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Review Article

Modern View of the Inflammatory Cytokines in Coronary Artery Disease

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Abstract: This review summarizes role of the pro-inflammatory cytokines on the development of coronary artery disease and atherosclerosis. The relationship between the increase in the level of inflammation markers and the development of coronary heart disease, the prognostic value of these inflammation markers in patients suffering from stable forms of coronary heart disease is discussed.

Keywords: coronary artery disease; cytokines; inflammation; atherosclerosis.

INTRODUCTION

Coronary artery disease (CAD) is the most urgent problem of cardiology due to the widespread and high risk of developing cardiovascular complications and death (Alyavi, A., & Uzokov, J. (2017). In the pathogenesis of atherosclerosis and exacerbation of CAD, the role of the main link is assigned to the inflammatory reaction (Alyavi, A. L.,*et al.,*2018). The inflammatory process develops at the local level, which is determined by the basic mechanisms of inflammation, and systemic – systemic inflammatory response (SIR). An important role in the development of atherosclerosis and CAD arising on its basis belongs to immune-inflammatory reactions, oxidized fatty acids and pro-inflammatory cytokines as well as, potential pro-inflammatory factors (Hermus, L.,*et al.,*2010) . Pro-inflammatory cytokines (IL-1, IL-6, TNF-α) mediate intercellular interactions and support local inflammation in an atherosclerotic plaque, activating endothelial cells and inducing the expression of adhesion molecules and chemokine, acute phase proteins, and prothrombotic activity of endothelium. Anti-inflammatory cytokines (IL-4, IL-10) inhibit the secretion of pro-inflammatory cytokines, inhibit macrophage activity, reduce the expression of adhesion molecules and reduce cytotoxicity. The reality of the inflammatory theory of atherosclerosis is confirmed by the discovery in the blood of patients with cardiovascular diseases, primarily CAD, of an elevated level of systemic inflammatory response markers, of which CRP is the widely studied (Alyavi, B.,*et al.,*2018). It is known that the synthesis and secretion of CRP is regulated by pro-inflammatory cytokines, primarily IL-6, as well as IL-1 and TNF-α at the level of transcription of the CRP gene. However, the role of inflammatory mediators, such as pro- and anti-inflammatory cytokines, in the clinical setting in patients with CAD remains unclear. Atherosclerosis of the coronary arteries is the pathomorphological basis of CAD (Usarov, M., et al. 2016). In atherosclerosis, signs of local and systemic non-specific inflammatory processes are observed already in the early stages of damage to the blood vessel wall. Atherosclerosis is known to be a chronic inflammatory process and even in the early stages of atherogenesis - intra- and extracellular deposition of lipids and the formation of lipid spots, inflammatory cells (macrophages and T-lymphocytes) are already presented (Mukhamedova, M.,*et al.,*2019; Piepoli, M. F.,*et al.,*2016). When activated, these cells secrete a large number of cytokines, chemokines, and matrix metalloproteinase, which cause progression in the development of atherosclerotic plaque.

With atherosclerosis, there is an increase in the expression of VCAM-1 adhesion molecules on endotheliocytes, which, under the influence of pro-inflammatory chemoattractants, leads to the migration of monocytes to the intima of arteries and their subsequent transformation into foam cells. T lymphocytes also migrate, secreting cytokines that enhance local inflammation. After the formation of the plaque, the constant interaction of lymphocytes and macrophages supports the inflammatory process (Mayer, F. J.,*et al.,*2016). Cytokines are peptides that mediate intercellular interactions through specific receptors on the cell surface. Both immunocompetent cells, which include T-lymphocytes, macrophages and monocytes, and non-immunocompetent cells (cardiomyocytes, endotheliocytes) secrete Cytokines (Abdullaev, A. Kh.,*et al.,*2016). The family of interleukins (IL), interferons, tumor necrosis factor, and trophic factors are distinguished. Cytokines regulate the activation, differentiation, growth, death, and effector functions of various types of cells, which makes them important factors in the pathophysiology of CAD. The reasons for the increase in the level of pro-inflammatory cytokines are still not fully understood. Among them, the presence of a mechanical load on endotheliocytes characteristic of hypertension, hypoxia and myocardial ischemia, an increase in the concentration of low-density lipoprotein cholesterol (LDL cholesterol) (Babaev, M.,*et al.,*2018). In addition, the activation of cytokines in CAD is closely associated with autoimmune mechanisms, oxidative stress, the infectious process, and the accumulation of endotoxins as a result.

There is evidence that the degree of increase in blood concentrations of cytokines such as interleukin-1β (IL-1β) and

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tumor necrosis factor (TNF-α) are directly related to stages of CAD (AL, A.,*et al.,*2018). This allows to use them as markers of severity of CAD. A number of studies have demonstrated that persistent immune activation in vivo is characteristic of patients with CAD. This is reflected in increased levels of pro-inflammatory cytokines in the blood (TNF-a, interleukins - IL-1β and IL-6) and chemokines (monocytic chemoattractant protein-1 and IL-8), as well as enhanced expression of various inflammatory mediators (TNF-a, IL-6 and adhesion molecules) in the myocardium, regardless of the etiology of CAD (Alyavi, A.,*et al.,*2018).

Despite the absence of specific activation of cytokines in patients with CAD, it can be assumed that pro-inflammatory mediators are not only markers of immune activation (as a sign of disease severity), but they can also play a pathogenic role in CAD. First, transgenic mice with cardiac-specific overexpression of TNF-a developed dilated cardiomyopathy (Hirata, Y., *et al.,* 2011a). Secondly, the systemic administration of TNF-α even at concentrations comparable to those determined in the blood of patients with CAD can induce a phenotype similar to dilated cardiomyopathy in animal models (Konishi, M., *et al.,* 2010).

Pro-inflammatory cytokines can modulate the functions of the cardiovascular system by various mechanisms. Cytokines such as TNF-α and IL-1β inhibit myocardial contractility. This may be due to the blocking of β-adrenergic signals, an increase in the content of nitric oxide in the heart, or changes in intracellular calcium homeostasis(Shimabukuro, M.,*et al.,*2013) . TNF-α and members of the IL-1β family can also cause structural changes in the myocardium in patients with heart failure, such as cardiomyocyte hypertrophy and interstitial fibrosis(Uzokov, J.*et al.,*2017). In addition, TNF-α and IL-1β promote apoptosis cardiomyocytes, and also activate metalloproteinase and disrupt the expression of their inhibitors, possibly contributing to heart remodeling (Takaoka, M.,*et al.,*209) .

Autoimmune processes and microorganisms are known to play a pathogenic role in patients with dilated cardiomyopathy (DCMP), and these mechanisms could presumably contribute to an increase in cytokine levels in CAD. However, elevated levels of cytokines were found not only in DCMP, but also in patients with ischemic cardiopathy. Moreover, it is believed that endotoxins are capable of triggering immune activation in patients with CAD (Henrichot, E.,*et al.,*2005). Therefore, persistent stimulation with microbial antigens could lead to the activation of cytokines in CAD. The increase in cytokine levels occurs in CAD, regardless of chronic infection, however, some other factors can cause severe inflammatory reactions in such patients.

Both mechanical overload and shear stress can cause the expression of cytokines (monocytic chemoattractant protein-1 and IL-8) in both endothelial and smooth muscle cells (Ketonen, J.,*et al.,*2010). Moreover, hypoxia and ischemia are powerful inducers of inflammatory cytokines (TNF-α, monocytes chemo attractant protein-1 and IL-8) in the myocardium.(Alyavi, B.A.,*et al.,*2019). Finally, oxidized low-density lipoproteins can increase the expression of cytokines (TNF-a, IL-1β, IL-6, and IL-8) in endothelial cells and monocytes, and such mechanisms can be especially important in CAD (Bundhun, P. K.,*et al.,*2017). The relative importance of cytokine production stimuli in various forms of heart failure has not been determined.

Positive role of pro-inflammatory cytokines becomes problematic at the moment when the degree of activation ceases to be adequate and when the protective mechanism initially develops into a pathological process (over-expression of certain types of adhesive molecules). Hyper proliferation of fibroblasts and subsequent tissue fibrosis due to an increased concentration of TGF-β is an example of the negative effect of overproduction of cytokines — this is a typical example of the transition of the inflammatory process into a chronic course (Lowe, G.,*et al.,*2014). With the development of the inflammatory reaction, endothelium, platelets, white blood cells, plasma coagulation system and complement system always interact. Considering the auto-aggressive potential of some mediators produced by the mentioned systems, it is necessary that the inflammatory reaction - as a protective reaction of the body - proceeds at a pace and volume corresponding to the degree of damage. The most important condition for this is the targeted interaction between the above systems. Dysregulation and delocalization are critical factors in the development of auto-aggressive inflammation. The main means of intercellular interactions are cytokines and adhesive molecules. The spectrum of adhesive molecules on the cell surface depends on whether an immunocompetent cell is activated or not. After activation of the cell, expression of other adhesive molecules than at rest begins on its surface; Due to this, the activated cell is capable of new contacts and can interact with other cellular systems, which in many cases leads to the further production of various types of cytokines (Owens, G. K.,*et al.,*2004).

The results of several studies have shown a direct relationship between elevated plasma levels of inflammatory cytokines and severity of CAD (Lutfullayevich, A. A.,*et al.,*2017). More importantly, these inflammatory mediators carry important prognostic information about patients with CAD.

Regarding the effect of cardiovascular therapy on cytokine levels in patients with CAD, the following can be noted. There is some evidence on the effect of traditional cardiovascular drugs on the immune activation that occurs with CAD. In a multicenter PRAISE study (Prospective Randomized Amlodipine Survival Evaluation), the level of IL-6 decreased under the influence of calcium antagonist amlodipine, suggesting that this agent mediates a positive effect on mortality in patients with dilated cardiomyopathy (Ahmedov, I., *et al.,*2017) . Thus, an important "antihypertrophic" mechanism of the influence of ACE inhibitors on the myocardium may be a decrease in the level of IL-6, possibly combined with a deterioration in signal transduction of IL-6. However, with the exception of the beneficial effect on IL-6, all other immunological parameters were significantly increased in patients with CAD and remained unchanged during treatment with enalapril (Lumeng, C. N., *et al.,*2007).

There are reports that ACE inhibitors can prevent the activation of nuclear factor kB and the expression of monocytic chemoattractant protein-1, as well as reduce macrophage infiltration in both experimental and clinical atherosclerosis (Uzokov, J., *et al.,*2016). In addition, the combination of ACE inhibitors and angiotensin II receptor antagonist reduces cardiac macrophage infiltration after acute myocardial infarction in animal models (Uzokov.J. *et al.,* 2016). However, whether ACE inhibitors have such an effect in CAD remains unknown.

Several studies have shown that β-adrenergic stimulation modulates cytokine production in various subpopulations of lymphocytes and monocytes (Сайдалиев, Р. С., и др.,2015). In rats, adrenergic activation increases the expression of pro-inflammatory cytokines in the myocardium (TNF-α and IL-1), which decreased under the influence of β-blocker metoprolol (Mazurek, T.,*et al.,* 2003) . However, in patients with dilated cardiomyopathy, some suppressive effect of β-blockers on the plasma level of both pro-inflammatory (TNFα) and anti-inflammatory (IL-10) cytokines was observed (Park, J. B. 2016). With long-term treatment with a β1-selective prolonged-release metoprolol blocker, there was no significant effect on the cytokine content compared with placebo in patients with CAD Mamatkulov, Kh. A.,*et al.,*Therefore, it is still necessary to determine whether a complete blockade of β-receptors (i.e. non-selective) or a combined blockade of a- and β-receptors with carvedilol can change the ratio of cytokines.

Analysis of the data from several studies showed that statins have direct cardiovascular effects, such as attenuating inflammatory reactions and stabilizing atherosclerotic plaques,

which are clearly not associated with their hypocholesterolemic effect. Statins lower the level of C-reactive protein and are effective in preventing coronary events in patients with a relatively low lipid content but with an increased level of C-reactive protein (Uzokov, J., & Alyavi, B. 2018). Standard treatment with acetylsalicylic acid also reduces the levels of IL-6 and C-reactive protein in patients with stable angina pectoris (Ridker, P. M.,*et al.,*2000). A decrease in the levels of cytokines and C-reactive protein when using statins and acetylsalicylic acid may explain part of their therapeutic effect. However, their ability to reduce systemic and myocardial inflammation in patients with other type of CAD (such as, silent myocardial ischemia, unstable angina) requires further study.

CONCLUSION

Anti-inflammatory cytokines are involved in limiting the activity of inflammatory response, inhibit the secretion of pro-inflammatory cytokines and regulate the severity of tissue damage. A decrease in the level of anti-inflammatory cytokines in the blood plasma and an increased content of pro-inflammatory cytokines and acute phase proteins indicate a higher risk and poor prognosis of CAD. The number of markers of inflammation (pro- and anti-inflammatory cytokines) is constantly increasing. The introduction of measurements of their level in practice will improve the quality of diagnosis, identify risk groups, and more accurately evaluate treatment outcomes and prognosis.

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