Peer reviewed article

The role of inflammation, humoral and cell mediated autoimmunity in the pathogenesis of atherosclerosis

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Summary

The pathogenesis of atherosclerosis has not been well defined and many questions remain unanswered. Many studies have discussed the importance of inflammation as the first step in promoting endothelial dysfunction and atherosclerosis. The association of inflammatory markers such as fibrinogen and C reactive protein (CRP) with atherosclerosis and cardiovascular/cerebrovascular clinical events reinforces the pivotal role that inflammation plays in the atherosclerotic process. The humoral and cellular autoimmune response against antigens expressed in the endothelium and the greater prevalence of atherosclerosis in immune-mediated rheumatic diseases such as Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) strongly suggest the involvement of autoimmunity in the atherosclerotic process. The role of inflammation and autoimmune responses in atherosclerosis are discussed in order to better understand their close link on its pathogenesis.

Key words: atherosclerosis; inflammation; cellular immunity; autoantibodies; autoimmunity

It is important to emphasise that in normal population, no classic risk factor for atherosclerosis can be determined in approximately 50% of the coronary disease events. In fact, mechanisms that lead to atherosclerosis are not well defined in this subgroup [1].

Previous studies about pathogenesis of the atherosclerotic plaque have identified a close link with high total cholesterol levels. In the last 15 years, a growing body of evidence supports the notion that inflammation plays a pivotal role in the onset and progression of atherosclerosis, and also in transforming a stable plaque into an unstable one [2–6]. Besides inflammation, recent studies have also suggested a cellular role in atherosclerosis and autoantibodies against antigens expressed in plaques of atherosclerosis have been described [3, 5]. Therefore, it is crucial to understand mechanisms involved in the pathogenesis of atherosclerosis that can possibly lead to other treatment options in the future.

Abbreviations

CRP	C reactive protein;
TNF	tumor necrosis factor;
IL	interleukin;
Hsp	heat shock protein;
beta2-gp1	beta2 glycoprotein 1;
aCL	anticardiolipin;
CVA	cerebrovascular accident;
RA	rheumatoid arthritis;
SLE	systemic lupus erythematosus;
AMI	acute myocardial infarction;
OPG	osteoprotegerin;
VCAM 1	vascular cell adhesion molecule;
oxLDL	oxidized low density lipoprotein;
Lp-PLA2	phospholipase A2 associated to lipoprotein;
PAPP-A	plasmatic A protein associated to pregnancy;
NT-proBNP	prohormone brain-type natriuretic peptide.

No financial support to declare.

Inflammation and the link with atherosclerosis

In the normal population, atherosclerosis has been related to systemic inflammatory markers such as fibrinogen and CRP. In fact, atherosclerosis results from an inflammatory process in the artery, which has lead some authors to suggest changing the nomenclature of atherosclerosis to atherosclerosis [2, 5–11]. These statements are due to a large number of studies demonstrating the presence of macrophages, monocytes and T lymphocytes in the atheroma plaque, as well as identification of CRP, components of complement, and serum A amyloid protein inside plaques [1, 2].

In fact, atherosclerosis begins with the subendothelial deposition of apolipoprotein B-containing (apoB) lipoproteins as a consequence of endothelial permeability and lipoprotein plasma levels, charge and size [12]. The exclusive role of apoB lipoproteins in atherosclerosis have been questioned since low LDL levels are detected in some patients with coronary artery disease, and other lipoproteins such as lipoprotein(a) and remnant lipoproteins also become trapped inside plaques besides apoB lipoproteins [13]. Indeed, in some well known atherosclerotic conditions such as diabetes mellitus and the metabolic syndrome there is an increase of remnant lipoprotein levels which may account for their enhanced risk for atherosclerosis. These data also reinforce the importance of lipoprotein size since extremely large lipoproteins do not cross the arterial wall [14].

Although endothelial permeability to lipoproteins is still not completely understood, an animal model study showed that a reduction in systemic blood pressure decreases permeability to LDL [15]. Moreover, subendothelial lipoprotein deposition is mediated by its physical interaction with subendothelial matrix molecules, mainly proteoglycans [12]. Beside this, lipoproteinase lipase, secretory sphingomyelinase and secretory phospholipase A2 also promote lipoprotein deposit [12].

Animal models of cholesterol-rich diet induced atherosclerosis have shown that monocytes are the first cells to adhere to endothelium through the increased expression of adhesion molecules by activated endothelial cells, mainly vascular cell adhesion molecule (VCAM1). Thereafter, these cells migrate through subendothelial layers by diapedesis due to a chemical gradient. Once located in the artery intima layer, they become activated and then express scavenger receptors on their surface, responsible to the phagocytosis of oxidised low-density lipoproteins (oxLDL). Activated macrophages get loaded with these modified lipoproteins as lipid droplets in their cytoplasm and then are called foam cells. Foam cells and T lymphocytes of the intima produce and induce the release of a variety of inflammatory mediators such as proinflammatory cytokines (IL-1, TNF-alpha), growth factors, adhesion molecules and matrix metalloproteinases that amplify the inflammatory process. These mediators also increase the recruitment of other inflammatory cells to the site, increase migration and proliferation of endothelial cells, stimulate proliferation of vessel smooth muscle cells, and promote the break of collagen on the surface of atherosclerotic plaques.

Although the size of plaques can reduce the arterial blood flow to vital organs leading to a complete obstruction of the arterial lumen due to their thickness, the main risk of acute myocardial infarction (AMI) or cerebrovascular accident (CVA) is a consequence of the plaque rupture [4]. Interestingly, the inflammatory process that occurs on artery walls and contributes to the formation of atherosclerotic plaques shows many similarities with the pathological aspects found in the synovial membrane inflammation in rheumatoid arthritis (RA) [8, 12].

Cellular immunity and atherosclerosis

Regarding cellular immunity, T lymphocytes detected in plaques play an important role in the pathogenesis of atherosclerotic lesions. In fact, mice with depletion of CD4 cells have a striking reduction in the formation of these lesions. Moreover, mice with cellular immunodeficiency develop prominent atherosclerosis after receiving CD4 cells from immunocompetent animals [17, 18].

A specific cellular immune response against heat shock proteins (Hsp), oxLDL, and beta2glycoprotein 1 (beta2-gp1) has been found in animal models with atherosclerosis [19]. Interestingly T cells do not react to native LDL components, only after the oxidative modification of LDL. Most oxLDL-reactive CD4 cells have a T helper 1 (Th1)-cell phenotype and these Th1 cells produce proinflammatory cytokines that stimulate atherosclerosis [20]. The great expression of Th1 cells and proinflammatory cytokines (such as interferon-gama, IL-1 IL-12, IL-15, IL-18, and TNF) found in mouse models of atherosclerosis and also in human plaques contrast with few cells producing the Th2-type cytokine IL-4, thus characterising the lost of the balance between Th1/Th2 cytokines. Since there is an accumulation of macrophages and T cells as showed in histopathology, it is reasonable to accept that atherosclerosis is indeed mediated by Th1-cells [21].

Prospective epidemiological studies have shown a close link between CRP, serum A amyloid protein, IL6, adhesion molecules levels and the future risk of cardiovascular events in the normal population [22–24]. Recently, some proatherogenic enzymes have been identified as new independent risk factors for atherosclerosis, which include phospholipase A2 associated to lipoprotein (Lp-PLA2), myeloperoxidase and plasmatic A protein associated to pregnancy (PAPP-A) [25, 26].

Secretory phospholipase A2 is an acute phase protein and their levels are associated to CRP, which is also an independent risk factor for coronary disease [25]. Myeloperoxidase enzyme levels are increased in patients with angiographically documented cardiovascular disease and high levels of this enzyme are expressed in unstable plaques prompt to rupture [26–28]. A recent study in patients with chest pain showed that myeloperoxidase levels were predictors of a greater risk of AMI, need for coronary revascularisation, and death in 30 days and 6 months after onset of cardiovascular event [29]. PAPP-A also have a proatherogenic role and is currently known to be a specific activator of the insulin-like growth factor, an atherosclerotic mediator. This enzyme is produced by vessels' smooth muscle cells and is expressed in greater quantities in the atherosclerotic plaque cells, particularly in extracellular matrix of plaques with erosions, but not in stable plaques [30]. PAPP-A levels are variable in patients with AMI and seem to increase as late as 30 hours after the onset of chest pain [31, 32].

Osteoprotegerin (OPG), also known as an osteoclast inhibitor factor, is a cytokine antagonist, member of the TNF receptor family [33]. Recently it has been demonstrated that OPG is produced not only in bone but also in several other tissues, including the cardiovascular system, lungs, kidneys, immune tissues, and blood vessel walls in rodents. Interestingly, OPG-deficient mice develop severe osteoporosis and vascular calcifications in the aorta and renal arteries [34]. In animal models of arterial calcifications induced by warfarin or vitamin D intoxication, subcutaneous administration of OPG prevented the appearance of vascular lesions [35]. OPG is expressed in the smooth muscle layer of coronary vessels and increases the survival of these endothelial cells by interfering in their apoptosis [36]. In humans submitted to coronary angiography, OPG levels were significantly higher in those with more advanced atherosclerotic disease [37]. In the vascular system, increased OPG levels may be related to endothelial lesion, intimal hyperplasia, smooth cell hypertrophy, or advanced plaque calcifications [38]. One study assessed OPG concentration in 490 women over 65 years-old, and high OPG levels were associated with global and cardiovascular mortality [39].

In addition, elevated plasma levels of amino terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP) predict cardiovascular events or death independently of other available prognostic tests and identify at-risk individuals even in the absence of systolic or diastolic dysfunction by echocardiography. NT-proBNP levels may help in the stratification of high-risk individuals such as those with coronary heart disease [40].

Humoral autoimmunity and atherosclerosis

Recent studies in animal models show the role of humoral immunity in the pathogenesis of atherosclerosis. Active immunisation of LDL cholesterol receptor deficient mice with cardiolipin or beta2-gp1 induced an increase in atherosclerosis [41, 42]. IgG and IgM antibodies against oxLDL were detected in animal and human plasma forming immunocomplexes with the oxLDL found in atherosclerotic lesions [43]. Likewise, clinical studies showed that anti-oxLDL antibodies are associated with the progression and extension of atherosclerosis and should be considered as a risk factor for coronary disease [44–47].

Immune and inflammatory processes that have the participation of Hsp are provoking great interest as autoimmune pathogenic factors in the development of atherosclerosis [48]. Hsp 60 and 65 are immunogenic proteins involved in atherogenesis [49–51]. In fact, Hsp 60 can induce production of proinflammatory cytokines (such as TNF alpha and matrix metalloproteinases) by macrophages and enhance expression of adhesion molecules by endothelial cells, suggesting a possible mechanism of plaque instability. Moreover, Hsp 60 is mainly detected in vessel sites with atherosclerotic lesions [52].

Clinical studies have shown a clear association of high levels of soluble Hsp 60 with other risk factors for atherosclerosis, especially LDL cholesterol levels [53]. In addition, high levels of antibodies against mycobacteria Hsp 65 have been associated with carotid coronary atherosclerosis, myocardial infarction, and restenosis post-coronary angioplasty [54–56]. The sequential homology between infecting microorganism Hsp and human Hsp suggest a possible pathogenic link between infection and atherosclerosis. Infections with microorganisms that contain homologue Hsp proteins can initiate an autoimmune response by molecular mimetics [57–59]. In this regard,

antibiotic therapy for *Chlamydia pneumoniae* infection has been tried but a reduction of cardiovascular mortality or cardiovascular clinical events was not demonstrated [60].

Antiphospholipid antibodies are present in several autoimmune rheumatic diseases, especially systemic lupus erythematosus (SLE). These antibodies can react against cardiolipin antigens or proteins linked to cardiolipin such as beta2-gpl, also known as apolipoprotein H. These antibodies are particularly associated with venous and/or arterial thrombosis that characterise the antiphospholipid syndrome (APS), which is currently considered the most common acquired coagulopathy [61]. Recently it was demonstrated that immunisation of mice with beta2-gp1 determined the formation not only of antibodies against beta2-gp1, but also against cardiolipin, which might explain the onset of APS manifestations [62].

Besides thrombosis, antiphospholipid antibodies have also been associated to atherosclerosis [63, 64]. Case control studies have shown the association of anticardiolipin antibodies (aCL) with CVA and AMI [65–71]. Moreover, aCL was identified as an independent predictive factor for the increase in IMT [72]. In an experimental model a clear link between aCL and atherosclerosis was also demonstrated since immunisation of LDL cholesterol receptor deficient mice with cardiolipin determined high aCL titles and accelerated atherosclerosis [41].

Beta2-gp1 is a circulating glycoprotein that is also a target antigen of antiphospholipid antibodies. Like aCL, antibodies against beta2-gp1 have been related to the atherosclerotic immune process [73]. Studies have shown a greater expression of beta2-gp1 alongside T CD4 lymphocytes in atherosclerotic lesions [74]. LDL cholesterol receptor deficient mice when immunised with beta2-gp1 develop antibodies against beta2-gp1 and are prone to more severe atherosclerosis. Of note, transfer of T lymphocytes from these mice immunised with beta2-gp1 to other mice also determines atherosclerosis, which did not occur when T cells were depleted [75]. Antibodies against beta2-gp1 increase the expression of adhesion molecules (ICAM-1 and VCAM-1) by endothelial cells, and increase production of IL6. Fluvastatin abolish this effect by blocking the expression of NF-kappa beta by endothelial cells [76].

Moreover, it was demonstrated that oxLDL links to beta2-gp1 forming stable oxLDL/beta2-gp1 complexes that are potentially pathogenic in the atherosclerosis process [77, 78]. In an oral tolerance study, the ingestion of human or bovine beta2-gp1 in LDL cholesterol receptor deficient mice previously immunised with beta2-gp1 has demonstrated a reduction in the reactivity of lymph node lymphocytes against beta2-gp1 and a reduction in the extension of atherosclerotic lesions [79].

Clinical studies have demonstrated the association of antibodies against beta2-gp1 with ischaemic CVA and coronary artery disease [80, 81]. Staub et al. [82] have demonstrated that ischaemic cerebral vascular accident was associated to high titles of IgA anti-beta2-gp1 and IgG anti-Hsp 60 and 65 antibodies. In addition, IgA isotype of antibodies against beta2-gp1 was also associated with AMI and peripheral vascular disease [83, 84].

It should be emphasised that the link between atherosclerosis with systemic inflammation and autoimmunity is further supported by the greater prevalence of atherosclerotic events in autoimmune rheumatic diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) in which these autoantibodies have been extensively demonstrated [5, 85].

Treatment options for atherosclerosis should also address these inflammatory conditions. In this regard, it is known that statins, besides their action on the lipid profile, also have pleiotropic effects improving endothelial function. They can reduce oxLDL formation, reduce macrophage protease production, inhibit smooth muscle cell proliferation, and monocyte chemotaxis [86]. Importantly, statins also have actions on the MHC class II transactivator and reduce immune activation in the plaque [87].

In this regard, immunological features of atherosclerosis outline new opportunities for treatment of this condition. Immune therapy against target molecules seems to be a future alternative and vaccines have been tried in experimental animal models. Parenteral immunisation against modified LDL seems to decrease atherosclerosis progression but this was not observed with vaccines against Hsp60/65 [46]. Active immunisation with antigenic epitopes of the human apolipoprotein B100, an important structural component of LDL, has reduced atherosclerotic lesions in hyperlipidemic mice. Therefore a vaccine based on apolipoprotein B100-related peptide should also be considered to have a potential role in reducing atherosclerosis [88].

Conclusions

Atherosclerosis has indeed a complex multifactorial pathogenesis with a well defined participation of lipoproteins and inflammatory cells. But the contribution of autoimmune events is increasingly evident since several studies have demonstrated autoantibodies against multiple antigens found inside atherosclerosis plaques. Further studies are necessary to determine the definitive role of these autoantibodies as protectors or inducers of atherosclerosis as well as its possible use as markers of future cardiovascular events.

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References

1 Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature. 1993;362:801–9.
2 Libby P. Inflammation in atherosclerosis. Nature. 2002;420: 868–74.
3 Wick G, Knoflach M, Xu Q. Autoimmune and inflammatory mechanisms in atherosclerosis. Ann Rev Immunol. 2004;22:361–403.
4 Badr K, Wainwright. Inflammation in the cardiovascular system: here, there and everywhere. Curr Opin Pharmacol. 2004;4:107–9.
5 Doria A, Sherer Y, Meroni PL, Shoenfeld Y. Inflammation and accelerated atherosclerosis: Basic mechanisms. Rheum Dis N Am. 2005;31:355–62.
6 Paoletti R, Gotto AM, Hajjar DP. Inflammation in atherosclerosis and implications for the therapy. Circulation. 2004;109(suppl.III): III-20-III-26.
7 Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA. 1998;279:1477–82.
8 Ross R. Atherosclerosis- an inflammatory disease. N Engl J Med. 1999;340:115–26.
9 Li JJ, Fang CH. Atherosclerotic is a more rational term for the pathological entity currently known as atherosclerosis. Med Hypotheses. 2004;63:100–2.
10 Fichtlscherer S, Heeschen C, Zeiher A. Inflammatory markers and coronary artery disease. Curr Opin Pharmacol. 2004;4:124–31.
11 Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. Circulation. 2004;109(suppl.II):II-2-II-10.
12 Tabas I, Williams KJ, Borén J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis. Update and therapeutic implications. Circulation. 2007;116:1832–44.
13 Twickler T, Dallinga-Thie GM, Chapman MJ, Cohn JS. Remnant lipoproteins and atherosclerosis. Curr Atheroscler Rep. 2005;7:140–7.
14 Proctor SD, Vine DF, Mamo JC. Arterial retention of apolipoprotein B(48)- and B(100)-containing lipoproteins in atherogenesis. Curr Opin Lipidol. 2002;13:461–70.
15 Bretherton KN, Day AJ, Skinner SL. Effect of hypertension on the entry of 125 I-labeled low density lipoprotein into the aortic intima in normal-fed rabbits. Atherosclerosis. 1976;24:99–106.
16 Gerly R, Schillaci G, Giordano A, et al. T lymphocytes contribute to early atherosclerotic damage in rheumatoid arthritis patients. Circulation. 2004;109:2744–8.
17 Emeson EE, Shen ML, Bell CG, et al. Inhibition of atherosclerosis in CD4 T-cell depleted and nude (nu/nu) C57BL/6 hyperlipidemic mice. Am J Pathol. 1996;149:675–85.
18 Zhou X, Nicoletti A, Elhage R, et al. Transfer of CD4 + cells agravates atherosclerosis in immunodeficient, apolipoprotein E knockout mice. Circulation. 2000;102:2919–22.
19 Sherer Y, Shoenfeld Y. Atherosclerosis: is atherosclerosis a cellular or humoral mediated auto-immune disease? Ann Rheum Dis. 2002;61:97–9.
20 Frostegård J, Ulfgren AK, Nyberg P, Hedin U, Swedenborg J, Andersson U, Hansson GK. Cytokine expression in advanced human atherosclerotic plaques: dominance of pro-inflammatory (Th1) and macrophage-stimulating cytokines. Atherosclerosis. 1999;145(1):33–43.
21 Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol. 2006;508–19.
22 Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. Circulation. 1998;98:731–3.
23 Ridker PM, Hennekens CH, Roitman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. Lancet. 1998;351:88–92.
24 Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin 6 and the risk of future myocardial infarction among apparently healthy men. Circulation. 2000; 101:1767–72.
25 Hurt-Camejo E, Paredes S, Masaa L, Camejo Sartipy P, Rosengren B, et al. Elevated levels of small, low-density lipoprotein with high affinity for arterial matrix components in patients with rheumatoid arthritis: possible contribution of phospholipase A2 to this atherogenic profile. Arthritis Rheum. 2001;44:2761–7.
26 Zhang R, Brennan ML, FU X, et al. Associated between myeloperoxidase levels and risk of coronary artery disease. JAMA. 2001;286:2136–42.
27 Sugiyama S, Okada Y, Sukhova GK, Virmani R, Keinecke JW, Libby P. Macrophage myeloperoxidase regulation by macrophage colony-stimulating factor in human atherosclerosis and implications in acute coronary syndromes. Am J Pathol. 2001;158:879–91.
28 Eiserich JP, Baldus S, Brennan ML, et al. Myeloperoxidase, a leukocyte-derived vascular NO oxidase. Science. 2002;296: 2391–4.
29 Brennan ML, Penn MS, Van Lente F, et al. Prognostic value of myeloperoxidase in patients with chest pain. N Engl J Med. 2003; 349:1595–604.
30 Bayes-Genis A, Conover CA, Overgaard MT, et al. Pregnancy-associated plasma protein A as a marker of acute coronary syndromes. N Engl J Med. 2001;1022–9.
31 Qin QP, Laitinen P, Majamaa-Voltti K, et al. Release patterns of pregnancy associated plasma protein A (PAPP-A) in patients with acute coronary syndromes. Scand Cardiovasc J. 2002:36:358–61.
32 Lund J, Qin QP, Ilva T, Petterson K, Voipio-Pulkki LM, Porela P, Pulkki K. Circulating pregnancy-associated plasma protein A predicts outcome in patients with coronary syndrome but no troponin I elevation. Circulation. 2003;108:1924–6.
33 Simonet WS, Lacey DL, Dunstan CR, et al. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell. 1997;89:309–19.
34 Bucay N, Sarosi I, Dunstan CR, et al. Osteoprotegerin-deficient mouse develop early onset osteoporosis and arterial calcification. Genes Dev. 1998;12:1260–8.
35 Price PA, June HH, Buckley JR, Williamson MK. Osteoprotegerin inhibits artery calcification induced by warfarin and by vitamin D. Arterioscler Thromb Vasc Biol. 2001;21:1610–6.
36 Malyankar UM, Scatena M, Suchland KL, et al. Osteoprotegerin is a alpha vbeta 3-induced, NF-Kappa B-dependent survival factor for endothelial cells. J Biol Chem. 2000;275:20959–62.
37 Schoppet M, Sattler AM, Schaefer JR, et al. Increased osteoprotegerin serum levels in men with coronary artery disease. J Clin Endocrinol Metab. 2003;88:1024–8.
38 Schoppet M, Preissner KT, Hofbauer LC. Rank ligand and osteoprotegerin. Paracrine regulators of bone metabolism and vascular function. Arterioscl Thromb Vasc Biol. 2002;22:549–53.
39 Browner WS, Lui LY, Cummings SR. Associations of serum osteoprotegerin levels with diabetes, stroke, bone density, fractures,

and mortality in elderly women. J Clin Endocrinol Metab. 2001;86:631–7.
40 Bibbins-Domingo K, Gupta R, Na B, Wu AH, Schiller NB, Whooley MA. N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP), cardiovascular events, and mortality in patients with stable coronary heart disease. JAMA. 2007;297(2):169–76.
41 George J, Afek A, Gilburd B, et al. Atherosclerosis in LDL-receptor knockout mice is accelerated by immunization anticardiolipin antibodies. Lupus. 1997;6:723–9.
42 Afek A, George J, Shoenfeld Y, et al. Enhancement of atherosclerosis in beta2-glycoprotein1-immunized apolipoprotein E-deficient mice. Pathobiology. 1999;67:19–25.
43 Yla-Herttuala S, Palinski W, Butler SW, Picard S, Steinberg D, Witztum JL. Rabbit and human atherosclerotic lesions contain IgG that recognizes epitopes of oxidized LDL. Arterioscler Throm. 1994;14:32–40.
44 Salonen JT, Yla Herttuala S Yamamoto R, Butler S, Korpela H, Salonen R, et al. Autoantibody against oxidized LDL and progression of carotid atherosclerosis. Lancet. 1992;339:883–7.
45 Ryan M, Owens D, Kilbride B, Collins P, Johson A, Tomkin GH. Antibodies to oxidized lipoproteins and their relationship to myocardial infarction. Q J Med. 1998;91:411–5.
46 Palinski W, Witztum JL. Immune responses to oxidative neoepitopes on LDL and phospholipids modulate the development of atherosclerosis. J Intern Med. 2000;247:371–80.
47 Bergmark C, Wu R, De Faire U. et al. Patients with early onset of peripheral vascular disease have high levels of autoantibodies against oxidized low-density lipoproteins. Arterioscler Thromb Vasc Biol. 1995;15:441–5.
48 Wick G, Perschinka H, Millonig G. Atherosclerosis as an autoimmune disease: an update. Trends Immunol. 2001;22:665–9.
49 Mehta TA, Greenman J, Ettelaie C, et al. Heat shock proteins in vascular disease – A review. Eur J Endovasc Surg. 2005;29: 395–402.
50 Lamb DJ, El-Sankary W, Ferns GAA. Molecular mimicry in atherosclerosis: a role for heat shock proteins in immunisation. Atherosclerosis. 2002;167:177–85.
51 Benagiano M, D'Elios MM, Amedei A, et al. Human 60-KDa Heat Schock Protein is a target autoantigen of T Cells derived from atherosclerotic plaques. J Immunol. 2005;174:6509–17.
52 Kol A, Sukhova GK, Lichtman AH, Libby P. Chlamydial heat shok protein 60 localizes in human atheroma and regulates macrophage tumor necrosis factor-alpha and metalloproteinase expression. Circulation. 1998;98(4):300–7.
53 Ghayour-Mobarhan M, Lamb DJ, Lovell DP, et al. Plasma antibody titres to heat shock proteins-60, -65 and -70: Their relationship to coronary risk factors in dyslipidaemic patients and healthy individuals. Scand J Clin Lab Invest. 2005;65:601–13.
54 Xu Q, Willeit J, Marosi M, et al. Association of serum antibodies to heat shock-protein 65 with carotid atherosclerosis. Lancet. 1993;341:256–9.
55 Hoppichler F, Lehleitner M, Tragweger C, et al. Changes of serum antibodies to heat-shock protein 65 in coronary heart disease and acute myocardial infarction. Atherosclerosis. 1996;126:333–8.
56 Mukherjee M, De Benedictis C, Jewitt D, Kakkar VV. Association of antibodies to heat-shock protein-65 with percutaneous transluminal coronary angioplasty and subsequent restenosis. Thromb Haemost. 1996;75:258–60.
57 Hoshida S, Nishino M, Tanouchi J, et al. Acute Chlamydia pneumoniae infection with acute coronary syndrome. Atherosclerosis. 2005;183:109–12.
58 Huittinen T, Leinonen M, Tenkanen L, et. Al. Autoimmunity to human heat shock protein 60, Chlamydia pneumoniae infection, and inflammation in predcting coronary risk. Arterioscler Thromb Vasc Biol. 2002;22:431–7.
59 Mayr M, Meltzer B, Kiechl S, et al. Endotelial cytotoxicity mediated by serum antibodies to heat shock proteins of Escherichia coli and Chlamydia pneumoniae: immune reactions to heat shock proteins as a possible link between infection and atherosclerosis. Circulation. 1999;99:1560–6.
60 Andraws R, Berger JS, Brown D. Effects of antibiotic therapy on outcomes of patients with coronary artery disease. JAMA. 2005;293:2641–7.
61 Hughes GR, Harris NN, Gharavi AE. The anticardiolipin syndrome. J Rheumatol. 13:486–9.
62 Gharavi AE, Sammaritano L.R, Wen J, Elkon, E.B. Induction of antiphospholipid antibodies by immunization with beta2-GP 1 (apolipoprotein H). J Clin Invest. 1992;90:1105–9.
63 Shoenfeld Y, Harats D, George J. Atherosclerosis and the antiphospholipid syndrome: a link unravelled? Lupus. 1998;7(suppl): 140–3.
64 Matsuura E, Kobayashi K, Tabuchi M, Lopes LR. Accelerated atheroma in the antiphospholipid syndrome. Rheum Dis Clin North Am. 2006;32:537–51.
65 Angelini L, Ravelli A, Carporali R, Rumi V, et al. High prevalence of antiphospholipid antibodies in children with idiopatic cerebral ischemia. Pediatrics. 1994;94:500–3.
66 Chakravarty KK, Al-Hillawi AH, Byron MA, Durkin CJ. Anticardiolipin antibody associated ischemic strokes in eldery patiens without system lupus erythematosus. Age Ageing. 1990;19:114–8.
67 Kushner MJ. Prospective study of anticardiolipin antibodies in stroke. Stroke. 1990;21:295–8.
68 Hess DC, Krauss J, Adams R, Nicholas FT, Zhary DL, Rountree HA. Anticardiolipin antibodies: a study of frequency in TIA and stroke. Neurology. 1991;41:525–8.
69 Nagaraja D, Cristopher R, Manjari T. Anticardiolipin antibodies in ischemic stroke in the young: Indian experience. J Neurol Sci. 1997;150:137–42.
70 Tuhrim S, Rand JH, WU X, et al. Elevated anticardiolipin antibody titer is a stroke risk factor in a multiethnic population independent of isotype or degree of positivity. Stroke. 1999;30:1561–5.
71 Brey RL, Abott RD, Curb D, et al. Beta2-Glycoprotein 1-dependent anticardiolipin antibodies and risk of ischemic stroke and myocardial infarction. The Honolulu Heart Program. Stroke. 2001;32:1701–6.
72 Ames PR, Margarita A, Delgado AJ, Tommasino C, Iannacone L, Brancaccio V. Anticardiolipin amtibody titre and plasma homocysteine level independently predict intima media thickness of carotid arteries in subjects with idiopatic antiphospholipid antibodies. Lupus. 2002;11:208–14.
73 Harats D, George J. Beta2-glycoprotein 1 and atherosclerosis. Curr Opin Lipidol. 2001;12:543–6.
74 George J, Harats D, Gilburd B, et al. Immunolocalization of Beta2-glycoprotein I (apolipoprotein H) to human atherosclerotic plaques: potential implications for lesion progression. Circulation. 1999;99:2227–30.
75 George J, Harats D, Gilburd B, et al. Adoptive transfer of Beta-2-glycoprotein-I reactive lymphocyte enhances early atherosclerosis in LDL receptor-deficient mice. Circulation. 2000;102:1822–7.
76 Meroni PL, Raschi E, Camera M, Testoni C, Khamashta MS, Temoli E. Fluvastatin inhibits the activation of endotelial cells induced by antiphospholipid antibodies in vitro. Arthritis Rheum. 2000;43(suppl.):115.
77 Lopez LR, Simpson DF, Hurley BL, Matsuura E. OxLDL/B2GP1 Complexes and autoantibodies in patients with systemic lupus erythematosus, systemic sclerosis, and antiphospholipid syndrome. Pathogenic implications for vascular involvement. Ann N Y Acad Sci. 2005;1051:313–22.
78 Horkko S, Miller E, Dudl E, et al. Antiphospholipid antibodies are directed against epitopes of oxidized phospholipids. Recognition of cardiolipin by monoclonal antibodies to epitopes of oxidized low density lipoprotein. J Clin Invest. 1996;98:815–25.
79 George J, Yacov N, Breitbart E, et al. Suppression of early atherosclerosis in LDL-receptor deficient mice by oral tolerance with-beta2-glycoprotein I. Cardiovasc Res. 2004;62:603–9.
80 Chen WH, Liu JS. An unusual increase of blood anti-beta2-glycoprotein I antibody but not antiphospholipid antibody in cerebral ischemia: a case report. Angiology. 2001;52:149–54.
81 Farsi A, Domeneghetti MP, Fedi S, Capanni M, Giustu B, Marcucci R, et al. High prevalence of anti-beta2-glycoprotein I antibodies in patients with ischemic heart disease. Autoimmunity. 1999;30:93–8.
82 Staub HL, Norman GL, Crowter T, da Cunha VR, Polanczyk A, Bohn JM, Fernandes JG, Chahade WH von Muhlen CA. Antibodies to the atherosclerosis plaque components beta2-glycoprotein I and heat-shock proteins as risk factors for acute cerebral ischemia. Arq Neuropsiquiatr. 2003;61:757–63.
83 Ranzolin A, Bohn JM, Norman GL, Manenti E, Bodanese LC, von Mullen CA, et al. Anti-beta2-glycoprotein I antibodies as risk factors for acute myocardial infarction. Arq Bras Cardiol. 2004;83:141–4.
84 FranCk M, Staub HL, Petraco JB, Norman GL, Lassen AJ, Schiavo N, et al. Autoantibodies to the atheroma component beta2-glycoprotein I and risk of peripheral artery disease. Angiology. 2007;58:295–302.
85 Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis . A population-based study. Arthritis Rheum. 2005;52:722–32.
86 Lahera V, Goicoechea M, de Vinuesa SG, Miana M, de las Heras N, Cachofeiro V, Luño J. Endothelial dysfunction, oxidative stress and inflammation in atherosclerosis: beneficial effects of statins. Curr Med Chem. 2007;14(2):243–8.
87 Kwak B, Mulhaupt F, Myit S, March F. Statins as a newly recognized type of immunomodulator. Nature Med. 2000;1399–402.
88 Shah PK, Chyu KY, Fredrikson GN, Nilsson J. Immuno\\\modulation of atherosclerosis with a vaccine. Nat Clin Pract Cardiovasc Med. 2005;639–46.

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