УДК 616.127-005.8-036.11

Role of the acquired immune response in the development of acute coronary syndrome

T.V. Talaieva, V.O. Shumakov, V.V. Bratus

National Scientific Center «M.D. Strazhesko Institute of Cardiology NAMS of Ukraine», Kyiv, Ukraine

KEY WORDS: atherosclerosis, ischemic heart disease, acute coronary syndrome, immune inflammation, modified lipoproteins

There are actually no strict criteria for the evaluation of the risk of acute coronary syndrome (ACS) development. Many clinical studies showed absence of dependence between severity of the coronary arteries stenosis and ischemic heart disease (IHD) clinical course, including possibility of the development of its acute forms, and more than in 50 % cases acute myocardial infarction (MI) develops on the background of stenosis less than 50 %. Approximately in half or even 2/3 patients that died because of acute MI, IHD was not diagnosed vitally and sudden coronary death was the first and last of its manifestations.

During recent years it became obvious that the reason of ACS development is neither the severity of stenosis nor the dimension of atherosclerotic plaque; the features of its structure and composition predict its instability. The propensity of the plaque to disruption is not directly related to the severity of the traditional risk factors, first of all – hypercholesterolemia (HCE) and increased low density lipoprotein cholesterol (LDL CH).

It becomes more obvious that the most clear factor of both initiation and progression of atherosclerosis is inflammation, and the plaque destabilization is determined by high intensity of the chronic inflammatory process occurring in the damaged vascular wall. It is indicated in particular by the significant gradient of temperature between normal and damaged vascular segments which is more than one Celsius degree and reflects high-intensity local inflammation. The similar temperature gradient was noted between stable and unstable, disrupting plaques [26].

Distinct differences in the structure of the plaque prone to disruption were also shown. It is characterized by the presence of a big necrotic lipid core, great amount of invaded macrophages and T-cells determining initiation and maintenance of the chronic inflammation. It coincides with less amount of vascular smooth muscle cells (SMC) capable to produce collagen and other components of extracellular matrix that increase the stability of atherosclerotic plaque. Transferring animals to diet with low lipid content or use of lipid-lowering treatment normalize plaque temperature along with decrease of lipids and macrophages content, though increased collagen doesn't change plaque dimension and its propensity to disruption [26].

The distinctive feature of the plaque prone to disruption is its intensive neo-vascularization, and in patients with high risk of ACS the plaque density of the micro vessels is much higher. The amount of the newly developed micro vessels in the plaque is significantly increased along with pronounced macrophage infiltration, being an independent prognostic sign of the threatening plaque disruption [15]. At post-mortem investigations the severity of inflammatory infiltration and intima macrophage content were increased by 2–4 times, and the density of micro-vascular network was by 32 % more in patients with acute coronary events than in control subjects [8]. Anti-inflammatory interventions in mice with model of atherosclerosis prevented plaque progression and disruption [16].

The vascular endothelial growth factor-1 (VEGF-1) is one of the most important inflammatory mediators, the product of activated macrophages

Шумаков Валентин Олександрович, д. мед. н., проф., зав. відділу
03151, м. Київ, вул. Народного Ополчення, 5.
Тел. +380 (44) 275-66-00. E-mail: valex_s@ukr.net

and SMC secretion. It stimulates development of the micro vessel network in the plaque from the endotheliocytes of vasa vasorum. Newly formed vessel with thin wall is constantly under action of the proteolytic enzymes released in the plaque from disrupting macrophages. Thus, a permanent threat of melting of these vessel wall and development of intramural hemorrhage appears. This results in the increased plaque dimension and severity of the stenosis leading to clinical events even without disturbing plaque integrity.

Sometimes the spontaneous activation of the local plaque inflammation is enough for its disruption without additional external factors. The local concentration of inflammatory mediators in the disrupting plaque or in blood close to it is much higher than in systemic circulation indicating their local production [14]. In patients with unstable angina and MI the combined amount of macrophages, C-reactive protein (CRP), complex of membrane attack and oxidized LDL in plaques is much more than in patients with stable angina. In patients with acute MI the plaque macrophage amount was 50 % higher than in patients with unstable angina and 2.2 times higher than in patients with stable angina. In these conditions, CRP is produced by plaque macrophages seven times more than in the hepatocytes. Therefore, CRP plaque content is significantly higher than its serum level that is not a reliable index of the plaque inflammation.

Such type of the disease course may be characterized by absence of the systemic inflammation. Approximately in 50 % cases acute MI is not combined with significant increase of CRP and other inflammatory mediators. An abrupt development of MI without previous unstable angina with relatively favorable course and outcome is most typical for these cases.

Systemic inflammation may be involved in the development of ACS as well. The risk of MI distinctly increases after performing any surgical interventions and during periods of flu, while anti-influenza vaccination diminishes prevalence of MI. Strong relation between inflammatory infiltrate in the unstable atherosclerotic plaque and circulating neutrophils, lymphocytes and monocytes activation was observed. Acute MI develops on background of highly active systemic inflammation approximately in 50 % cases. Increase of serum CRP concentration observed during first hours of the ACS did not correlate with myocardial damage markers (troponin I, phosphocreatine) and thus may probably reflect the course of MI. Plaque instability, determined by infiltration by macrophages and their activation, is directly related to plasma oxidized LDL [18]. However, the specificity of systemic inflammation, factors of its development and mechanisms of the local plaque inflammation becoming trigger of its destabilization yet remain hypothetical.

Oxidized LDL play a dominant role in activation of systemic inflammation, destabilization of atherosclerotic plaque and development of ACS. They promote macrophage activation, expression of induced cyclioxigenase-2 (COG-2), increased production of pro-inflammatory prostaglandins (PGE2 and PHI2), both as matrix proteinases (MMP-2 and MMP-9), which are directly related to the atherosclerotic plaque fibrose cap destruction. The incubation of culture endotheliocytes with oxidized LDL was followed by the dramatic increase of MMPs expression mediated by lectin-like receptors LOX-1, capable to bind oxidized LDL on endotheliocytes and SMC [13].

In a prospective study, the blood level of oxidized LDL in patients with IHD was strongly related to the risk of ACS development and endpoints during 52 months of follow-up. Wherein patients were divided into 2 subgroups according to the 75th percentile of blood oxidized LDL content, the frequencies of ACS development differed by 3.6 times between groups [20].

The blood level of oxidized LDL is an independent predictor of MI development in patients with or without IHD clinical signs. In the study including 3033 patients the risk of MI development in subjects with high-oxidized LDL was increased in average by two times, and in the highest quintile of their content – by 5,7 times. This index was strongly related to the blood level of atherogenic small dense LDL particles [10].

Recently it was supposed that «the complete oxidized LDL» with modified apo-B are not formed directly in circulation. The sharp increase of the oxidized LDL blood content during ACS development may reflect atherosclerotic plaque instability, its disruption and release of the oxidized LDL from plaque into the blood [25].

Nevertheless, the blood permanently contains minimally modified LDL (MMLDL), in which oxidative modification is limited only to unsaturated fatty acids included in phospholipids and esterified cholesterol. The normal concentration of these MMLDL is equal to 0,02 % from the total amount

of LDL, but under intense systemic inflammation and oxidative stress it can be increased to 5 % [18]. It occurs because under oxidative stress LDL function as scavengers of free radicals, undergo free-radical oxidation, obtain pro-atherogenic, cytotoxic and antigenic properties. The damaging properties of MMLDL are prevented by their quick elimination from blood through capturing by macrophages and endotheliocytes by scavenger-receptors (accordingly SR-A and LOX-1), and also through activation of the humoral immune response with accelerated production of specific antibodies and forming immune complexes. These changes result in accumulation of the modified LDL and their antibodies in the vessel wall, inflammatory reaction with invasion of monocytes characteristic for unstable atherosclerotic plaque. The level of oxidized LDL in the plaque was shown to exceed their level in intima of undamaged artery by 6 times (1.86 compared to 0.30 ng/μkg apo-B) [18].

It was shown that unstable atherosclerotic damages are characterized by high content of oxidized LDL and macrophages, specific antibodies to oxidized LDL along with the diminished content of SMC and collagen [24]. The oxidized LDL accumulation in the plaque is combined with increased plaque instability because oxidized LDL promote synthesis and liberation of MMPs from macrophages and plaque disruption. The development of significant aorta atherosclerotic damage with accumulation of macrophages, oxidized LDL and specific antibodies to them was shown in mice without B, E-receptors that were on high-lipid diet. On the contrary, significant accumulation of SMC and collagen in the aortic wall was revealed in control mice kept on standard diet and receiving antioxidative therapy [7].

The developing autoimmune reaction initially has a protective character and directed at clearance of the extrinsic aggressive antigen (MMLDL). Therefore, plasma content of antibodies to modified LDL is inversely related to the content of the particles themselves. Application of human IgG antibodies to mice with genetic absence of apo-E increased modified LDL binding and elimination, decreased their accumulation in plaques, macrophages infiltration and severity of atherosclerosis. Autoimmune response was manifested by both activation of systemic inflammation and atherosclerotic plaque destruction through complement system activation and forming the complex of membrane attack on the surface of endotheliocytes [19].

The amount of modified LDL in patients with ACS was significantly increased; raising the titer of autoantibodies indicated at extremely high risk of MI development [11]. It allowed suggesting that atherogenic modification of LDL is one of the most important factors of the IHD destabilization. According to some investigators, increased modified LDL is a manifestation of atherosclerosis and a prognostic sign of future clinical manifestations or because of secondary activation of systemic inflammation and oxidative stress in MI. The uncertainty regarding causative relations between LDL modification, activation of systemic inflammation and atherosclerotic plaque destabilization, along with distinct clinical and theoretical significance of this problem served a basis for performing our study.

Material and methods

The research is based on analysis of the results received in 15 patients with chronic IHD (control group) and 15 patients with ACS, hospitalized and investigated within 6 hours after appearance of its first signs. The protocol included assessment of the systemic inflammation activity by measuring CRP and main indexes of blood lipid and lipoproteins: blood content of total cholesterol (TCH), triglycerides (TG), apoproteins (apo-B and apo-A-1), high, low and very low-density lipoproteins – HDL CH, LDL CH and VLDL CH. The plasma levels of modified LDL and VLDL were determined by means of plasma biotesting with mouse macrophages (MM), activity of the immune reactions – by measuring concentration of the circulating small, middle and large immune complexes (CIC), immunogenity of modified lipoproteins – by the content of CH and TG in CIC. In detail, the methods were described in the earlier paper [1]. The obtained results were processed statistically using Excel 2000 program and the Student criterion.

Results and discussion

The obtained data indicates the significantly much more intensive systemic inflammation in patients with ACS compared to the control group. The CRP blood content in patients with chronic IHD was in average 4.15±0.29 mg/L and exceeded the normal value (1.75±0.12 mg/L), determined in

normal donors, by 2.4 times (P<0.001). In patients with ACS CRP blood content reached in average 15.56±1.22 mg/L and exceeded normal almost by 9 times (P<0.001), and CRP blood content in patients with chronic IHD – by 3.8 times (P<0.001) *(fig. 1)*.

Elevated activity of systemic inflammation in patients with ACS was combined with moderate but significant changes in the plasma lipids and lipoproteins. Total CH content in patients with ACS was by 25 % higher than in the control group (25.0±0.42 vs 4.21±0.35 mmol/mL, P<0.05), TG content – by 28 % higher (1.56±0.13 vs 1.22±0.09 mmol/mL, P<0.05). The blood concentration of CH LDL and VLDL in patients with IHD was also higher than in the control group approximately in the same range (25–28 %, P<0.05).

The direct determination of apoproteins (apoB-100 and apoA-1) in patients with ACS indicated much more pronounced atherogenic changes of blood lipoproteins. They were manifested by higher plasma concentration of apoB-100 (by 36 %, 1.61±0.12 vs 1.12±0.08 g/L in control patients, P<0,02). As a result, the ratio of CH LDL to apoB-100 was 3.75±0.20 conventional units in control patients and by 15 % less (3.26±0.16 conventional units, P<0.05) in patients with ACS. These data indicate proportional decrease of CH content in LDL particles and the appearance of highly atherogenic small dense LDL particles in patients with ACS. Their significance in the development of acute IHD forms was further shown by prospective 15-year follow-up of 2072 patients without clinical manifestations of IHD. Strong and independent relation between the risk of coronary endpoints (coronary death, non-fatal MI, unstable angina) and blood content of small dense LDL (< 255 A) was observed. On the contrary, increase of the > 260 A particle content during 13 years of follow-up was not combined with elevated risk of coronary endpoints [22].

The development of ACS was significantly related to the less content of apoA-1 both as an absolute value (by 35 %, 1.30±0.09 and 0.96±0.08 g/L, P<0.01), and in relation to the HDL CH content (by 33 %, 1.50±0.11 and 1.01±0.09 conventional units, P<0.01). It indicates both the decrease of HDL and lowering their anti-oxidative, anti-inflammatory and anti-atherogenic potential, determined by presence of apoA-1. Because of multidirectional changes of main apoproteins,

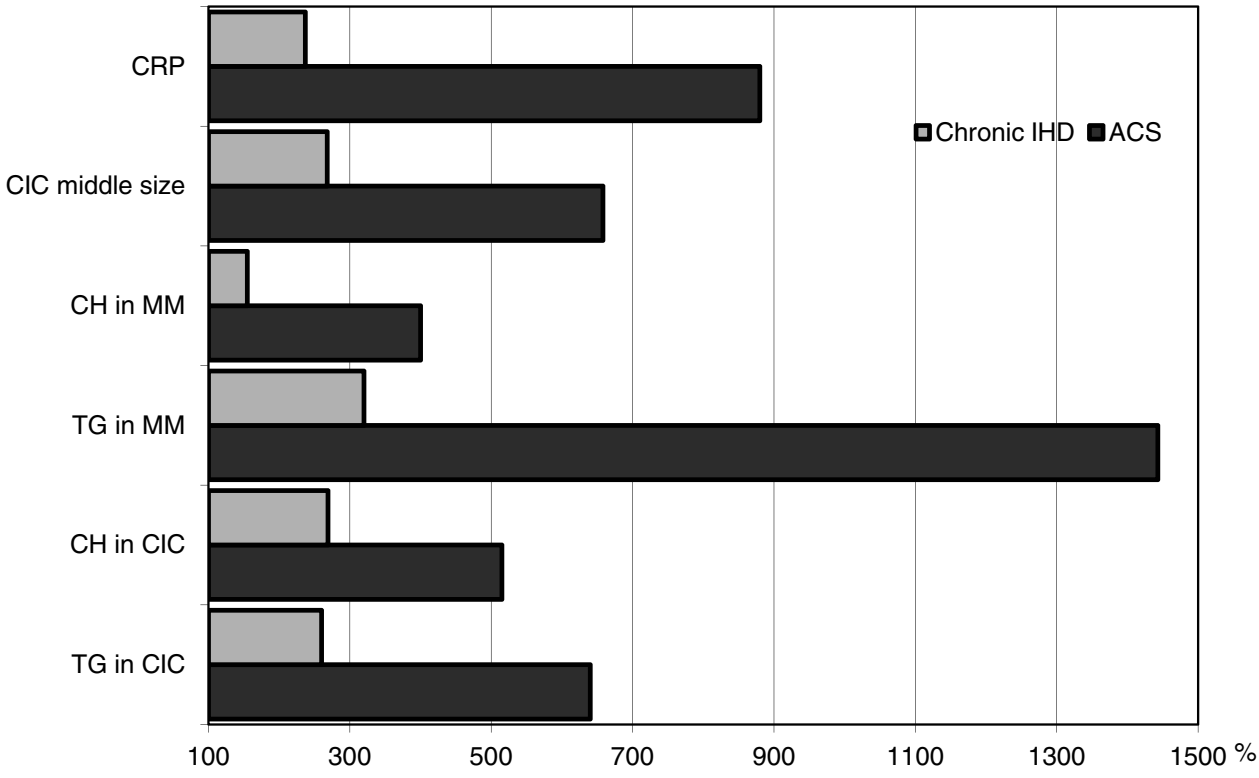

Fig. 1. Changes of the indexes of systemic inflammation, its autoimmune component and plasma atherogenity in patients with acute and chronic forms of IHD (expressed in percent to normal values). All changes are statistically significant (P<0,05).

atherogenity index, determined by apoB-100: apoA-1 ratio was almost two times higher in patients with ACS compared to the control group (1.71 vs 0,88 conventional units, P<0.001) *(fig. 2)*.

Changes of lipoprotein in ACS were also manifested by their modification with appearance of their oxidized particles. As a result of CH accumulation in MM after incubation with plasma of the patients with ACS, the content of modified LDL was 400 μkg/mg of protein in patients with ACS which was by 2.6 times higher than in the control group (P<0.001). Moreover, the development of ACS was combined with blood accumulation of modified lipoproteins enriched with TG, and their content in MM was equal to 563.5 μkg/mg of protein and exceeded the amount of TD in MM after incubation with plasma of control patients by 45 times (P<0.001).

The systemic inflammation in patients with ACS was reflected by the pronounced acquired immune response. This was manifested by the increased amount of small (by 118 %, P<0.01) and middle (by 145 %, P<0.01) CIC compared to patients with chronic IHD. It may indicate at accumulation of the CIC fractions capable to activate macrophages and the system of complement with creation of the «complex of membrane attack» determining their damaging action. The amount of large CIC promoting elimination of antigen and not activating macrophages and the system of complement in patients with ACS was 25 % less than in chronic IHD.

Modified lipoproteins were apparently one of main factors of autoimmune component of inflammation in patients with ACS. This was indicated by pronounced increase of CH (by 92 %, P<0.01) and TG (by 132 %, P<0.01) content in CIC compared to the patients with chronic IHD. These data confirm increased blood content of modified immunogenic LDL and even more – VLDL included in the CIC in patients with ACS *(fig.1)*.

These results indicate strong direct relation between activity of the systemic inflammation, accumulation of modified lipoproteins, the severity of autoimmune reaction and ACS risk.

The systemic inflammation may significantly influence risk of ACS development in patients with manifested atherosclerosis. It was suggested that plaque destabilization is a result of complex interaction of activation of the plaque cells and inflammatory mediators (cytokines, lymphokines and chemokines) acting upon plaque [12]. In particular, CRP not only predicts but also partici-

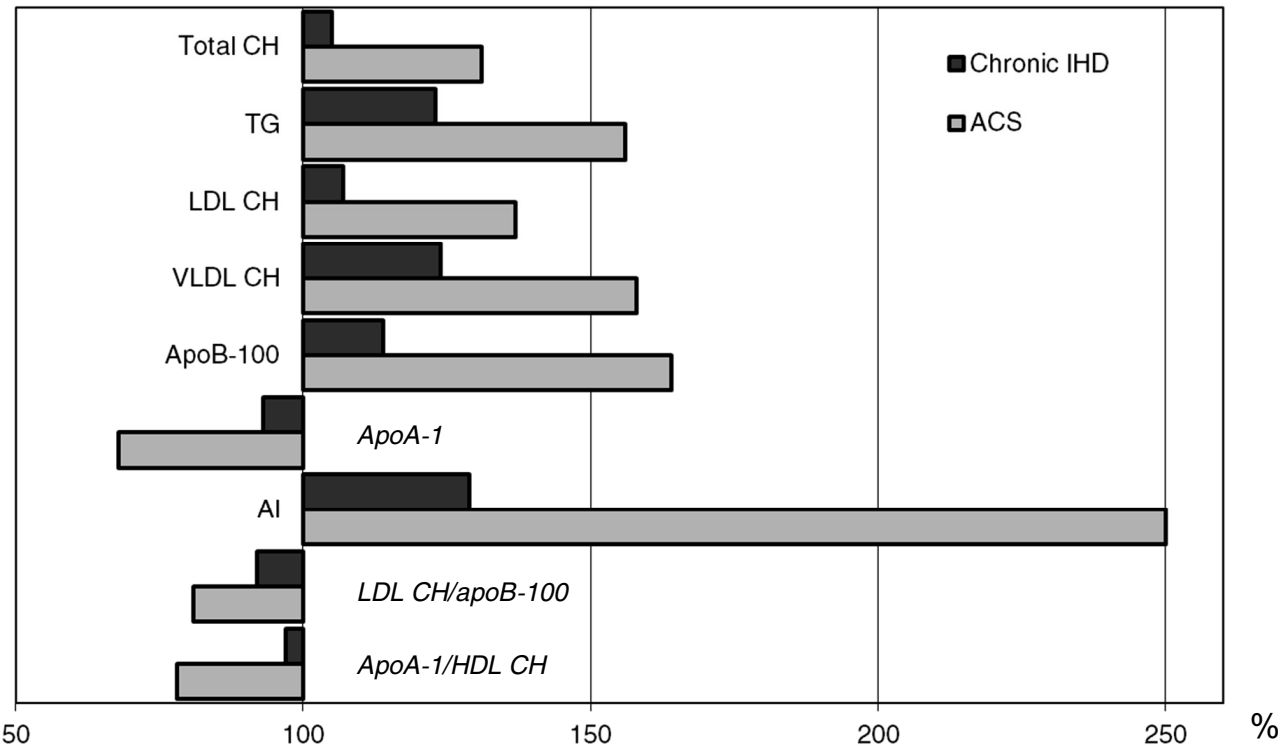

Fig. 2. The indexes of plasma lipid and lipoprotein content in patients with chronic IHD and ACS (expressed in percentage to normal values). All changes are statistically significant (P<0,05).

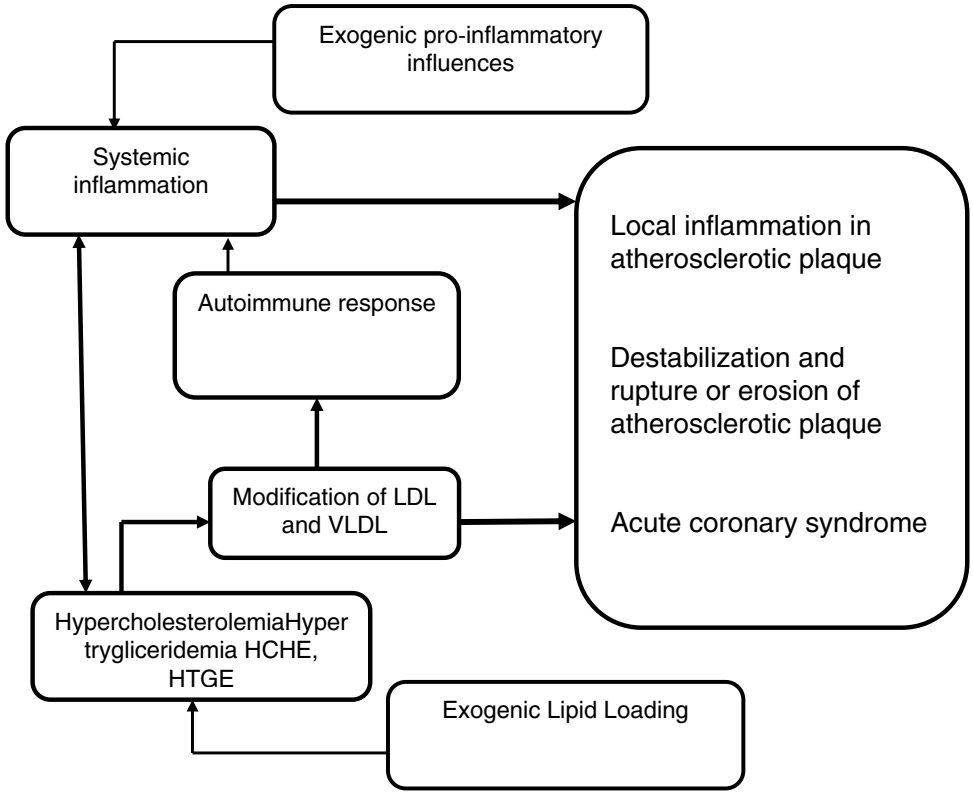

Fig. 3. Scheme of the principal mechanisms participating in the destabilization of atherosclerotic plaque and development of ACS.

pates in acute coronary events. It is produced not only in liver but and also in macrophages; it acts also as an opsonin for modified lipoproteins, promote their fixation in the vascular wall, activates the system of complement, induces SMC apoptosis promoting plaque destabilization [3].

The interferon-γ (IFN-γ) produced in T-cells specific to oxidized LDL plays an important role in plaque destruction and destabilization [4]. This effect is promoted by increase of interleukin-18 (IL-18) content in autoimmune inflammation. IL-18 induces secretion of IFN-γ by plaque macrophages leading to SMC apoptosis and weakening connective tissue matrix [2]. Blood level of IL-7 is especially increased in patients with unstable angina; it is produced by activated platelets where it is stored in a-granules [6].

Contemporary data show that modified lipoproteins are the main factor of the development or activation of inflammatory reaction in the vascular wall. Due to the selective capture, their content in plaques of patients with IHD was approximately 70 times higher than in blood (11.9 vs 0.18 ng/μkg apoB-100) and much more (19.6 ng/μkg apoB-100) – in unstable plaques enriched with macrophages. It is accompanied by the increased plasma level of modified lipoproteins than in patients with stable IHD (0.20 vs 0.13 ng/μkg apoB-100). These data mean that high level of modified lipoproteins both in the plaques and in circulation increases plaque propensity to disruption and ACS development [18].

One of the main mechanisms of the modified lipoproteins damaging action is their ability to increase expression of the nuclear transcription factor κB (NF-κB) in endothelial cells with intensive intracellular production of superoxide radicals, cytokines, chemokines and adhesive molecules [5]. The ability of oxidized LDL to induce inflammation was shown through application of oxidized phosphoryl choline to the internal carotid artery wall which was followed by increase of the monocyte chemotaxic protein-1 (VCH-1), tissue factor (TF) and IL-6 genes expression, increased production of P-selectin, rolling and then firm adhesion of the monocytes to endothelium [9]. The study of 46 control persons and 135 patients with different forms of IHD showed that the serum level of oxidized

LDL in patients with acute MI was much higher than in patients with unstable, stable angina and in control persons (1.95; 1.19; 0.89 and 0.58 ng/μkg apoB-100, accordingly). Wherein the serum level of total CH, CH LDL and CH HDL did not differ between patients of investigated groups. Much more pronounced accumulation of macrophages comprising oxidized LDL was observed in atheroma of patients with unstable angina compared to the stable patients [7].

The study of patients with dyslipidemia and IHD indicated that titer of antibodies to oxidized LDL is strongly related to the speed of atherosclerotic plaque progression and is an independent index of MI development during 5 years [27]. The most important factor is a high level of IgG antibodies mediating tissue damage through complement activation. The titer of IgM antibodies that are not complement activators, does not predict future MI.

The role of autoimmune response to oxidized LDL in the development of plaque instability was confirmed in the study carried out in mice with deficit of apo-E. Induced hyper expression of IL-18 increased by 2,5 times the frequency of instability and even plaque hemorrhage without influence on its dimension. The collagen plaque content was decreased by 44 % and the size of the cap – by 41 % in relation to the necrotic core. This effect was determined by the IL-18 ability to activate IFN-g and matrix metalloproteinase production both in macrophages and SMC [21]. IL-18 plasma level clearly reflected the risk of ACS development [23].

These data show substantial role of systemic inflammation and, especially, its autoimmune component, stipulated by blood lipoprotein modification, in the ACS development in patients with IHD. This link is mediated by both direct action of systemic inflammation factors upon atherosclerotic plaque and by their ability to activate inflammation leading to the plaque destruction. It is not yet clear whether the systemic inflammation is leading to the lipoprotein modification and autoimmune process or lipoprotein modification is followed by autoimmune reaction (fig. 3). It remains also unclear whether exogenic factors of pro-inflammatory character or alimentary lipid overloading cause activation of systemic inflammation, blood lipoprotein modification and, finally, a plaque disruption. These issues are very important for understanding ACS pathogenesis, ways of its prevention and treatment.

Conclusion

The obtained results and the contemporary data analysis indicate that the acquired immune response to the oxidized LDL is one of the main factors of the atherosclerotic plaque destabilization and the development of acute coronary syndrome.

References

1. Талаева Т.В., Корниенко О.В., Братусь В.В. и др. Атерогенная модификация липопротеинов крови и гиперхолестеринемия как следствия острого воспалительного процесса // Журн. АМН Украины.– 1997.– Т. 3, № 3.– С. 463–471.
2. Blankenberg S., Luc G., Ducimetiere P. et al. Interleukin-18 and the risk of coronary heart disease in European men // Circulation.– 2003.– Vol. 108.– P. 2453–2439.
3. Blaschke F., Bruemmer D., Yin F. et al. C-reactive protein induces apoptosis in human coronary vascular smooth muscle cells // Circulation.– 2004.– Vol. 110.– P. 579–587.
4. Buono C., Pang H., Ucida Y. et al. B7-1/B7-2 costimulation regulates plaque antigen-specific T-cell responses and atherogenesis in low-density lipoprotein receptor-deficient mice // Circulation.– 2004.– Vol. 109.– P. 2009–2015.
5. Cominachini L., Garbin U., Pasini A.F. et al. Oxidized low-density lipoprotein increases the production of intracellular reactive oxygen species in endothelial cells: inhibitory effect of lacidipine // J. Hypertens.– 1998.– Vol. 16.– P. 1913–1919.
6. Damas J.K., Waehre T., Yndeatad A. et al. Interleukin-7 – mediated inflammation in unstable angina. Possible role of chemokines and platelets // Circulation.– 2003.– Vol. 107.– P. 2670–2676.
7. Ehara S., Ueda M., Naruko T. et al. Elevated levels of oxidized low density lipoprotein show a positive relationship with the severity of acute coronary syndromes // Circulation.– 2001.– Vol. 103.– P. 1955–1960.
8. Fleiner M., Kummer M., Mirlacher M. et al. Arterial neovascularization and inflammation in vulnerable patients. Early and late signs of symptomatic atherosclerosis // Circulation.– 2004.– Vol. 110, N 18.– P. 2843–2850.
9. Furnkranz A., Schober A., Bochkov V.N. et al. Oxidized phospholipids trigger atherogenic inflammation in murine arteries // ATVB.– 2005.– Vol. 25.– P. 633–641.
10. Holvoet P., Collen D. β-VLDL hypercholesterolemia relative to LDL hypercholesterolemia is associated with higher levels of oxidized lipoproteins and a more rapid progression of coronary atherosclerosis in rabbits // ATVB.– 1997.– Vol. 17.– P. 2376–2382.
11. Inoue T., Saniabadi A.R., Matsunaga R. et al. Impaired endothelium-dependent acetylcholine-induced coronary artery relaxation in patients with high serum remnant lipoprotein particles // Atherosclerosis.– 1998.– Vol. 139, N 2.– P. 363–367.
12. Lerman A., Zeiher A.M. Endothelial function. Cardiac events // Circulation.– 2005.– Vol. 111.– P. 363–368.
13. Li L., Roumeliotis N., Sawamura T., Renier G. C-reactive protein enhances LOX-1 expression in human aortic endothelial cells. Relevance of LOX-1 to C-reactive protein-induced endothelial dysfunction // Circ. Res.– 2004.– Vol. 95.– P. 877–884.
14. Maier W., Altwegg L.A., Corti R. et al. Inflammatory markers at the site of ruptured plaque in acute myocardial infarction. Locally increased of interleukin-6 and serum amyloid A but decreased C-reactive protein // Circulation.– 2005.– Vol. 111, N 11.– P. 1355–1361.
15. Moreno P.R., Purushothaman R., Fuster V. et al. Plaque neovascularization is increased in ruptured atherosclerotic lesions of human aorta. Implication for plaque vulnerability // Circulation.– 2004.– Vol. 110, N 14.– P. 2032–2038.
16. Moulton K.S., Vakili K., Zurakowski D. et al. Inhibition of plaque neovascularization reduces macrophage accumulation and progression of advanced atherosclerosis // Proc. Natl. Acad. Sci.USA.– 2003.– Vol. 100.– P. 4736–4731.
17. Nicholls S.J., Dusting G.J., Cutri B. et al. Reconstituted high-density lipoproteins inhibits the acute prooxidant and proinflam-

matory vascular changes induced by a periarterial collar in normocholesterolemic rabiits // Circulation.– 2005.– Vol. 111, N 12.– P. 1543–1550.
18. Nishi K., Itabe H., Uno M. et al. Oxidized LDL in carotid plaques and plasma associates with plaque instability // ATVB.– 2002.– Vol. 22.– P. 1649–1654.
19. Schiopu A., Bengtsson J., Soderberg I. et al. Recombinant human antibodies against aldehyde-modified apolipoprotein B-100 peptide sequences inhibit atherosclerosis // Circulation.– 2004.– Vol. 110, N 14.– P. 2047–2052.
20. Shimada K., Mokuno I.I., Matsunaga I. et al. Predictive value of circulating oxidized LDL for cardiac events in type 2 diabetic patients with coronary artery disease // Diabetes care.– 2004.– Vol. 27.– P. 843–844.
21. SoRelle R. Interleukin-18 predicts coronary events // Circulation.– 2003.– Vol. 108.– P. e9051–e9065.
22. St-Pierre A.C., Cantin B., Dagenais G.R. et al. Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men // ATVB.– 2005.– Vol. 25.– P. 553–559.
23. Thüsen von der., Verkleij C.J.N., Kuiper J. et al. Overexpression of IL-18 decreases intimal collagen content and promotes a vulnerable plaque phenotype in apolipoprotein-E–deficient mice // ATV Biol.– 2004.– Vol. 24.– P. 2313–2320.
24. Torzewski M., Shaw P.X., Han K.-R. et al. Reduced in vivo aortic uptake of radiolabeled oxidation-specific antibodies reflects changes in plaque composition consistent with plaque stabilization // ATVB.– 2004.– Vol. 24.– P. 2307–2713.
25. Tsimicas S., Bergmark C., Beyer R.W. et al. Temporal increases in plasma markers of oxidized low-density lipoprotein strongly reflect the presence of acute coronary syndromes // J. Am. Coll. Cardiol.– 2003.– Vol. 41.– P. 360–370.
26. Verheye S., De Meyer R.Y., Langenhove G.V. et al. In vivo temperature heterogeneity of atherosclerotic plaques is determined by plaque composition // Circulation.– 2002.– Vol. 105.– P. 1596–1601.
27. Wu R., Nityanand S., Berglund L. et al. Antibodies against cardiolipin and oxidatively modified LDL in 50-year-old men predict myocardial infarction // ATVB.– 1997.– Vol. 17.– P. 3159–3163.

Received 8.04.2015

Роль набутої автоімунної відповіді в розвитку гострого коронарного синдрому

Т.В. Талаєва, В.О. Шумаков, В.В. Братусь
ДУ «Національний науковий центр "Інститут кардіології ім. акад. М.Д. Стражеска" НАМН України», Київ

Мета роботи – визначити механізми розвитку гострого коронарного синдрому (ГКС) та значущості для нього набутої імунної відповіді.
Матеріал і методи. У дослідження залучено 15 хворих з ГКС, госпіталізованих протягом 6 год після появи клінічних симптомів. Групу контролю становили 15 пацієнтів зі стабільною стенокардією.
Результати. Характерною особливістю картини ГКС було різко виражене системне запалення, середній вміст С-реактивного білка у плазмі перевищив аналогічний показник в осіб контрольної групи в 3,7 разу. Це запалення мало характер набутої імунної відповіді, і вміст у крові циркулюючих імунних комплексів зріс у 2,5 разу більш виражено, ніж в осіб зі стабільною стенокардією. Розвиток імунної відповіді поєднувався зі значним зростанням концентрації в крові модифікованих ліпопротеїнів – ліпопротеїнів низької щільності (ЛПНЩ) у 2,6 разу, ліпопротеїнів дуже низької щільності (ЛПДНЩ) – у 4,5 разу більш виражено, ніж у контрольній групі. Про автоімунний характер відповіді й значущість модифікованих ліпопротеїнів як автоантигенів свідчив значно більший вміст холестерину (у 2 рази) та тригліцеридів (у 2,5 разу) в циркулюючих імунних комплексах у плазмі крові хворих з ГКС. Ці реакції поєднувалися з достовірними, проте помірно вираженими змінами спектра ліпопротеїнів крові: вміст холестерину ЛПНЩ у осіб з ГКС був більшим на 25 %, холестерину ЛПДНЩ – на 27 %. Більш вираженими були зміни функціональних властивостей ліпопротеїнів, які відображували появу в крові значної кількості дрібних щільних частинок ЛПНЩ, та зниження протекторних властивостей ліпопротеїнів високої щільності в результаті зменшення вмісту в них апоА-1.
Висновки. Одним із найважливіших механізмів дестабілізації атеросклеротичної бляшки, яка лежить в основі розвитку ГКС, є атерогенна та імуногенна модифікація ліпопротеїнів з наступним розвитком автоімунної відповіді.

Ключові слова: атеросклероз, ішемічна хвороба серця, гострий коронарний синдром, імунне запалення, модифіковані ліпопротеїни.

Роль приобретенного аутоиммунного ответа в развитии острого коронарного синдрома

Т.В. Талаева, В.А. Шумаков, В.В. Братусь
ГУ «Национальный научный центр "Институт кардиологии им. акад. Н.Д. Стражеско" НАМН Украины», Киев

Цель работы – определить механизмы развития острого коронарного синдрома (ОКС) и значимость для него приобретенного иммунного ответа.
Материал и методы. В исследование включены 15 больных с ОКС, госпитализированных в пределах 6 ч после появления клинических симптомов; 15 пациентов со стабильной стенокардией напряжения составили контрольную группу.
Результаты. Характерной особенностью картины ОКС было резко выраженное системное воспаление, среднее содержание С-реактивного белка в плазме превышало аналогичный показатель у лиц контрольной группы в 3,7 раза. Это воспаление имело характер приобретенного иммунного ответа, и содержание в крови циркулирующих иммунных комплексов возрастало в 2,5 раза более выраженно, чем у лиц со стабильной стенокардией. Развитие иммунной реакции сочеталось со значительным возрастанием концентрации в крови модифицированных липопротеинов – липопротеинов низкой плотности (ЛПНП) в 2,6 раза, липопротеинов очень низкой плотности (ЛПОНП) – в 4,5 раза более выраженно, чем в контрольной группе. Про аутоиммунный характер реакции и значимость модифицированных липопротеинов как аутоантигенов свидетельствовало значительно большее содержание холестерина (в 2 раза) и триглицеридов (в 2,5 раза) в циркулирующих иммунных комплексах в плазме крови больных с ОКС. Отмеченные реакции сочетались с закономерными, но умеренно выраженными изменениями спектра липидов и липопротеинов крови: содержание холестерина ЛПНП у лиц с ОКС было большим на 25 %, холестерина ЛПОНП – на 27 %. Более выраженными были изменения функциональных свойств липопротеинов, которые отражали появление в крови значительного количества мелких плотных частиц ЛПНП, и снижение протекторных свойств липопротеинов высокой плотности в результате уменьшения содержания в них апоА-1.
Выводы. Одним из основных механизмов дестабилизации атеросклеротической бляшки, лежащей в основе ОКС, является атерогенная и иммуногенная модификация липопротеинов с последующим развитием аутоиммунного ответа.

Ключевые слова: атеросклероз, ишемическая болезнь сердца, острый коронарный синдром, иммунное воспаление, модифицированные липопротеины.