

Review Article

ROLE OF IMMUNO-INFLAMMATORY REACTIONS IN THE PATHOGENESIS OF CLINICAL VARIANTS OF CORONARY HEART DISEASE

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Abstract:

The role of inflammation in the pathogenesis of atherosclerotic lesion in CHD is widely discussed. In the study the relationship between the production of cytokines IL1, IL4, IL10, TNF α and clinical variations of ischemic heart disease has been studied. Patients with ischemic heart disease with stable and unstable angina were examined. The level of production of cytokines in blood serum was determined by immunoenzyme analysis. Studies show strong evidence for the participation of cytokines in immune inflammation mechanisms in coronary heart disease. The high functional class of angina accompanied by hyperproduction of pro-inflammatory cytokines dictates the need to develop new therapeutic approaches to reduce the production of proinflammatory cytokines in order to reduce the progressive inflammatory process and prevent the transition to an unstable form of the disease.

Keywords: Ischemic heart disease, proinflammatory cytokines, anti-inflammatory cytokines

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Introduction

Coronary heart disease (CHD) is the leading cause of morbidity, primary disability and mortality in the vast majority of the world's countries [Sanchis-Gomar, F., Perez-Quilis, C., Leischik, R., & Lucia, A. (2016). *Epidemiology of coronary heart disease and acute coronary syndrome. Annals of translational medicine*, 4(13), Gupta, R., Joshi, P., Mohan, V., Reddy, K. S., & Yusuf, S. (2008). *Epidemiology and causation of coronary heart disease and stroke in India. Heart*, 94(1), 16-26.]. In this regard, close attention is paid to the study of pathogenesis of CHD. Recently the role of immune inflammation in the pathogenesis of atherosclerotic lesion in CHD has been widely discussed [Zakyntinos, E., & Pappa, N. (2009). *Inflammatory biomarkers in coronary artery disease. Journal of cardiology*, 53(3), 317-333., McCarthy, C. P., McEvoy, J. W., & Januzzi Jr, J. L. (2018). *Biomarkers in stable coronary artery disease. American heart journal*, 196, 82-96.]. Cytokines of the immune system are key inflammatory factors that control all stages of the atherosclerotic process, participate in the formation of CHD and its complications [Kilic, T., Ural, D., Ural, E., Yumuk, Z., Agacdiken, A., Sahin, T., ... & Komsuoglu, B. (2006). *Relation between proinflammatory to anti-inflammatory cytokine ratios and long-term prognosis in patients with non-ST elevation acute coronary syndrome. Heart*, 92(8), 1041-1046., Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium. (2012). *The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. The Lancet*, 379(9822), 1214-1224., Tashkenbaeva, E.N., Ziyadullaev Sh.H., Togaev D.H., F.Sh.

Kadyrova. *The role of regulatory cytokines in the formation and progression of coronary heart disease associated with asymptomatic hyperurichemia. Journal of biomedicine and practice* 2018, vol. 1, issue 1, pp. 30–35.]. Thus, anti-inflammatory cytokines interleukin-1 (IL-1) and tumor necrosis factor (TNF α) cause or enhance the synthesis of cell adhesion molecules ICAM-1 and VCAM-1 by endothelial cells. Expression of the last endothelial cells on the membrane leads to the appearance of microthrombosis, development of tissue and cellular hypoxia, excessive vascular permeability and hyperproduction of free radicals, which contributes to the progression of inflammation and, as a result, leads to tissue damage [Simon, A. D., Yazdani, S., Wang, W., Schwartz, A., & Rabbani, L. E. (2000). *Circulating levels of IL-1 β , a prothrombotic cytokine, are elevated in unstable angina versus stable angina. Journal of thrombosis and thrombolysis*, 9(3), 217-222.]. In turn, anti-inflammatory cytokines - IL-4, -10, -13, -17 - are involved in limiting the activity of inflammatory response by inhibiting the secretion of proinflammatory cytokines such as IL1, IL6 and TNF α and regulate the severity of tissue damage [Mosser, D. M., & Zhang, X. (2008). *Interleukin-10: new perspectives on an old cytokine. Immunological reviews*, 226(1), 205-218., Gordeeva, E.K., & Cade, A.H. (2016). *Change of cytokine status at stable voltage angina. Medical Journal of the South of Russia*, (1)]. The aim of this study was to study the relationship between the production levels of cytokines IL1, IL4, IL10, TNF α and clinical variations of ischemic heart disease.

Material and methods

Patient information

106 patients with coronary heart disease were examined, 48 (45%) of them were patients with stable angina and 58 (55%) patients with unstable angina. Diagnosis of CHD with different angina course was made according to ESC recommendations for chronic stable angina (CSAP), unstable angina or myocardial infarction without ST segment elevation (UA/NSTEMI) and myocardial infarction with ST segment elevation (STEMI) [Task Force Members, Montalescot, G., Sechtem, U., Achenbach, S., Andreotti, F., Arden, C., ... & Di Mario, C. (2013). 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *European heart journal*, 34(38), 2949-3003.; Roffi, M., Patrono, C., Collet, J. P., Mueller, C., Valgimigli, M., Andreotti, F., ... & Gencer, B. (2016). 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *European heart journal*, 37(3), 267-315.] Basic therapy for CHD included antiagregants, β-adrenoblockers, calcium antagonists, nitrates, statins, ACE inhibitors. A total of 64 healthy individuals were examined as a control group, including 31 men and 33 women with an average age of 63 years. Individuals in the control group were physically healthy, without cardiovascular disease. In order to characterize immuno-inflammatory reactions, the content of proinflammatory (IL-1β, TNFα) and anti-inflammatory (IL4, IL10) cytokines in blood serum was studied

by means of immunoenzyme analysis using test systems - Vector-Best JSC (Novosibirsk, Russia).

Statistical data processing

For the analysis of the obtained data, the BioStat 5.8.4.3 software was used. The data were presented in the form of an average value and a standard error (M±m). Correlation analysis of quantitative values was carried out using the Pearson correlation coefficient. The level of reliability P<0.05 was taken as statistically significant changes.

Results

The results of the study of the production level of proinflammatory (IL-1β, TNFα) and anti-inflammatory (IL4, IL10) cytokines in patients with CHD and control group are presented in tables 1,2,3. The concentration of proinflammatory IL-1β and TNFα cytokines in blood serums of patients with CHD was significantly higher than in practically healthy individuals in the control group. The average IL-1β value on admission to the hospital was 101.4±1.44 pg/ml, which was 3.8 times higher than in the control group. In the general group of patients with CHD, an increased level of TNFα was also observed in 3.3 times (70.4±0.70 pg/ml) on admission to the hospital. Production of anti-inflammatory cytokine IL-4 according to our studies did not have any significant differences between the group of patients with CHD and healthy persons in the control group. Reduction of IL-10 concentration was registered in the general group of patients with CHD, hospitalized in hospital (p<0,05).

Table 1. Level of immunocytokine production in patients with CHD and practically healthy persons in the control group

Indicators	CHD general group	KG	T	p
IL-1β pg/ml	101,4±1,44	26,6±0,93	44,2	<0,001
TNFα pg/ml	70,4±0,70	21,2±0,60	53,3	<0,001
IL-4 pg/ml	23,8±0,36	24,1±0,82	0,33	>0,05
IL-10 pg/ml	12,4±0,15	15,2±1,02	2,71	<0,05

The increased level of proinflammatory production in CHD revealed in the studies testifies to the strengthening of proinflammatory blood potential with a change in the balance of the immune response in the direction of Th1-mediated cellular reactions, which generally reflects the instability of the immunological phenotype and the likelihood of association with the severity of the disease course and phase.

Therefore, we analyzed the obtained results of the level of proinflammatory and anti-inflammatory serum cytokines of cro-vi patients of CHD depending on the FC stable angina of tension and the phase of the disease course. In the group of

patients of CHD CVA II FCs increased indices of proinflammatory cytokines (IL-1β 98,5±1,68 pg/ml, TNFα 68,4±1,6 pg/ml) and decreased indices of anti-inflammatory cytokines (IL-4 22,5±1,52 pg/ml, IL-10 11,9±0,60 pg/ml) were revealed (Table 2). The average level of proinflammatory cytokines IL-1β and TNFα concentration was the highest in patients with CHD CVA IV FC, the lowest average level of anti-inflammatory cytokine IL-10 concentration was also registered in the group of patients with CHD CVA IV FC. The level of anti-inflammatory cytokine IL-4 did not differ significantly in the comparison groups.

Table 2. Results of proinflammatory and anti-inflammatory cytokines depending on PCI patients

The indicator	KG	II FC	III FC	IV FC
IL-1β pg/ml	26,6±0,93	98,5±1,68*	101,0±1,34**	109,1±2,23***
TNFα pg/ml	21,2±0,60	68,4±1,6*	74,0±1,34**	74,8±1,21***
IL-4 pg/ml	24,1±0,82	22,5±1,52	27,4±1,57*	22,4±1,05
IL-10 pg/ml	15,2±1,02	11,9±0,60**	14,0±0,71	11,4±0,31**

Note: * - p<0.05 - reliability of the difference with the control group; ** - p<0.05 - reliability of the difference between the groups; *** - p<0.05 - reliability of the difference between the groups and the control group.

In the course of our study of cytokine parameters depending on the phase of CHD flow (Table 3), an increase in the content of proinflammatory cytokines was found in both clinical variants

of IBS. The concentration of proinflammatory IL-1β and TNFα cytokines in the HC group was statistically significantly increased in comparison with both the group of patients with SS and the control group. The levels of anti-inflammatory cytokines IL-4 and IL-10 tended to decrease in the group of patients with NS.

Table 3. Indexes of cytokines depending on the flow phase of CHD

The indicator	KG	CC	NS
IL-1 β pg/ml	26,6 \pm 0,93	98,8 \pm 1,90*	116,7 \pm 1,18***
TNF α pg/ml	21,2 \pm 0,60	68,5 \pm 0,93**	74,5 \pm 1,16***
IL-4 pg/ml	24,1 \pm 0,82	23,9 \pm 0,42	23,8 \pm 0,97
IL-10 pg/ml	15,2 \pm 1,02	12,4 \pm 0,18*	12,1 \pm 0,33*

Note: * - p<0.05 - reliability of the difference with the control group; ** - p<0.05 - reliability of the difference between the groups; *** - p<0.05 - reliability of the difference between the groups and the control group.

Thus, the pathogenesis of CHD is inextricably linked with inflammation, in the realization of which the immune system is involved. The revealed features of the cytokine blood profile of patients with CHD determine the severity of the course and the outcome of the disease.

Discussion

Our studies show strong evidence for the participation of the cytokines studied in the immune mechanisms of inflammation in coronary heart disease. Studies have shown that IL-1 β concentration in blood serum is elevated in patients with hypercholesterolemia, coronary heart disease and angina [Hasdai, D., Scheinowitz, M., Leibovitz, E., Sclarovsky, S., Eldar, M., & Barak, V. (1996). *Increased serum concentrations of interleukin-1 beta in patients with coronary artery disease. Heart, 76(1), 24-28.*, Ferroni, P., Basili, S., Vieri, M., Martini, F., Labbadia, G., Bellomo, A., ... & Alessandri, C. (1999). *Soluble P-selectin and proinflammatory cytokines in patients with polygenic type IIa hypercholesterolemia. Pathophysiology of Haemostasis and Thrombosis, 29(5), 277-285.*]. Statin therapy has been shown to reduce IL-1 β levels in these patients [Ferroni, P., Martini, F., Cardarelli, C.M., Gazzaniga, P.P., Davi, G., and Basili, S. *Enhanced interleukin-1beta in hypercholesterolemia: effects of simvastatin and low-dose aspirin. Circulation. 2003; 108: 1673-1675.*]. Our studies show that proinflammatory IL-1 β cytokines and TNF α , which characterize the state of the immune system and the events of systemic inflammatory response, were associated with CHD and its clinical forms. Positive associations between the proinflammatory cytokines and CHD are consistent with the data of the authors [Schroder, J., Mygind, N. D., Frestad, D., Michelsen, M., Suhrs, H. E., Bove, K. B., ... & Prescott, E. (2019). *Pro-inflammatory biomarkers in women with non-obstructive angina pectoris and coronary microvascular dysfunction. IJC Heart & Vasculature, 24, 100370.*]. Their role in atherosclerotic progression and transformation of a plaque from stable to unstable is confirmed by many studies [Kofler, S., Nickel, T., & Weis, M. (2005). *Role of cytokines in cardiovascular diseases: a focus on endothelial responses to inflammation. Clinical science, 108(3), 205-213.*, Ferns, G. A., & Saadeddin, S. M. (2002). *Markers of inflammation and coronary artery disease. Medical science monitor, 8(1), RA5-RA12.*].

In our studies we evaluated the condition of the anti-inflammatory cytokine system. Important cytokines with anti-inflammatory activity are IL-4 and IL-10, and according to some researchers' anti-inflammatory activity of IL-10 is preserved even in the presence of significantly high levels of proinflammatory cytokines [Mousavi, S. Z., Salehi, A., Jorjani, E., Manzari, R. S., Farazmandfar, T., & Shahbazi, M. (2018). *Association assessment of Interleukine-10 gene polymorphism and its expression status with susceptibility to coronary artery disease in Iran. Egyptian Journal of Medical Human Genetics, 19(1), 31-35.*]. Literature data show that with the increase of angina-diethylene FC the level of anti-inflammatory cytokines IL-4 and IL-10 decreases [Zakirova, N.E. *Immunoinflammatory reactions in coronary heart disease // Rational pharmacotherapy in cardiology.-2007.- №2.-pp.16-19.*]. Our studies have shown that IL-10 is mainly involved in the pathogenesis of atherosclerotic lesion in CHD. When analyzing the cytokines we studied in groups of people with different

severity and flow phase of IBS, it is clear that the level of IL-4 remained without significant changes.

Conclusion

The results of the present study indicate a reliable connection between cytokines and CHD and its clinical forms. High functional class of angina is accompanied by hyperproduction of proinflammatory cytokines that testifies to the presence of progressive inflammatory process at the stage of stable angina, which, in its turn, increases the risk of transformation from stable to unstable form of the disease. From the point of view of possible definition of long-term clinical effect of ischemic heart disease course stabilization, the development of new therapeutic approaches to decrease proinflammatory cytokines production is very actual.