

EXERCISE AND THE AGEING IMMUNE SYSTEM

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ABSTRACT

Life expectancy in the developed world has increased exponentially over the last century. There is now a strong body of evidence demonstrating that aging is accompanied by severe alterations in the immune system, a process known as “immunosenescence”, commonly defined as the functional decline of the adaptive immune system with age. Inflamm-aging, a chronic progressive increase in the inflammatory status has attracted great attention in recent years in age-related research field. This process plays an important role in the age-related diseases, such as heart disease, atherosclerosis, Alzheimer’s disease, type II diabetes, among others. Exercise impacts immune function both acutely and chronically. This article describes how exercise activates the release of hormones, myokines and cytokines, as well as modulates the expression of various immune-reactive molecules, which all contribute to anti-inflammatory effects and possible attenuation of immunosenescence.

Keywords: immunosenescence, inflamm-aging, exercise

GIBANJE IN IMUNSKI SISTEM MED PROCESOM STARANJA

IZVLEČEK

V zadnjem stoletju je pričakovana življenjska doba v zahodnem svetu eksponentno narasla. Staranje spremljajo velike spremembe v imunskem sistemu. Ta proces, ime-

novan immunosenescenca, je definiran kot funkcionalni upad adaptivnega imunskega sistema s staranjem. Za staranje je značilno tudi progresivno naraščanje vnetja, ki ima pomembno vlogo pri s staranjem povezanih boleznih, kot so bolezni srca, ateroskleroza, Alzheimerjeva bolezen, sladkorna bolezen tipa 2 in druge. Gibanje vpliva na imunski sistem tako akutno kot kronično. Gibanje povzroči sproščanje hormonov, miokinov in citokinov in spremeni ekspresijo različnih z imunostjo povezanih molekul, kar vpliva na protivnetne učinke in zmanjšanje immunosenescence, kar opisuje članek.

Ključne besede: immunosenescenca, s staranjem povezano kronično vnetje, gibanje

INTRODUCTION

Life expectancy in the developed world has increased exponentially over the last century. There is now a strong body of evidence demonstrating that aging is accompanied by severe alterations in the immune system, a process known as “immunosenescence”, commonly defined as the functional decline of the adaptive immune system with age. Indeed, according to Arnold et al. (2011), the assurance of longevity and healthy aging occurs by maintaining the integrity of immunity. The worldwide increase of the proportion of people older than 65 years has led to the rising costs of age-related diseases; therefore, a better understanding of immunosenescence could help us to limit the development and progression of age-related diseases.

Immunosenescence results from the accumulation of molecular and cellular defects due to thymic involution (the age-related reduction in thymus size and activity), oxidative damage, and hyper stimulation of both the innate and adaptive immune system. Thymic involution results in significant exhaustion of naive T cells, and the shrinkage of the T-cell repertoire (Nguyen, Mendelsohn, & Larrick, 2017). Moreover, the progressive functional B lymphocyte deficits have also been suggested as the main responsible factors for age-associated disorders (Gruver, Hudson, & Sempowski 2007). However, in general, all immune cells are affected by aging, but the adaptive response seems to be more affected by the age-related changes in the immune system (Franceschi, Bonafè, & Valensin, 2000). Poor immune function in elderly combined with continued exposure to antigens, results in chronic activation of macrophages and other pro-inflammatory cells and contributes to chronic low-level systemic inflammation common in older age (Franceschi et al., 2000).

INFLAMMATION, OXIDATIVE STRESS AND AGING

Chronic low-grade systemic inflammation is a common manifestation of aging. While acute inflammation is normally tightly controlled and is a part of the common physiological healing processes, low-grade systemic inflammation describes a chronic,

mostly asymptomatic, low-grade inflammatory state that can eventually lead to chronic illness in the elderly such as cardiovascular diseases (CVD), diabetes, osteoarthritis, obesity, physical disability, Alzheimer's disease (AD), sarcopenia, among others (Singh & Newman, 2011). But, as with all other physiological systems, with aging there are also significant declines in the immune function that promote inflammation (Chung et al., 2009). Age-related chronic inflammation is often attributed to the immune system (Franceschi et al., 2000; Vasto et al., 2007), because as we age, we accumulate an "antigenic burden," the sum of all the antigenic stresses (both internal and external) that we unavoidably encounter throughout life, which causes the progressive activation of macrophages and other immune-cell types. This low-level chronic activation leads to the continuous production of inflammatory factors such as cytokines and chemokines, which raises the basal levels of these factors throughout the body. This process, termed "inflamm-aging" has been thoroughly described elsewhere and is supported by a substantial body of data (Franceschi et al., 2000; Singh & Newman, 2011). Indeed, 2-4 fold increase in the primarily serum levels of pro-inflammatory cytokines such as interleukin-7 (IL-7), IL-6, tumor necrosis factor- α (TNF- α) and acute phase proteins such as C-reactive protein (CRP) are typical for aged individuals when compared to younger individuals, even in the absence of chronic diseases (Bruunsgaard, 2006; Vasto et al., 2007; Xia et al., 2016). Thus, circulating levels of inflammatory mediators such as IL-6 and CRP have been found to be useful prognostic markers in very old people (Jylhä et al., 2007; Singh & Newman, 2011). Indeed, elevated levels of IL-6 and TNF- α in the serum of elderly have been found to be associated with some diseases (De Martinis, Franceschi, Monti, & Ginaldi, 2005). IL-6 is a pro- and anti-inflammatory cytokine produced by the cells of the immune system, vascular endothelial cells, adipocytes, and skeletal muscles. Another cytokine, TNF- α is produced mainly by macrophages, but also by vascular endothelial cells, adipocytes, and some others, and has been shown to increase muscle protein degradation and impair muscle protein synthesis. Its elevated levels have been observed in many inflammatory diseases, such as osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, idiopathic inflammatory myopathies, metabolic syndrome, type 2 diabetes mellitus and congestive heart failure (Thomas, 2013). CRP is an acute phase protein produced by the liver and its levels are up-regulated in response to elevation in IL-6 (Singh & Newman, 2011). The exact mechanism for the increase in pro-inflammatory cytokines with age is still not fully understood.

Accumulating evidence indicates that obesity and systemic inflammation are highly interrelated. Obesity is associated with diabetes and CVD as well as growing number of other diseases with inflammatory components including dementia and cancer (Knight, 2011). Adipose tissue (AT) acts as an endocrine organ by releasing some pro- and anti-inflammatory cytokines, which originate from adipose cells and/or infiltrated macrophages (Ouchi, Parker, Lugus, & Walsh, 2011). AT is infiltrated with macrophages in two separate polarization states: M1, which produce pro-inflammatory cytokines and M2, producing anti-inflammatory cytokines. Therefore, it has been proposed that in AT a phenotypic switch takes place toward macrophages of the M1-phenotype, promoting the inflammatory state (reviewed in Müller & Pawelec, 2014).

Moreover, increases in oxidative stress with aging may also contribute to the development of chronic inflammation and disease (Cannizzo et al., 2011). There are several potential mechanisms linking oxidative stress to inflammation (Xia et al., 2016). Aging is associated with increases in both tissue and circulating levels of reactive oxygen species (ROS) as well as a decline in antioxidant capacity (Kregel & Zhang, 2007). To protect itself, organisms have developed various antioxidative defenses that include superoxide dismutase (SOD), glutathione (GSH) peroxidase, and catalase, as well as non-enzymatic ROS scavengers, vitamin E, vitamin C, and uric acid (Lykkesfeldt, Hagen, Vinarsky, & Ames, 1998). Among all this, GSH is the most abundant and effective biological anti-oxidative reductant (Cross et al., 1997). ROS cause both oxidative damage and elicit release of additional “inflamm-aging-cytokines” perpetuating a vicious cycle. Recently, it has been shown that ROS activation of toll-like receptors on a variety of immune cells play an important role in activating the inflammatory cascade (Gill, Tsung, & Billiar, 2010). Therefore, the continual presence of circulating pro-inflammatory factors may keep the immune system in a state of chronic low-level activation and eventually this chronic immune activation causes immunosenescence.

Moreover, low-grade chronic inflammation has also been related to frailty, defined as an increased vulnerability to stress in old age (Hubbard, O'Mahony, Savva, Calver, & Woodhouse, 2009). Frailty results from the accumulation of functional declines in multiple systems that decrease overall physiological reserve leading to weight loss, especially loss of muscle, reduced strength and endurance, and overall poor physical function (Fried et al., 2001). Sarcopenia, one of the most noticeable changes occurring in elderly, is defined as the age-related loss of muscle mass, strength and function and is a major component of frailty and a risk factor for disability outcomes (Lang et al., 2010). It has been shown by Visser et al. (2002) that older people with high cytokine levels (IL-6 and TNF- α) have a tendency to develop sarcopenia (Visser et al., 2002). In addition, a growing body of literature indicates that inflammatory processes are also related to cognitive decline and the development of dementia, including the vascular and Alzheimer's types (Yaffe et al., 2003; Engelhart et al., 2004).

ACUTE EFFECTS OF EXERCISE

As aging is an inevitable process, there is a lot of interest in certain strategies that would reduce age-related inflammation and may therefore improve the quality of life in older adults. As such, there has been recent interest in the manipulation of certain lifestyle factors like increasing physical activity levels, as a way of moderating the effects of aging on the immune system. Regular exercise is recommended for older people for a variety of reasons including increasing muscle mass and reducing risk for chronic diseases of the heart and metabolic systems.

Acutely, exercise induces local and systemic cytokine responses in skeletal muscle. Effects of different types of exercise and different intensities on inflammation in inflammatory conditions were reviewed by Thomas (2013). Eccentric exercise causes

greater muscle damage than concentric and seems to be associated with higher interleukine-6 expression, higher serum creatine kinase and greater recruitment of monocytes, dendritic cells, and memory T cells to sites of infection and injury, although results vary due to differences in the participants' training status, exercise protocols and sampling times. Furthermore, exercise intensity governs the amount of the inflammatory response that follows the exercise bout: while strenuous high-intensity exercise increases TNF- α level, low intensity exercise, if sustained over time, decreases TNF- α level (Thomas, 2013). In a study of acute effect of walking for four consecutive days at a self-selected pace for 30 km a day in twenty octogenarians, changes in immune cell numbers and functions were observed with an emphasis on response of CD4+ T cells, rather than CD8+ T cells or NK cells (van der Geest et al., 2017), with naïve CD4+ subsets dominating the CD4+ T cell compartment.

IMPACT OF CHRONIC PHYSICAL ACTIVITY ON INFLAMMATORY AND OXIDATIVE STATUS

It has been shown that lifelong physical activity is associated with increased lifespan, lower risk of functional and cognitive impairment, and lower levels of inflammatory markers in older adults (Simpson & Guy, 2010). Exercise has also been reported to favorably impact immune function (Simpson & Guy, 2010). Repeated bouts of exercise seem to have a protective effect on the inflammatory response in patients with inflammatory conditions, which might have an important role in skeletal muscle adaptation (Thomas, 2013). Therefore, reducing inflamm-aging via exercise could be an efficient therapeutic approach to either prevent or delay the onset of those chronic diseases associated with low-grade chronic inflammation and thus reduce frailty and mortality in the elderly.

Some cross sectional studies have shown an association between low-grade inflammation and physical inactivity in healthy older subjects (Pedersen & Bruusgaard, 2003; Colbert et al., 2004). In our study of complete inactivity, we observed increased inflammation after 14 days of bed rest (Jurdana et al., 2015). The inflammatory response differed between elderly and young subjects: the elderly group responded to 14-days complete inactivity by pronounced increases in IL-6 and TNF- α while for the young subjects the TNF- α levels did not change and IL-6 levels decreased. Moreover, regular exercise training has been shown to reduce circulating levels of TNF- α , IL-6, and CRP in a population of healthy older adults (Colbert et al., 2004, Nicklas et al., 2008; Phillips, Flynn, McFarlin, Stewart, & Timmerman, 2010; Woods, Wilund, Martin, & Kistler, 2012).

The exact mechanism for reducing the levels of inflammatory markers by physical activity is not clear, but some possible mechanisms have been proposed for the anti-inflammatory effects of exercise (Gleeson et al., 2011). The anti-inflammatory effects of regular exercise may be mediated via reduction in visceral fat mass. Regular exercise reduces fat mass and AT inflammation, both known to contribute to systemic inflamma-

tion (Calder et al., 2011). Independently of losses of fat mass, exercise also increases muscle production of IL-6. In contrast to what occurs in sepsis, contracting muscle produces IL-6 independently of TNF- α (there is, in fact, no TNF- α increase during exercise), which suggests the cytokine cascades in the contracting muscle are markedly different from those during infection (Pedersen & Febbraio, 2008). Exercise derived IL-6 is considered to possess a central role in anti-inflammatory activities and to be responsible for reducing TNF- α production – and increase anti-inflammatory cytokines, as for example anti-inflammatory adiponectin (Starkie, Ostrowski, Jauffred, Febbraio, & Pedersen, 2003). In addition, the anti-inflammatory effects of regular exercise may be mediated via increased production and release of anti-inflammatory cytokines, or reduced expression of toll-like receptors on monocytes and macrophages (Gleeson et al., 2011; Singh & Newman, 2011). Moreover, increases in antioxidant capabilities with regular exercise may prevent cellular DNA and structural damage from attacking ROS thus preventing premature biological aging of specific immune cells (Mota et al., 2010). For example, it has been shown that proper physical exercise blunts the age-related decrease of GSH the body's major anti-oxidative reductant (Carter et al., 2007).

As mentioned above, AD is also associated with chronic low-grade inflammation. Physical activity influences inflammation, and both affect brain structure and AD. Indeed, higher levels of physical activity have been associated with a lower risk of developing AD (Luck et al., 2013). Although the main mechanism for this reduced risk is still unclear, physical activity may be associated with lower brain amyloid levels in humans (Liang et al., 2010; Head et al., 2012; Brown et al., 2013). Further, while imaging techniques in humans showed that exercise positively correlated with brain-derived neurotrophic factor (a marker of adult neurogenesis), spatial memory, and various cognitive functions (Voss, Vivar, Kramer, & van Praag, 2013), enhanced neurogenesis due to exercise was directly shown in rodent studies (Voss et al., 2013).

Although it is possible that exercise as part of lifestyle acts to prevent or treat immunosenescence, there is no clear answer to this question thus far. However, several interventions, including different types of exercises, have been proposed to restore immune function in elderly people. It has been shown that moderate exercise training might up-regulate monocytes and dendritic cells, thereby possibly improving T-cell mediated immunity in elderly (Shimizu et al., 2008; Shimizu et al., 2011). Moreover, it has been shown, that regular exercise is associated with improved immune responsiveness to influenza vaccination in elderly (Kohut & Senchina, 2004; Woods et al., 2009). Thus, the accumulated data thus far suggest that exercise may be a powerful approach to restoring immune function in elderly people.

CONCLUSIONS

Taken together, we conclude that physical activity, such as regular exercise, activates the release of hormones, myokines and cytokines, as well as modulates the expression of various immune-reactive molecules, which all contribute to anti-inflammatory

effects and possible the attenuation of immunosenescence. Moreover, the reduction of visceral fat mass alone already leads to a decreased production and release of pro-inflammatory adipokines from fat tissue. Therefore, lifestyle attitudes, particularly aerobic exercise in the elderly may provide low cost and long-term ways to limit inflammation and slow declines in the elderly.

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