Academic Research in Educational Sciences VOLUME 3 | ISSUE 1 | 2022
ISSN: 2181-1385
Scientific Journal Impact Factor (SJIF): 5.723
Directory Indexing of International Research Journals-CiteFactor: 0.89
DOI: 10.24412/2181-1385-2022-1-366-375

ROLE OF CYTOKINES IN THE PATHOGENESIS OF CHRONIC CORONARY SYNDROME

Z. T. Sabirjanova, SH. K. Muminov, X. O. Ruzieva, B. B. Nigmonov
Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan

ABSTRACT

The review presents the current understanding of the role of inflammation in coronary heart disease. Most patients can be given the diagnosis of chronic coronary syndrome (CCS), also referred to as stable ischemic heart disease (SIHD), based on a classic history of angina pectoris in the presence of either risk factors for or known atherosclerotic cardiovascular disease. Angina pectoris, or angina for short, refers to chest discomfort that occurs when myocardial oxygen demand exceeds oxygen supply. Stable angina refers to chest discomfort that occurs predictably and reproducibly at a certain level of exertion and is relieved with rest or nitroglycerinIn recent years, the concept of atherosclerosis has been formed as a chronic low-intensity inflammatory process, accompanied by the release of cytokines by blood and endothelial cells, which have the properties of activators and inhibitors of inflammation, which ends in atherothrombosis, which is the main cause of myocardial infarction. Possible ways of influencing this pathological process in the treatment of cardiovascular diseases are discussed.

Keywords: ischemic heart disease, inflammation, cytokines, chronic coronary syndrome, heart failure

INTRODUCTION

The present-day perceptions of inflammation role in ischemic heart disease are reviewed. Recent investigations resulted in the emerging of a new idea of atherosclerosis - the majority of the researchers consider atherosclerosis to be a chronic inflammatory process of low-grade intensity accompanied by the cytokines discharge by the blood and endothelial cells which possess the property to activate and inhibit inflammation. Atherothrombosis is the final stage of this process and the main cause of myocardial infarction. The possible ways of intervention into this process in the treatment of cardiovascular diseases are discussed.

Cardiovascular disease (CVD) continues to be the leading cause of death in all the world. This mainly applies to diseases associated with common pathogenesis -

ISSN: 2181-1385
Scientific Journal Impact Factor (SJIF): 5.723
Directory Indexing of International Research Journals-CiteFactor: 0.89
DOI: 10.24412/2181-1385-2022-1-366-375

atherosclerosis, the most important factor in the development of coronary heart disease (IHD).

The point of view is becoming generally accepted, according to which the most real factor in the initiation and progression of IHD is inflammation, and destabilization atherosclerotic plaque is determined by the high activity of the current chronic inflammatory process. Research in molecular biology allowed to obtain convincing evidence of the participation of cytokines in the process of damage to atherosclerotic plaque in the coronary vessel as a result of its inflammation and rupture. This is the main mechanism leading to the development of acute coronary events - unstable angina pectoris (NS), myocardial infarction (MI) and sudden death [5, 6, 28, 33, 39].

The inflammatory theory of atherogenesis is confirmed detection in the blood of CVD patients, first of all, an increased concentration of markers of the inflammatory response, such as cytonins IL-1 β, IL6, IL-10,TNF- α, adhesion molecules, etc. [1]. IL-6 is a multifunctional cytokine and stimulates the proliferation of T-lymphocytes, macrophages, endothelial cells [11]. With the help of IL-6, endothelial cells, monocytes are activated and procoagulative reactions occur [8,10]. Cytokines have a strong effect on the production of each other. In this network of mutual influences, almost all effects are stimulating, and only IL-6 suppresses the production of IL-1 and TNF- α.This the peculiarity of IL-6 determines its dual role in development of inflammation: being a typical pro-inflammatory cytokine in its effects, it also has an anti-inflammatory effect. Biological the meaning of this phenomenon boils down to the fact that IL-6, as it were completes the formation of the inflammatory process.

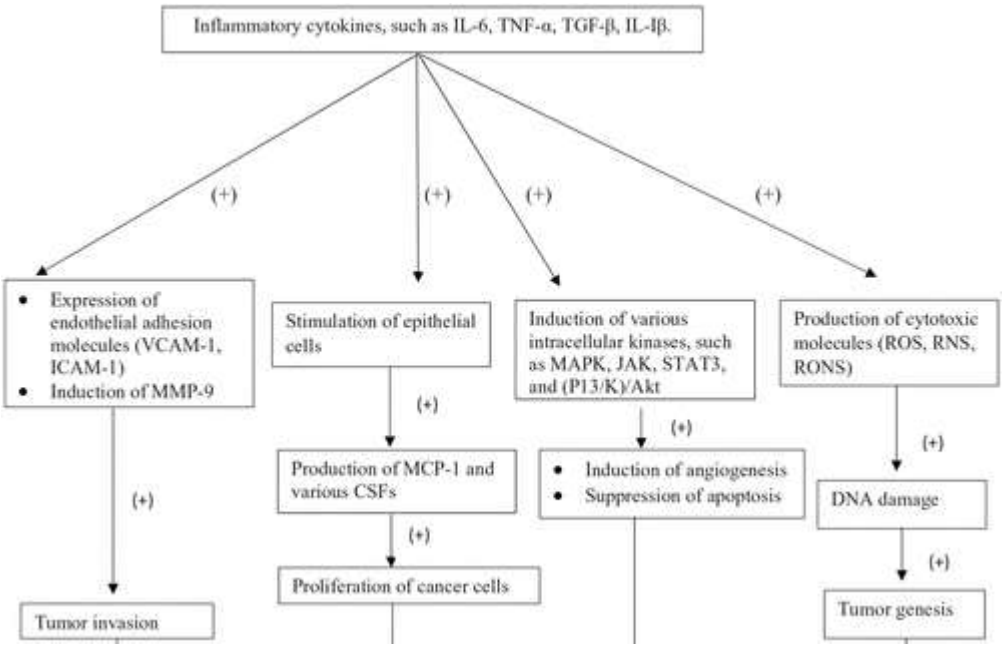
The main functions of IL-6 also include stimulation synthesis of proteins of the acute phase of inflammation, antibodies, activation of endothelial cells and hyperthermia [38]. Relatively recently it was found that high FC of angina pectoris are accompanied by cytokine hyperexcretion. This indicates the presence already at the stage of stable angina pectoris persistent inflammation, which, in its turn, increases the risk of thrombotic complications and ACS [2].

IL-1β is a secretory cytokine that acts both locally and at the systemic level [4]. Experiments have shown that IL-1β has no less than 50 different biological functions, and almost all organs and tissues are targets. One relatively small molecule stimulates development a whole complex of protective reactions of the body, aimed at limiting the spread of infection, restoring the integrity of damaged tissues.

ISSN: 2181-1385
Scientific Journal Impact Factor (SJIF): 5.723
Directory Indexing of International Research Journals-CiteFactor: 0.89
DOI: 10.24412/2181-1385-2022-1-366-375

An integral part of the biological action of IL-1β is a stimulating effect on the metabolism of connective tissue. The mediator stimulates the proliferation of fibroblasts and increases their production prostaglandins, growth factors and a number of cytokines [9].

One of the pro-inflammatory cytokines directly involved in inflammation in atherosclerosis is tumor necrosis factor - α (TNF- α). TNF-is predominantly produced by monocytes / macrophages, endothelial cells and mast cells. TNF-affects the endothelium, enhances the expression of adhesion molecules on it, activates macrophages, neutrophils, causes the synthesis of acute phases of inflammation. Disruption of TNF-metabolism undoubtedly plays a role in the development of CVD. [38, 46]. It was found that postischemic reperfusion the myocardium is accompanied by an increase in the level of cytokine. According to some reports, the level of TNF-in serum increases both in patients with unstable and in patients with stable angina pectoris III-IV functional class [7, 21]. TNF production in the acute post-infarction period is triggered mainly by ischemia. In the early postinfarction phase, a certain degree of mediator production is physiological, because during this period cytokines play a protective role in decreasing cell apoptosis [25, 35]. In experimental models, the actual immediate inotropic effect of TNF-was obtained, which lasts until



complete elimination of the cytokine. However, this cytokine not only has a negative inotropic effect, it summarizes cellular and biochemical disorders found in cardiac damage muscles. TNF-causes a hypertrophic response the growth of cardiomyocytes, which is an adaptation to hemodynamic disturbances [22].

ISSN: 2181-1385
Scientific Journal Impact Factor (SJIF): 5.723
Directory Indexing of International Research Journals-CiteFactor: 0.89
DOI: 10.24412/2181-1385-2022-1-366-375

Cytokines play a major role in the pathogenesis of atherosclerosis. Some of them may show anti-atherogenic and anti-inflammatory effects by inhibiting TNF and IL-6. This cytokine is IL-10 [23]. Data on the presence and action of IL-10 in the ischemic myocardium were obtained in studies experimental models of myocardial infarction [24, 32, 44]. In the course of experiments on dogs, direct evidence was obtained that IL-10 is formed in the myocardium during ischemia and reperfusion [23]. The authors especially emphasize the significant increase in the expression of IL-10 during the resumption of myocardial circulation and suggest that this is probably a consequence of the increased access of lymphocytes to the ischemic zone caused by reperfusion. In the recovering myocardium, the main sources of IL-10 synthesis are T-lymphocytes [16]. The produced cytokine plays a special role in scar formation in the damaged area. In the absence of experimental animal gene responsible for IL-10 production, inflammatory response after MI was more pronounced compared to ordinary animals. In this group of experimental animals, an increase in the size of the MI zone, an increase in the level of TNF-and the expression of MCP-1 was determined [44]. So Thus, endogenous IL-10 plays a protective role in the time of myocardial ischemia / reperfusion as a result of a decrease in the acute inflammatory process. IL-10 is a potent monocyte deactivator and suppressor various pro-inflammatory cytokines. It is proved that IL-10 reduces the severity of the inflammatory response and leads to improved LV function and remodeling processes [29]. An inverse relationship was found between the level of IL-10 and the severity of exertional angina.

Like cells in other tissues, tissues of the cardiovascular system are not only producers, but also targets of another inflammatory mediator - TGF-β (transforming growth factor β). It was found that TGF-β stimulates the growth of cardiomyocytes. TGF-β promotes an increase in the time of tolerance of hypoxia by cardiomyocytes [42, 43] and an increase in proliferation of myofibroblasts [20]. Introducing TGF-β in animals before the induction of ischemia or immediately after it reduced the rate of pathological changes in the myocardium [30].

The authors believe that this cytoprotective effect of TGF-is due to inhibition of the release of TNF-into the circulatory system. Data on the regulatory effect of TGF-on homeostasis and functional activity of blood vessel cells indicates its ability to influence the formation of new capillaries. Thus, TGF-β is involved in the regulation of a large number of vital functions of cells of the cardiovascular system through cell proliferation and migration, and also keeping them alive. Special

ISSN: 2181-1385
Scientific Journal Impact Factor (SJIF): 5.723
Directory Indexing of International Research Journals-CiteFactor: 0.89
DOI: 10.24412/2181-1385-2022-1-366-375

molecules, integrins, play an important role in intercellular interactions and triggering cytokine cascades [3]. In atherosclerosis, intercellular adhesion molecules (ICAMs) should be isolated. The role of molecules of the ICAM group is most significant in the migration of leukocytes to the inflammation focus. ICAM-1 is expressed under the influence of activation by cytokines such as IL-1β, TNF-α, α-interferons. Revealed increase concentration of soluble ICAM-1 in blood plasma in patients with ACS, as well as after episodes of anginal pain in patients with unstable angina pectoris or myocardial infarction (MI) without Q wave [31]. The high level of soluble ICAM-1 persisted for 6 month An increase in the level of MCP-1 (monocytic chemotactic protein-1) in blood plasma is observed in patients with coronary artery disease, and the highest values are determined during ACS [12, 19]. Increased levels of circulating MCP-1 have a positive correlation with most risk factors for CVD [18, 39]. During studies of patients who underwent ACS, it was found that an increase in the level of MCP-1 more than 238 pg / ml is a predictor of mortality in the same way like CRP and BNP. It was found that MRS-1 through activation macrophages can cause destabilization of atherosclerotic plaque, and thereby cause an episode of myocardial ischemia [17]. In an experiment on rats with by modeling MI, the administration of antibodies to MCP-1 leads to a decrease in the size of the infarction zone, which was explained by a decrease in the expression of adhesion molecules and infiltration by macrophages, as well as to a decrease in ventricular dilatation and preservation of contractile function [26].

The classic option for the treatment of coronary artery disease is the restoration of coronary blood flow. Opening of special molecules capable of stimulating angiogenesis in the myocardium contributed to the growth of interest in the implementation of these knowledge into practice. The increase in angiogenesis is explained by the activation of growth factors, mainly of the family

VEGF (vascular endothelial growth factor). However, the role VEGF in atherosclerosis and coronary artery disease is dual: there are clinical experimental data in favor of the participation of VEGF in stimulating the growth of atherosclerotic plaques [39]. The literature indicates that hopes for the therapeutic effect of angiogenic factors in ischemia myocardium as a whole was not confirmed [40]. Established that VEGF, acting in combination with other factors growth and cell receptors, stimulates the proliferation of mesenchymal cells [13], this can contribute to the development of fibrosis and atherosclerosis. Besides Moreover, VEGF can enhance vascularization of atherosclerotic plaques, contributing to their instability

ISSN: 2181-1385
Scientific Journal Impact Factor (SJIF): 5.723
Directory Indexing of International Research Journals-CiteFactor: 0.89
DOI: 10.24412/2181-1385-2022-1-366-375

[15]. The benefit of local angiogenesis in the ischemic zone is questionable, since ischemia is usually caused by obstruction of the vessels located in the epicardium, and the narrowing is located proximal to the focus ischemia. Therefore, weakening of ischemia can be facilitated by functioning collaterals, but not by enhancement of microcirculation in the ischemic zone [34, 36].

With the establishment of the role of inflammatory processes in the development of atherosclerosis, determination of plasma levels of inflammation has become an important tool for predicting cardiovascular risks. Recent data assign a special role to the pro-inflammatory cytokine IL-18. It is a pleiotropic proinflammatory cytokine that plays a leading role in triggering the inflammatory cascade [24]. Recently, in experimental studies, it was found that the expression of IL-18 is closely associated with the progression and instability of atherosclerotic plaque. According to the AtheroGene Study, the concentration of circulating IL-18 is a harbinger of future acute conditions in patients with stable and unstable angina pectoris [14]. The main function of the IL-18 is to launch production of interferon- α, and triggering the Th1 response. IL-18 stimulates the expression of IL-6, ICAM-1, mononuclear phagocytes and a number of other chemokines, has a strong regulatory activity on NK cells. IL-18 can cause an increase in the production of IL-1 β, TNF- α, by mononuclear cells of peripheral blood, in addition to chemokines such as MCP-1. According to several recent studies, increased production of IL-18 is directly related to the growth of atherosclerotic plaques.

CONCLUSION

Since the relationship between the levels of markers of inflammation (primarily IL-1 β, TNF- α, IL-6, etc.) with the onset of myocardial infarction was established, of course, and the assumption that a decrease in the severity of inflammation may be accompanied by a decrease in the likelihood the development of complications of myocardial infarction. So far only evidence is accumulating that various interventions can lower levels of inflammatory markers. Considering the current state of the issue of the inflammatory component of a heart attack myocardium, it is advisable to assess the dynamics of the cytokine profile during treatment, which makes it necessary to study possible ways of influencing of that.

ISSN: 2181-1385
Scientific Journal Impact Factor (SJIF): 5.723
Directory Indexing of International Research Journals-CiteFactor: 0.89
DOI: 10.24412/2181-1385-2022-1-366-375

REFERENCES

1. Братусь, В.В. Атеросклероз, ишемическая болезнь сердца, острый коронарный синдром / В.В.Братусь, В.А.Шумаков, Т.В. Талаева. – Киев: Четверта хвиля, 2004. – 576 с.
2. Закирова, Н.Э.Иммуновоспалительные реакции при ишемической болезни сердца / Н.Э. Закирова, Н.Х. Хафизов, И.М. Карамова // Рациональная фармакотер. в кард. – 2007. – № 2. – С.16-19
3. Залесский,В.Н. Апоптоз при ишемии и реперфузии миокарда / В.Н.Залесский, Т.И. Гавриленко, А.А. Фильченков // Лїкарьска справка. – 2002. – № 1. – С. 21-24.
4. Кашкин, К.П. Цитокины иммунной системы: основные свойства и иммунобиологическая активность / К.П.Кашкин // Клин. лаб. диагностика. – 1998. – № 11. – С.21-32
5. Королева, О.С. Биомаркеры в кардиологии:регистрация внутрисосудистого воспаления / О.С.Королева, Д.А.Затейщиков / / Фарматека. – 2007. – № 8-9. – С. 30-36.
6. Литвин, Е.И. Динамика экспрессии цитокинов у больных с острым коронарным синдромом / Е.И.Литвин // Укр. кардиол. журнал. – 2002. – № 1. – С. 21-24.
7. Лутай, М.И. Атеросклероз: современный взгляд на патогенез / М.И.Лутай // Украинский медицинский журнал. – 2004. – № 1. – С. 22-34.
8. Маянский, А.Н. Современная эволюция идей И.И. Мечникова о внутрисосудистом воспалении / А.Н.Маянский // Иммунология. – 1995. – № 4. – С. 8-14.
9. Симбирцев, А.С. Новые подходы к клиническому применению Беталейкина рекомбинатного интерлейкина-1β / А.С. Симбирцев, С.А. Кетлинский, М.Л. Гершанович // TerraMedica. – 2000. – № 1. – С.3-5.
10. Талаева, Т.В. Механизмы инициации острого коронарного синдрома: роль модифицированных липопротеинов как аутоантигенного фактора / Т.В.Талаева, Е.Н. Амосова, В.В. Братусь / / Украинский кардиол журнал. – 2006. – № 9. – С. 18-24
11. Титов, В.Н. Общность атеросклероза и воспаления: специфичность атеросклероза как воспалительного процесса (гипотеза) / В.Н.Титов // Биохимия. – 2000. – №4. – С. 3-10

ISSN: 2181-1385
Scientific Journal Impact Factor (SJIF): 5.723
Directory Indexing of International Research Journals-CiteFactor: 0.89
DOI: 10.24412/2181-1385-2022-1-366-375

12. Aukrust, P. Interaction between chemokines and oxidative stress: possible pathogenic role in acute coronary syndromes / P.Aukrust, R.K.Berge, T. Ueland // J. Am.Coll. Cardiol. – 2001. – Vol. 37. – P. 485-491
13. Ball, S.G. Vascular endothelial growth factor can signalthrough platelet-derived growth factor receptors / S.G. Ball, C.A. Shuttleworth, C.M. Kielty // J. Cell. Biol. – 2007. -Vol. 177(3). – P. 489-500.
14. Blankenberg, S. Interleukin-18 is a strong predictor of cardiovascular death in stable and unstable angina / S. Blankenberg, L. Tiret, C. Bickel // Circulation. – 2002. – Vol. 106. – P.24-30.
15. Chen, F. Apoptosis and angiogenesis are induced in the unstablecoronary atherosclerotic plaque / F. Chen, P. Eriksson, T. Kimura// Coron. Artery Dis. – 2005. – Vol. 16(3). – P. 191-197.
16. Daftarian, P.M. IL-10 production is enhanced in human T-cells by IL-12 and IL-6 and in monocytes by tumor necrosis factora / P.M.Daftarian, A. Kumar, M. Kryworuchko // J. Immunology. – 1996. – Vol. 157, № 1. – P. 12-20.
17. de Lemos, J. A.Serial measurement of monocyte chemoattractant protein-1 after acute coronary syndromes: results from the A to Z trial/ J.A. de Lemos, D.A. Morrow, M. A., Blazing // J. Am. Coll. Cardiol. – 2007. – Vol. 50. – P. 2117-2124.
18. Deo, R. Association among plasma levels of monocyte chemoattractant protein-1, traditional cardiovascular risk factors, and subclinical atherosclerosis/ R. Deo, A. Khera, D.K. McGuire // J. Am. Coll. Cardiol. – 2004. – Vol. 44. – P. 1812-1818.
19. Economou, E. Chemokines in patients with ischemic heart disease and the effect of coronary angioplasty/ E. Economou, D. Tousoulis, A. Katinioti // Int. J. Cardiol. – 2001. – Vol. 80. – P. 55-60.
20. Eghbali, M. Cardiac fibroblasts are predisposed to convert into myocyte phenotype: specific effect of transforming growth factor beta / M.Eghbali, R. Tomek, C. Woods // Proc. Natl. Acad. Sci. USA. – 1991. – Vol. 88. – P. 795-799.
21. Entman, M.L. Postperfussion infamation; a model for reaction to ingury in cardiovascular disease / M.L.Entman, W.C. Smith // Cardiovasc Res. – 1994. – Vol. 28. – P. 1301-1311.
22. Feldman, A.The role of tumor necrosis factor in the pathophysiology of heart failure/ A. Feldman, A. Combes, D. Wagner et al//Journal of the American College of Cardiology. – 2001. – Vol. 35. – Is.3. – P. 537-544 23. Frangogiannis, N.G. IL-10 is induced in the reperfused myocardium and may modulate the reaction to injury / N.G.

ISSN: 2181-1385
Scientific Journal Impact Factor (SJIF): 5.723
Directory Indexing of International Research Journals-CiteFactor: 0.89
DOI: 10.24412/2181-1385-2022-1-366-375

Frangogiannis, L.H. Mendoza, M.L. Lindsey // J. Immunology. – 2000. – Vol. 5. – P. 2798-2808

23. Frangogiannis, N.G. IL-10 is induced in the reperfused myocardium and may modulate the reaction to injury / N.G. Frangogiannis, L.H. Mendoza, M.L. Lindsey // J. Immunology. – 2000. – Vol. 5. – P. 2798-2808 24. Gracie, J.A. Interleukin-18/ J.A.Gracie, S.E. Robertson, I.B. McInnes// J Leukoc Biol. – 2003. – Vol. 73. – P. 213-224.

25. Jacobs, M. Tumor necrosis factor-alpha at acute myocardial infarction in rats and effects on cardiac fibroblasts / M.Jacobs, S. Staufenberger, U. Gergs //J Mol Cell Cardiol. – 1999. -Vol. 31. – P. 1949-1959.

26. Kaikita, K. Targeted deletion of CC chemokine receptor 2 attenuates left ventricular remodeling after experimental myocardial infarction / K. Kaikita, T. Hayasaki, T. Okuma // Am. J. Pathol. – 2004. – Vol. 165. – P. 439-447.

27. Kereiakes, D.J. Inflammation as a therapeutic target: a unique role for abciximab / D.J. Kereiakes // Am Heart J. – 2003. – Vol. 146(Suppl. 4). – P. 1-4.

28. Knuefermann, P. The role of innate immune responses in the heart in health and disease / P.Knuefermann, J. Vallejo, D.L.Mann // Trends Cardiovasc. Med. – 2004. – Vol. 14. – P. 1-7.

29. Krishnamurthy, P. IL-10 inhibits inflammation and attenuates leftventricular remodeling after myocardial infarction viaactivation of stat3 and suppression of HuR / P. Krishnamurthy, J. Rajasingh, E. Lambers // Circ Res. – 2009. – Vol. 104. – P. 9-18.

30. Lefer, A.M. Mediation of cardioprotection by transforming growth factor-beta / A.M.Lefer, P.Tsao, N. Aoki // Science. – 1990. – Vol. 249 – P. 61-64.

31. Malik, I. Soluble adhesion molecules and prediction of coronary heart disease: a prospective study and meta-analysis / I. Malik, J. Danesh, P Whincup // Lancet. – 2001. – Vol. 358. – P. 971- 975.

32. Mallat, Z. Protective role of interleukin-10 in atherosclerosis/ Z. Mallat, S. Besnard, M. Duriez // Circ. Res. – 1999. – Vol. 85. – P. 17-24.

33. Nabel, E.G. Cardiovascular disease / E.G. Nabel // N Engl J Med. – 2003. – Vol. 349. – P. 60-72.

34. Nagy, J.A. VEGF-A(164/165) and PlGF: roles in angiogenesisand arteriogenesis / J.A. Nagy, A.M. Dvorak, H.F. Dvorak // Trends Cardiovasc. Med. – 2003. – Vol. 13(5). – P. 169-175.

ISSN: 2181-1385
Scientific Journal Impact Factor (SJIF): 5.723
Directory Indexing of International Research Journals-CiteFactor: 0.89
DOI: 10.24412/2181-1385-2022-1-366-375

35. Nian, M. Inflammatory cytokines and postmyocardial infarction remodeling / M. Nian, P. Lee, N. Khaper // Circ Res. – 2004. – Vol. 94. – P. 1543-1553.
36. Schaper, W. VEGF and therapeutic opportunities in cardiovascular diseases / W. Schaper, I. Buschmann // Curr. Opin. Biotechnol. – 1999. – Vol. 10(6). – P 541-543.
37. Skoog, T. Plasma tumor necrosis factor α and early carotid atherosclerosis in healthy middle-age men / T.Skoog, W.Dicht, S. Boquist // Eur Heart J. – 2002. – Vol. 23. – P. 376-383.
38. Tang, W. Association of sICAM-1 and MCP-1 with coronary artery calcification in families enriched for coronary heart disease or hypertension: the NHLBI Family Heart Study. BMC / W. Tang, J.S. Pankow, J. J. Carr // Cardiovasc. Disord. – 2007. – Vol. 7. – P. 30-41.
39. Taqueti, V.R. Protecting the pump: controlling myocardial inflammatory response / V.R.Taqueti, R.N. Mitchell, A.H.Lichtman / / Annu. Rev. Physiol. – 2005. – Vol. 68. – P. 67-95.
40. Testa, U. Vascular endothelial growth factors in cardiovascular medicine / U.Testa, G. Pannitteri, G.L. Condorelli // J. Cardiovasc. Med. (Hagerstown). – 2008. – Vol. 9(12). – P. 1190-1221.
41. Tsutsumi, Y. Double face of VEGF/ Y. Tsutsumi, D.W. Losordo/ / Circulation. – 2005. – Vo1.12(9). – P. 1248–1250.
42. Wunsch, M. In situ localization of transforming growth factor beta 1 in porcine heart: enhanced expression after chronic coronary artery constriction/ M. Wunsch, H.S. Sharma, T. Markert // J. Mol. Cell. Cardiology. – 1991. – Vol. 23. – P. 1051-1062
43. Yang, B.C. Hypoxia-reoxygenation-induced apoptosis in cultured adult rat myocytes and the protective effect of platelets and transforming growth factor-beta (1)/B.C. Yang, D.S. Zander, J.L. Mehta // J. Pharmacol. Exp. Ther. – 1999. – Vol. 291. – P. 733-738.
44. Yang, Z.Crucial role of endogenous interleukin-10 production in myocardial ischemia/reperfusion injury// Z. Yang, B. Zingarelli, C. Szabo // Circulation. – 2000. – Vol. 101. – P. 1019-1026.
45. Yong, J. Cytokines in the pathogenesis of atherosclerosis / J. Yong, P. Libby,U. Schonbeck // Thrombos haemostas. – 2002. – Vol. 88. – P. 554-567. П