prevalence of age-related, inflammation-associated diseases. However, the underlying physiological mechanisms that explain the effects of exercise are only partially elucidated.[8,22] In general, endurance exercises are widely used in both clinical and experimental settings. Recently, RT has been receiving an increasing emphasis due to its significant contribution to the functional capacity of older adults and to its potential in avoiding the effects of immunosenescence.[29]

Although the organic adaptations in response to the endurance exercise and the RT are complementary,[30] the benefits related to the anti-inflammatory effect induced by these exercises can be mediated both by the reduction of visceral fat (a source of inflammatory cytokines),[31] and by the production of anti-inflammatory mediators by the muscle itself (miocines) during intermittent contraction of skeletal muscle.[32] Thus, physically active older adults have may exhibited protection against the process of inflammaging and age-related comorbidities compared to sedentary counterparts.[33] It should be noted that several mechanisms can contribute to the genesis of an anti-inflammatory milieu, as a lower expression of TLR in $M/M_{ø}$, inhibition of infiltration activity of resident and circulating $M/M_{ø}$.[23,29] However, not all of the aforementioned mechanisms were evidenced in the elderly.[29]

Exercise intensity exerts distinct effects on neutrophil activity. While submaximal exercise reduces neutrophil adhesion and chemotaxis, increasing the exposure to pathogens, mild and moderate intensity tend to increase phagocytic and microbicide activity of neutrophil.[31,34] When the elderly begins the exercise protocol, there is an increase in adrenaline, in blood and in signaling molecules that stimulate the release of neutrophils, with redistribution to different tissues. However, when exercise intensity is sufficient to generate microinjuries (moderate), these cells produce cytokines such as IL-6, IL-8 and TNF-α that activate neutrophils and different reactive oxygen species.[34] This set of evidences indicates the need to carry out new studies where the dose-response of the exercise will be investigate, and compare different training protocols (resistance, strength, aerobic, concurrent, etc.).

Resistance Training and the innate immune in the elderly

The position stand of American College Sports Medicine[35] for elderly is that at least 150 minutes of physical exercises per week, consisting mainly of aerobic and RT. For aged individuals, it is suggested that RT is performed ≥2/wk, with intensity ranging from moderate (50-60% of 1RM) to hard (70-80% of 1RM), and composed by 8-10 exercises with 8-12 repetitions. Table 1 presents the results of studies that investigated the chronic effect of different RT protocols on the innate immunity of elderly subjects.

In the first study, Flynn et al.[36] found that RT performed for 12 weeks did not alter the count of mononuclear cells as well as the lymphocyte proliferation in mitogen response. NK cell mediated cytotoxicity and serum cortisol level were also preserved. There was an effect on the increase in NK cell concentration. Thus, RT appears as useful strategy to increase strength of older adults without immunosuppression. Bautmans et al.[37] observed that 6 weeks of intense RT induces significant changes in the expression of the molecular chaperones proteins – Hsp70, in monocytes and lymphocytes of the elderly. This change in Hsp70 expression may reflect an adaptive mechanism to improve cell protection against stressful pathological events such as trauma or infection.

Table 1. Main results from studies investigating the influence of physical exercise protocols on innate immune functions.

Authors	Method	Main results
Bartholomeu-Neto et al.[6]	Case control: 28 physically active vs. 26 sedentary (women), > 65 yrs. RT: 3 x 12 rep. 70% 1RM (3 times/wk, 8-month).	↑ the Phagocytosis index by neutrophils. ↔ the Phagocytosis index by monocytes.
Bautmans et al.[37]	31 (10 male) RT-trained without control group, > 60 yrs. RT: 3 x 10 rep. 70-80% 1RM (3 times/wk, 6-weeks).	↑ blood [ ] neutrophils and monocytes. ↑ Hsp70 activity.
Bobeuf et al.[38]	Case control: 16 RT vs. 13 sedentary, > 61 yrs (14 men and 15 women). RT: 3 x 8 rep. 80% 1RM (3 times/wk, 6-month).	↔ blood [ ] neutrophils and monocytes.
Córdova et al.[7]	Case control: 28 RT vs. 26 sedentary (women), > 65 yrs. RT: 3 x 12 rep. 70% 1RM (3 times/wk, 8-month).	↓ TNF-α, IL-6 and IFN-γ
Flynn et al.[36]	Case Control: 15 RT vs. 14 sedentary (women), 67-84yrs. RT: 3x all out (to failure). 80% 1RM (3 times/wk, 12-weeks).	↑ natural cell-mediated cytotoxicity after acute RT. ↔ lymphocyte proliferative after acute RT.

RT = resistance training; RM = maximum repetition; Rep = repetition; yrs = years. ↑ = increase; ↓ = impair; ↔ = maintenance; [ ] = concentration; Hsp70 = Heat Shock Protein 70; TNF-α – Tumoral Necrosis Factor-alfa; IL-6 = Interleukin-6; IFN-γ = interferon-gamma.

According to Bobeuf et al.[38], six months of RT did not change the total number and proportion of leukocyte subpopulations. In opposition, Córdova et al.[7] observed the effect of eight months of RT on the circulating levels of inflammatory citokines of elderly individuals. Results suggest that the RT-trained group exhibited lower levels of IL-6, TNF-α and intereferon-gamma (IFN-γ) compared to the sedentary group. Recently, Bartholomeu-Neto et al.[6] observed that long-term RT (eight months) increased the expression of the phagocytic neutrophil without altering the microbicidal activity. The volunteers did not show a significant alteration in the phagocytic activities of circulating monocytes. All together, these results suggest that TR promotes benefits to the innate immune system of aged adults. In this sense, RT should be recommended as a coadjuvant for the prevention of diseases and inflammatory processes related to age, although there is still the need to establish an appropriate RT protocol, just as there is a need to understand the underlying mechanisms.

In conclusion, resistance training is consistently recommended as assistent strategy for prevention of the inflamaging and associated chronic diseases, but establishing adequate program is still in demand. However, given the number of relevant studies, it is important to carry out further research with older volunteers, since RT has been shown to be a non-drug therapy with the potential to attenuate or reverse the adverse effects of aging on the innate immune. We emphasized that new protocols should be investigated, since the studies reviewed here, developed protocols for the muscle hypertrophy (about 12 repetitions per set). Therefore, none studies investigated the effect of RT focused on strength development (about 4 repetitions per set). We also emphasize that in the present study only five papers met the inclusion criteria, which makes the results analysis limited. Future studies should focus on estimating the optimal volume/intensity profiles of immunostimulatory RT-based protocols for older adults.

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