DOI: 10.20514/2226-6704-2020-10-6-414-421

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ФАКТОР НЕКРОЗА ОПУХОЛИ-АЛЬФА И ВОЗРАСТ-АССОЦИИРОВАННАЯ ПАТОЛОГИЯ

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Tumor Necrosis Factor-Alpha and Age-Related Pathologies

Резюме

В обзоре отражены современные представления о понятии «*inflammaging*» и роли субклинического воспаления при различной возраст-ассоциированной патологии. Особое внимание уделено фактору некроза опухоли-α — ключевому цитокину, принимающему важное участие как в патогенезе хронических воспалительных заболеваний, так и в процессах старения. Повышенное содержание фактора некроза опухоли-α приводит к возникновению и прогрессированию различных заболеваний, к усугублению старческой астении, к инвалидизации и смертности лиц пожилого и старческого возраста. Фактор некроза опухоли-α оказывает влияние на различные факторы риска сердечно-сосудистой патологии, способствует возникновению и прогрессированию атеросклероза и связанных с ним заболеваний. Этот цитокин может усугублять также различные метаболические нарушения, в первую очередь, инсулинорезистентность и сахарный диабет. Фактор некроза опухоли-α — ключевой цитокин, стимулирующий костную резорбцию (с возникновением остеопороза) и саркопению. Имеющиеся в настоящее время данные подтверждают важную роль фактора некроза опухоли-α при различных возраст-ассоциированных заболеваниях.

Ключевые слова: *воспаление, цитокины, фактор некроза опухоли-α (ФНО-α), атеросклероз, старение, старческий возраст, долгожители*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 26.05.2020 г.

Принята к публикации 08.07.2020 г.

Для цитирования: Тополянская С.В. ФАКТОР НЕКРОЗА ОПУХОЛИ-АЛЬФА И ВОЗРАСТ-АССОЦИИРОВАННАЯ ПАТОЛОГИЯ. Архивъ внутренней медицины. 2020; 10(6): 414-421. DOI: 10.20514/2226-6704-2020-10-6-414-421

Abstract

Modern concepts about the «inflammaging» and the role of subclinical inflammation in various age-associated pathology are described in the review. Particular attention is paid to the tumor necrosis factor-α, a key cytokine that

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plays an important role in the pathogenesis of chronic inflammatory diseases as well as in aging. The increased levels of tumor necrosis factor-α leads to the onset and progression of various diseases, to severity of frailty, to disability and mortality of elderly persons. Tumor necrosis factor-α affects different risk factors for cardiovascular diseases, contributes to the onset and progression of atherosclerosis and related pathology. This cytokine can also aggravate various metabolic disorders, mainly — insulin resistance and diabetes mellitus. Tumor necrosis factor-α is a key cytokine that stimulates bone resorption (up to osteoporosis) and sarcopenia (up to cachexia). Currently available data confirm the important role of tumor necrosis factor-α in various age-associated disorders.

Key words: *inflammation, cytokines, tumor necrosis factor-α (TNF-α), atherosclerosis, aging, old age, long-livers*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 26.05.2020
Accepted for publication on 08.07.2020

For citation: Topolyanskaya S.V. Tumor Necrosis Factor-Alpha and Age-Related Pathologies. The Russian Archives of Internal Medicine. 2020; 10(6): 414-421. DOI: 10.20514/2226-6704-2020-10-6-414-421

Chronic subclinical inflammation is increasingly considered as one of the key phenomena in the aging process and is termed *inflammaging* [1]. This kind of inflammation has five basic characteristics: it is minor, asymptomatic, controllable, chronic and systemic. In contrast to the typical response to a particular pathogenic agent, inflammation does not disappear with aging; it persists, resulting in various pathological changes [2].

Along with *inflammaging*, some authors propose the concept of *anti-inflammaging*, which means that long-livers seem capable of coping with chronic subclinical inflammation through an anti-inflammatory response [3, 4]. If inflammaging is considered the key to understanding aging processes and age-related diseases, then anti-inflammaging can obviously be considered one of the secrets of longevity.

It is noteworthy that despite the increased level of pro-inflammatory cytokines (including tumor necrosis factor-α), long-livers often maintain good health and do not develop any serious age-related diseases. From this perspective, subclinical inflammation in long-livers can be considered as a consequence of a favorable compensatory response aimed at reducing chronic antigenic load. However, an excessive inflammatory response can be harmful. Therefore, the rate of reaching the threshold pro-inflammatory state and personal ability to adapt to various stressful effects seem to be crucial for the development of age-associated diseases [5].

Both clinical and experimental studies show that pro-inflammatory cytokines (primarily, tumor necrosis factor-α and interleukin-6) play an important role in the onset and progression of age-associated subclinical inflammation. The increased level of these cytokines in the blood serum of elderly and senile patients is associated with increased morbidity, disability and mortality. [6, 7]. With aging, the expression of tumor necrosis factor-α (TNF-α) and interleukin-6 increases, and the imbalance between pro-inflammatory and anti-inflammatory cytokines results in subclinical inflammation, accelerates the aging process and contributes to different age-related diseases. Pro-inflammatory cytokines cause cell aging by stimulating the overproduction of reactive oxygen species, while damage to deoxyribonucleic acid (DNA), in turn, activates pro-inflammatory cytokines, blocks cell cycle and contributes to cell aging [2].

A common pro-inflammatory cytokine such as TNF-α, described in 1975 as a circulating antitumor cytokine, plays an important role in immune response in elderly people. TNF-α was previously thought to be produced mainly by activated macrophages and lymphocytes, but later, its expression was revealed in endothelial and epithelial cells, in smooth muscle cells of blood vessels and cardiomyocytes [8, 9].

It was later discovered that TNF-α is a key cytokine and an essential component of the immune system that stimulates the expression of genes required for controlling inflammation and tissue damage. The TNF-α family is considered as a group of cytokines that have critical functions in different immune responses, in the inflammation process, differentiation, and

control of proliferation of different cells and their apoptosis [10,11]. TNF-α is regarded as the main pro-inflammatory mediator responsible for the activation of the immune system during infectious processes. Bacterial agents and many other stimuli induce the synthesis of TNF-α, which (along with other pro-inflammatory mediators) recruits and activates neutrophils, macrophages and lymphocytes in tissue damage or infection sites [10].

The level of TNF-α increases with age and is associated with different age-related diseases. It was found that tumor necrosis factor-α increases in elderly people and even in long-livers [6, 7, 12]. An increased TNF-α level is accompanied by an increased risk of cardiovascular diseases [12]. According to several authors, TNF-α plays a role in the pathogenesis of atherosclerosis and Alzheimer's disease [12].

Increased blood TNF-alpha in elderly people is considered as a factor that enables to predict a fatal outcome regardless of the associated pathology [6, 13]. The relationship between TNF-α and mortality, regardless of dementia or cardiovascular diseases, suggests that TNF-α has an effect apart from cardiovascular disease [6]. Another study also demonstrated that higher levels of TNF-α are associated with increased mortality among elderly people [14]. Also, the relationship between high TNF-α concentration in plasma and mortality in long-livers suggests that this cytokine has specific biological effects and can be considered as a marker of senile asthenia in people at a very advanced age [13].

Analysis of TNF-α genetic polymorphisms in long-livers, octogenarians and younger people showed no differences in the distribution of TNF-α genotypes in the –308 position in these age groups. However, *GA* genotype (*TNF-α-308AG*) was associated with a lower frequency of dementia in long-livers. Few long-livers (carriers of *AA* genotype) had a higher risk of mortality and usually had an increased TNF-α level in blood plasma [15]. Other authors noted longer life expectancy in women with *TNF-α-308AG* genotype in comparison with women with *GG* genotype [16]. Genetic studies also revealed that the A allele of the *TNF-α-308* gene (*TNF-α-308A*) is associated with the risk of coronary heart disease [17].

Multifunctional pro-inflammatory cytokine TNF-α has an effect on several risk factors for cardiovascular diseases, in particular, insulin resistance, dyslipidemia, endothelial dysfunction and endothelial activation of cell adhesion molecules [18]. The high level of TNF-α in long-livers is associated with a low ankle-brachial index, which can be a sign of peripheral atherosclerosis. Other effects of TNF-α can also contribute to the development and progression of atherosclerosis and to the high risk of thromboembolic complications. This pertains to the stimulation of TNF-α synthesis of other pro-inflammatory mediators, for example, interleukin-6, C-reactive protein, fibrinogen, as well as white blood cells [8]. At the same time, TNF-α induces smooth muscle cell proliferation and increases the adhesion of leukocytes to endothelial cells, inducing the expression of cell adhesion molecules (E-selectin, ICAM-1 (CD54) and VCAM-1 (CD106)), as well as the expression of various endothelial cells cytokines, including interleukin-6 [8].

It was shown that already at the early stage of atherosclerosis, TNF-α stimulates endothelial dysfunction, increases the permeability of the endothelium, and promotes the migration of leukocytes into the vascular wall. Increased vascular permeability contributes, in turn, to the formation of atherosclerotic plaques. At later stages, this pro-inflammatory cytokine increases apoptosis of smooth muscle cells of blood vessels and macrophages (which contributes to the rupture of atherosclerotic plaques), induces the synthesis of matrix metalloproteinases and procoagulant activity, reducing the transcription of anticoagulant genes, thrombomodulin and protein C [19].

TNF-α contributes to dyslipidemia by increasing triglycerides, total cholesterol, as well as low-density lipoprotein cholesterol and lowering the concentration of high-density lipoproteins. TNF-α takes part in lipid metabolism, reducing the activity of 7-hydroxylase and lipoprotein lipase and stimulating the production of triglycerides in the liver [18].

Results of clinical and experimental studies indicate the important role of TNF-α in atherogenesis and the onset of vascular dysfunction with underlying arterial hypertension and pathological myocardial remodeling [9, 20]. Over the past 20 years, the idea that not only dyslipidemia but also inflammation is actively involved in atherosclerotic process and the development of cardiovascular diseases, including coronary heart disease (CHD), became firmly entrenched in cardiology [21, 22]. Both chronic coronary heart disease and acute myocardial infarction are inflammatory processes where pro-inflammatory cytokines such as TNF-α and acute-phase proteins, for example, C-reactive protein, play an important role [22, 23].

TNF-α is considered as a key pro-inflammatory cytokine, which is involved in atherogenesis and

contributes to mild systemic inflammation in the cardiovascular system. The effects of TNF-α on the cardiovascular system include not only its contribution to vascular dysfunction but also its effect on cardiomyocytes [9]. Direct evidence of TNF-α-stimulated vascular dysfunction was shown in a study conducted on healthy volunteers: intra-arterial injection of this cytokine in high doses led to acute local vascular inflammation in 30 minutes. Abnormal endothelium-dependent vasodilation and persistent increase in the release of plasminogen activator from endothelial cells were simultaneously registered [24]. Injection of a lower dose of TNF-α in healthy volunteers was accompanied by increased basal vascular resistance, that was blocked by pretreatment with a non-selective cyclooxygenase inhibitor [25]. It can be assumed that the registered effects of TNF-α were mediated not only by decreased bioavailability of nitric oxide but also by increased cyclooxygenase-dependent production of vasoconstrictors [26].

TNF-α concentration in the heart of healthy people is low and has no effect on its contractile function. However, the injection of exogenous TNF-α inhibits the contractile activity of cardiomyocytes. This pro-inflammatory cytokine can also reduce the absorption of calcium ions by sarcoplasmic reticulum and the sensitivity of myofilaments to calcium. In addition to reducing the contractility of cardiomyocytes, TNF-α can induce their hypertrophy [9].

Coronary artery occlusion in myocardial infarction causes a rapid increase in the level of pro-inflammatory cytokines, including TNF-α. Although an early increase in TNF-α after myocardial infarction helps to stabilize the function of the left ventricle, prolonged stimulation of TNF-α triggers its dysfunction in the later phases after acute coronary syndrome. Chronic exposure to high TNF-α concentrations results in dysfunction of the left ventricle and increased activity of matrix metalloproteinases, that contribute to the degradation of the matrix and, ultimately, to increased apoptosis of cardiomyocytes [27].

A number of studies demonstrated that high levels of TNF-α in serum can persist for many months after myocardial infarction [22, 28]. According to the observations of some authors, long-term maintenance of high TNF-α level becomes a risk factor for repeated cardiovascular events. Pro-inflammatory cytokines (including TNF-α) are produced predominantly in the peri-infarction zone. Therefore, a persistent increase in the level of cytokines after myocardial infarction may be the result of increased cardiac muscle infiltration by inflammatory cells. The expression of TNF-α after myocardial infarction can persist over time in intact cardiomyocytes, which suggests the possible long-term role of this cytokine in the remodeling of the myocardium and blood vessels [28].

In general, the effect of TNF-α on cardiomyocytes has many aspects and depends on the effect on a particular type of receptor and the cytokine form (membrane-associated or soluble). When acting type 1 receptors, TNF-α causes inhibition of myocardial contractility. This dysfunction can arise due to the stimulation of oxidative stress during the formation of reactive oxygen species and increased production of nitric oxide synthase (accompanied by the production of nitric oxide and peroxynitrite), activation of phospholipase A2, arachidonic acid and sphingomyelinase [9, 29]. TNF-α may have independent negative inotropic effects and inhibit the expression of contractile proteins (in particular, heavy chains of α-myosin and cardiac α-actin). Also, TNF-α can cross-interact with the β-adrenergic receptor system and inhibit the contractility of cardiomyocytes by altering signals to these receptors [29].

Besides reducing contractility, TNF-α enhances the transcription of genes that contribute to myocardial hypertrophy in heart failure. However, this pro-inflammatory cytokine stimulates apoptosis of cardiomyocytes, cardiac fibrosis, pathological myocardial remodeling, which contributes to the progression of heart failure [30, 31]. TNF-α activates the renin-angiotensin-aldosterone system (RAAS) in the heart, which leads to increased remodeling of the left ventricle, increased collagen level and apoptosis of cardiomyocytes [32].

Increased TNF-α level in patients with chronic heart failure (CHF) was demonstrated in a number of studies that confirmed the role of this pro-inflammatory cytokine in CHF pathogenesis, especially with an intact ejection fraction [29, 33]. The expression of TNF-α by cardiomyocytes leads to the inhibition of their contractile activity. At the same time, TNF-α can interact with β-adrenergic receptors, thereby exacerbating the negative inotropic effect [9, 29, 34–38].

TNF-α, along with other pro-inflammatory cytokines, plays a role in the pathogenesis of atrial fibrillation. A number of recent studies demonstrated that the risk of atrial fibrillation with increased TNF-α increases markedly [39]. There is no clear specific

pathogenetic relationship between pro-inflammatory cytokines (including TNF-α) and atrial fibrillation yet. However, several concepts link chronic inflammation with the development and progression of structural and electrophysiological atrial remodeling [39–40].

Both clinical and experimental studies have established that TNF-α can have a negative effect on the remodeling of the left ventricle and other heart chambers by inducing metalloproteinases and activating proteolytic processes [41]. At the same time, a reliable direct correlation was found between TNF-α level in serum and the diameter of the left atrium [42].

With a persistent but slightly increased TNF-α level, many mechanisms that contribute to vasoconstriction, and, therefore, arterial hypertension, are triggered [9]. Serum TNF-α is conclusively and independently associated with blood pressure in healthy individuals. In a study by Bautista L. E. et al. (2005), the average plasma TNF-α level was four times higher in patients with arterial hypertension [43]. There is a complex cross-regulation between RAAS and TNF-α signaling under physiological conditions. TNF-α inhibits renin expression in adrenal gland cells and juxtaglomerular kidney cells [9]. At the same time, there is a TNF-α-related decrease in the production of angiotensinogen in the cells of renal proximal tubules [44].

The TNF-α-triggered induction of such a powerful vasoconstrictor as endothelin causes a significant vasoconstrictor effect [45]. The endothelin B2 receptor, which mediates such vasoconstriction, is not expressed by smooth muscle cells under normal conditions. However, its amount increases with different cardiovascular diseases (for example, diseases of peripheral arteries, pulmonary hypertension, coronary heart disease and ischemic stroke). Such changes suggest the possible involvement of TNF-α in the development of abovementioned pathological processes [9]. Also, TNF-α induces the production of thromboxane A2 by endothelial and smooth muscle vascular cells and also reduces insulin-mediated vasodilation [9, 25].

According to some authors, TNF-α is one of the key cytokines that trigger and enhance inflammatory response after a stroke. Several studies showed that TNF-α-positive cells can be found in the brain of patients with severe ischemic stroke from the third day after the acute cerebrovascular event (stroke); these cells persist for up to 15 months after the vascular event. Serum concentration of TNF-α increases within 6 hours after stroke and remains high for 10 days [46].

Increased TNF-α level contributes to different metabolic disorders. The study by Swaroop J. J. et al. (2012) revealed, in patients with type 2 diabetes mellitus, a significant relationship between the TNF-α level and the functioning of pancreatic β-cells, insulin resistance index and insulin level [47]. Many authors believe that TNF-α is one of the key cytokines involved in the onset of insulin resistance and type 2 diabetes mellitus. High level of TNF-α induces insulin resistance in adipocytes and peripheral tissues, thus disrupting the transmission of insulin signals through serine phosphorylation [48]. TNF-α also interferes with the endothelial pathways of insulin signaling and exacerbates insulin resistance [49–50].

At the same time, a direct relationship was established between the level of pro-inflammatory cytokines, including TNF-α, and the concentration of blood creatinine, as well as the severity of chronic kidney disease [51]. It was shown that high levels of TNF-α and other pro-inflammatory mediators contribute to a more rapid decrease in glomerular filtration rate and progression of chronic kidney disease, even taking into account the influence of other factors [51]. In the kidneys, pro-inflammatory cytokines induce the expression of reactive oxygen radicals, lipids, and adhesion molecules, and stimulate pathological matrix accumulation and procoagulant activity of endothelial cells [51–53].

Also, TNF-α is a key factor that stimulates pathological bone resorption in cases of different inflammatory diseases. This pro-inflammatory cytokine can directly stimulate the synthesis of osteoclast precursors, and can indirectly enhance osteoclastogenesis by increasing RANKL expression (an essential mediator of osteoclastogenesis, cytokine of tumor necrosis factor family) on osteoclastic precursors. In addition, it was found that TNF-α was able to inhibit bone formation by suppressing osteoblast differentiation [54].

TNF-α (known as cachectin) causes increased basal energy expenditure, anorexia, and muscle loss in vivo. A definite relationship was found between TNF-α level and wasting (up to cachexia) in the cases of chronic inflammatory diseases, including infection with the human immunodeficiency virus, rheumatoid arthritis and oncological diseases [55]. High blood levels of TNF-α are coupled with lower muscle mass and strength in elderly patients [13].

According to some authors, increased TNF-α concentration is associated with senile asthenia, a significant decrease in muscle strength, the risk of cerebrovascular and cardiovascular diseases, as well as a more rapid decrease in cognitive abilities in elderly patients [56].

The effect of TNF-α and other pro-inflammatory cytokines on sarcopenia can be explained by several factors. For many years, it was believed that the induction of the breakdown of muscle proteins is the main pathway underlying the relationship between inflammation and sarcopenia. Later, additional mechanisms of the effect of pro-inflammatory cytokines (primarily, TNF-α) on muscles were found, including the stimulation of mitochondrial dysfunction and oxidative stress. In turn, the effect of TNF-α on mitochondrial dysfunction can be mediated by nitric oxide, which plays a significant role in mitochondrial functioning. It is known that TNF-α is a strong inducer of the synthesis of nitric oxide and so contributes to apoptosis stimulation and increased production of reactive oxygen species [57].

At the same time, several experimental and clinical studies demonstrated that TNF-α was able to inhibit the production of erythropoietin and activate hepcidin, which can cause anemia of chronic inflammation. It was established that this cytokine is involved in a complex mechanism that regulates erythropoietin synthesis in response to a hypoxic stimulus, and reduces the sensitivity of erythroid cells to the effects of erythropoietin. Stimulation of the synthesis of reactive oxygen species by TNF-α also makes a certain contribution to the suppression of erythropoietin production. At the same time, the inhibitory effect of TNF-α on the formation and differentiation of erythroid stem cells was revealed [58].

A recent experimental study demonstrated that TNF-α also plays a role in the regulation of megakaryocytic lineage. This pro-inflammatory cytokine stimulated platelet hyperreactivity and thrombosis in a mouse model of aging. Neutralization of TNF-α and its receptors, in contrast, decreased platelet hyperreactivity. Based on the data obtained, the authors of this work suggested that *inflammaging* contributes to platelet hyperreactivity and increases the risk of thrombosis during aging [59].

A clinical study involving 424 senile individuals observed over eight years revealed a gradual increase in plasma TNF-α concentration associated with cognitive dysfunction. According to the results of magnetic resonance imaging, an increased level of TNF-α was associated with decreased volume of brain gray matter and increased hyperintensity of white matter. This paper also shows an inverse correlation between TNF-α concentration and cognitive impairments, which were assessed using the Mini-Mental State Examination scale (MMSE) [60]. These results suggest that TNF-α level in the blood will be one of the potential biomarkers of age-related changes in the brain.

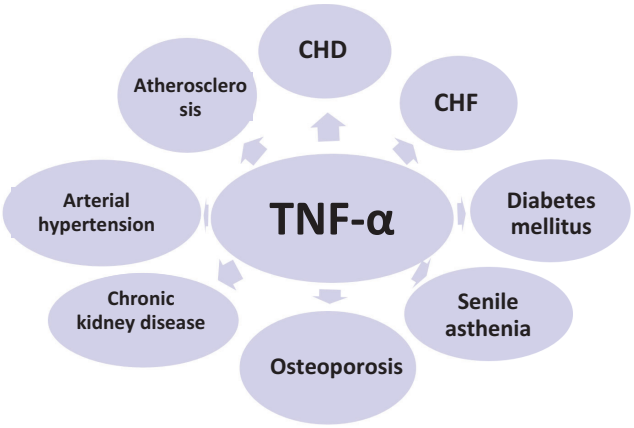

Figure 1. *TNF-α and age-related diseases*

Note: TNF-α — tumor necrosis factor-alfa, CAD — coronary artery disease, CHF — chronic heart failure

Clinical and experimental studies indicate the important role of TNF-α in immune response in elderly people and the increased level of cytokine with aging. This pro-inflammatory cytokine is associated with different age-related diseases and, most probably, with increased mortality. TNF-α can have an effect on several risk factors for cardiovascular diseases and contribute to the development and progression of atherosclerosis. Further studies are required to study the role of tumor necrosis factor-α in subclinical inflammation and the development of different pathological conditions in senile individuals and long-livers.

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