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Review Article

INFLAMMATION IN ELDERLY

Abstract

Recently ageing has become an important issue because of the dramatic changes in life expectancy. 'Ageing' at the individual level (senescence) is a biological phenomenon common to all high organisms. There is a strong relationship between ageing, inflammation, response to infection, and the progression of chronic inflammatory diseases. In fact, inflammation is necessary to cope with damageing agents and is crucial for survival. But chronic exposure to a variety of antigens for a period much longer than that predicted by evolution, induces a chronic low-grade inflammatory status that contributes to age-associated morbidity and mortality. Probably there is a final common pathway interaction of multiple factors that alters the microenvironment of an acute response to infection that, together with accumulation of anergic/nonresponse T and B cells, results in crossing the threshold of host resistance, resulting in the marked increase in common infections, susceptibility to epidemics, the poor vaccine response, and the occurence of some chronic diseases in elderly.

Key words: Elderly, Inflammation, Immune system

Derleme

YAŞLILARDA İNFLAMASYON

Öz

Yaşam süresindeki dramatik değişikliklere bağlı olarak son zamanlarda yaşlanma önemli bir konu haline gelmiştir. Bireysel bazda yaşlanma tüm yüksek organizmalarda ortak biyolojik bir fenomendir. Yaşlanma, inflamasyon, enfeksiyonlara yanıt ve kronik inflamatuar hastalıkların gelişimi arasında güçlü bir ilişki bulunur. Aslında inflamasyon hasar verici ajanlarla savaşmak için gerekli ve yaşam için şarttır. Fakat çok çeşitli antijenlere gereğinden fazla maruz kalmak yaşa-bağlı morbidite ve mortalitede artmaya neden olan kronik düşük-dereceli inflamatuar bir duruma yol açar. Muhtemelen çeşitli faktörler arasındaki ortak bir yolakla, infeksiyona karşı akut yanıttaki değişikliklerle beraber anerjik/cevapsız T ve B hücrelerin katılımıyla, konakçının direnç sınırı aşılmakta, böylece yaşlılarda sık görülen enfeksiyonlarda ve epidemilere yatkınlıkta artma, aşılara yanıtta yetersizlik ve bazı kronik hastalıkların ortaya çıkması söz konusu olmaktadır.

Anahtar sözcükler: Yaşlılık, İnflamasyon, İmmün sistem.

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Ageing

Ageing is defined as progressive loss of adapability with the passage of time so that the individual is less and less able to react adequately to the challanges from the external and internal environment. Widespread ageing at the population level is a recent phenomenon that emerged in affluent societies. In fact, inflammation is necessary to cope with damageing agents and is crucial for survival, particularly to cope with acute inflammation during our reproductive years. But chronic exposure to a variety of antigens for a period much longer than that predicted by evolution, induces a chronic low-grade inflammatory status that contributes to age-associated morbidity and mortality. This condition carries the proposed name "*inflammageing*" (1). The key to successful ageing and longevity is to decrease chronic inflammation without compromising an acute response when exposed to pathogens. Recently ageing has become an important issue because of the dramatic changes in life expectancy. Most of the gains in life expectancy have been achieved by treating diseases that used to kill in youth and middle age. In 2000, there were 600 million people aged 60 and over (%10 of the world population), and it is estimated that there will be 1.2 billion by 2025 and 2 billion by 2050 (%21 of the world population). Today about two thirds of all older people are living in the developed world and in those areas, the very old (age 80 and older) is the fastest growing population group. Women outlive men in virtually all societies; the ratio of women/men is 2:1. Vast majority of older people remain physically fit until later life. But a minority of elderly with chronic diseases as well as the growing number of older persons who reach a very advanced age pose a hightened demand for health and support services.

World Health Organisation define an *old* person who is 65 years and older. Demographers distinguish between the '*young old*' who is between 60-74 years old and '*old old*' who is older than 75 years old. Although to slow down ageing is possible, we now know that to prevent ageing is impossible. 'Ageing' at the individual level (senescence) is a biological phenomenon common to all high organisms and many of the lower ones. Its signs are a decrease in fuctional capacities like metabolic rate, ability to sense and respond to stimuli, ability to move and ability to reproduce (2). The main changes in human ageing include increase in rise of blood pressure causing cardiovascular and renal diseases, rise in blood glucose and cholesterol resulting in diabetes mellitus and atherosclerosis, reduction in bone mass that cause osteoporosis and fractures, muscle loss with functional weakness, cartilage degeneration resulting in arthritis, increased neuronal degeneration causing loss of cognitive function and dementia, and finally decline in immune functions with the increase risk in infections and cancer. Alterations in the neuro-endocrine axes and overall decline in the immune system play an essential role in the changes of the organism's immune function and stres response by ageing (2). Especially the changes of the immune system is very important since it is considered a major contributory factor to the increased frequency of morbidity and mortality among the elderly (3).

Immune Senescence

The gradual deterioration of the immune system brought on by natural age advancement is called as *immune senescence*. It is classically viewed as a simple, progressive, and irreversible age-associated decline of the functional capacity of the immunological machinery. More than just a simple waning of activity, immune senescence appears as the result of a true dysfunction of the immune system. The age-associated alterations of the complex network of interactions between the components of the immune system result in loss of some activities and the simultaneous increase in other activities. The association of these unbalanced immunological activities may result in an inefficient, inappropriate and sometimes detrimental immune response. Immune senescence can contribute to infection risk but this contribution is small until immunity is impaired further as a result of accumulating chronic illness, external conditions, or repeated or chronic infections (4). Recently there is much interest in how recurrent or chonic infections may result in progression of age-related '*inflammatory*' diseases, especially atherosclerosis. There is some evidence that the interaction of pathogenic burden with host genotype (eg, a mutation of Toll-like receptor (TLR) 4; a surface pathogen receptor on immune cells) may determine the character and enhanced and prolonged inflammatory responses known as 'inflamm-ageing' that may contribute to cardiovascular disease, autoimmunity, poor host resistance, tumor surveillance, and diminished longevity in the elderly (5). So the changes in the immune system is also very closely related to the chronic inflammation in the elderly. Ageing, illness, and chronic conditions clearly alter cytokine production and response, altering the integrity of the immune response, and may not only reduce host resistance but also potentiate inflammatory age-related diseases. In the elderly, it is the interaction of genetic

predisposition and environmental exposure that dictates proinflammatory status. It is now known that changes in innate immunity, antigen presentation, dendritic cells regulation, T-cell and B-cell function occurs with ageing (4,6,7). For example; neutrophils undergo spontaneous programmed cell death (apoptosis) without the support of proinflammatory stimulatiin in vitro. And neutrophils from older adults can not be rescued from apoptosis with proinflammatory cytokines, as can be demonstrated with neutrophils from younger adults, as multiple apoptotic pathways are favored in the aged neutrophils. This suggests that although elderly may have adequate number of neutrophils, they likely have functional impairments and an inability to sustain activity at the site of inflammation (8,9). Despite the consistent evidence about the changes in the elderly, understanding how age-related inflammatory diseases and altered immunity resulting from chronic infection are related, will be extremely difficult to unravel as it represents a chicken-versus-the egg story.

Ageing and Inflammatory Mediators

There is a strong relationship between ageing, inflammatory mediators, response to infection, and the progression of chronic inflammatory diseases. The finding that impaired immunity is correlated more with comorbidity than age in the elderly suggests that changes in the composition of inflammatory mediators that occur in the immune tissue microenvironment of older adults could play an important role in accelerating the gradual age-related decline in type 1 immune response caused by changes in T cells. The fact that excessive production of inflammation actually could be immunosuppressive is counterintuitive, and the effects of this increase in inflammatory mediators as a part of inflamm-ageing on the acute immune response largely has not been studied.

In the literature there are many studies that show an increase in plasma or serum levels of interleukin(IL)-6, IL-8, IL-10, tumour necrosis factor-alpha (TNF-·) and a decrease in IL-1 (10,11). A recent study defined markers of 'inflammation' as albumin less than 3.8 g/dL, cholesterol less than 170 mg/dL, IL-6 greater than 3.8 pg/mL, and C-reactive protein (CRP) greater than 2.65 mg/L (12). This study found a strong association with mortality in subjects who had 3 or 4 markers of inflammation, with the adjusted odds ratios for 3- and 7-year mortality 6.6 and 3.2, respectively, compared with those who had no abnormal markers. Subjects who had 1 or 2 markers were at more moderate and statistically insignificant increased risk for 3- and 7-year mortality with the adjusted odds ratios of 1.5 and 1.3, respectively. Similar results are supported by other studies (13,14).

Association with Diseases

It is clear that these markers are nonspesific and have many causes in addition to inflammation. In a recent longitudinal study, it is suggested that higher circulating levels of IL-6 and other inflammatory mediators are associated with and are predictive of functional disbility and increased mortality in older adults who had no functional impairment at entry into the study (15). An association also exists between physical activity and lower levels of serum IL-6 (16). Moreover, high serum IL-6 levels are reported in many chronic diseases, with slight increase (27% to 72%) in relative risk for mortality but siginificant increase in coronary heart disease, stroke and congestive heart failure in subjects 70 to 79 years of age who do not have evidence of cardiovascular diesase at baseline (12,17-19). In a geriatric population, one study showed an association between IL-6 and depressive symptomatology possibly showing an integrated involvement of inflammation in the pathophysiology of depression in the elderly (20). Another study investigated association between inflammation and neuropsychiatric symptoms in patients between 85- 90 years old. Their findings suggested that in old age inflammatory processes contribute to the development of depressive symptoms but not cognitive decline (21). The same association with the addition of a link with ischemic stroke has also been suggested (22). In a recent study, the cytokine profile of 54 patients with hypertension, coronary artery disease, atrial fibrillation or a previous stroke (with a mean age of 80.1±5 years) were compared with age-matched healthy individuals. There were significant increases of inflammatory cytokines that were associated with mortality, and IL-6 was the only cytokine to predict one-year mortality (23). In an other recent study, the inflammatory cytokine TNF-α was also found elevated in a large portion of community heart failure patients, and it was associated with a large decrease in survival (24).

It reamins unclear, however, what increased serum IL-6 levels represent. The association with disease more likely is from a hormonal effect of IL-6, secreated by adipose tissue, and mediated by catabolic changes in somatic muscle, rather than on an immunologic basis (4). As an endocrine and inflammatory organ, adipose tissue has been shown to be an important source of circulating pro-inflammatory cytokines

which supports that chronic inflammation is associated with body fat mass (25). Some studies have been done to compare how circulating levels of IL-6 or other markers of inflammation correlate with traditional measures of cell-mediated immunity. One mouse study showed that high inflammation, including plasma IL-6 levels, were associated with high mortality during infection, but mortality in the chronic phase was correlated with immunosuppression and very low IL-6 levels (26). In another study, only 1 out of 32 patients with Alzheimer's disease had a decline in production of IL-6 and TNF-α associated with severe dementia in comparison to IL-6 and TNF-α levels among patients who had mild to moderate dementia (17).

Alzheimer disease is known as a progressive dementia with unknown etiology that affects a growing number of the ageing population. Increased expression of inflammatory mediators in postmortem brains of people with Alzheimer disease has been reported. On the basis of this kind of evidence, inflammation has been proposed as a possible cause of Alzheimer disease. On the other hand, inflammation could simply be a byproduct of the disease process and may not substantially alter its course. Although there is still little evidence that inflammation triggers or promotes Alzheimer disease, increasing evidence from mouse models suggests that certain inflammatory mediators are potent drivers of the disease (27). Recent work suggests that the activation of microglia in response to injury, illness, ageing, or other causes begins a cascade of events that can best be characterized as an inflammatory process. This cascade is mediated by the proinflammatory cytokines including IL-1. Over a period of years, this slow, smoldering inflammation in the brain may destroy sufficient neurons to cause the clinical signs of Alzheimer disease (28). These studies may support the link between the inflammatory changes and some disease states in the elderly population.

Another disease state in the elderly which is also related with the ongoing chronic inflammation is the heart disease in older adults. In fact, in the past decade inflammatory markers have emerged as strong independent risk indicators for cardiovascular disease. Even though adults over the age of 65 experience a high proportion of such events, most epidemiologic data are from middle-aged populations. It is suggested that CRP, a marker of inflammation and insulin resistance, a metabolic disorder, are closely related, and they both are identified as significant risk factors of cardiovascular disease (CVD) (29). However, in a recent genetic study with 4941 men and women aged 50-74 years in which CRP genes and carotid intima-media thickness is asessed, it was suggested that the association of CRP with carotid atheroma indexed by carotid intima-media thickness may not be causal (30). Data on C-reactive protein on cardiovascular disease are inconsistent in the elderly population. Some suggest that CRP levels appear to be less useful in old-age than in middle-age (31). But there is a recent prospective 5-year follow-up data on the effect of inflammation and infection on subjects with early stages of atherosclerosis which suggest that elevated CRP concentrations may significantly influence the occurrence of cerebrovascular and cardiovascular events in patients with baseline subclinical carotid atherosclerosis (32). Despite the inconsistency in CRP levels in older adults, the inflammatory markers are non-specific measures of health in the elderly and predict both disability and mortality even in the absence of clinical cardiovascular disease. Thus it is possible that, in older age-groups, interventions designed to prevent cardiovascular disease through the modulation of inflammation would also be helpful in reducing disability and mortality.

There has been some studies that link the chronic inflammatory process and metabolic syndrome in the elderly (33). In a recent population-based, cross-sectional study, plasma CRP is found to be positively associated with HbA(1c) even in euglycaemic individuals suggesting that low-grade chronic inflammation is associated with risk for type 2 diabetes (34).

The chronic inflammation in the elderly can also contribute to other age-related conditions like senile osteoporosis as shown in a study with 36 elderly subjects with a mean age of 76.8 +/- 4.5 years. Increased IL-6 and TNF-alpha levels and elevated serum CRP were identified indicating the presence of inflammation in senile osteoporosis (35).

As a result, increased basal inflammation is a phenomenon emblematic of the ageing process. It is characterized by changes in the concentrations of several serum markers such as CRP, serum amyloid-A, ferritin, nitrite/nitrate, albumin, inflammation-associated cytokines like interleukins and TNF-α, resistin, beta2-microglobulin, white blood cell count, leptin, heat-shock proteins, neutral sphingomyelinase and cystatin C (2, 36-40). Nevertheless, further prospective well-controlled studies are needed to clarify these findings. The relationship between ageing, inflammatory mediators, response to infection, and the chronic inflammatory diseases is very important but complicated. Probably there is a final common pathway interaction of these factors that alters the microenvironment

of an acute response to infection that, together with accumulation of anergic/nonresponse T and B cells, results in crossing the threshold of host resistance, resulting in the marked increase in common infections, susceptibility to epidemics, and the poor vaccine response in chronically ill elderly.

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