ISSN: 2755-0141

Japan Journal of Clinical & Medical Research

SCIENTIFIC Research and Community

Mini Review

Open Access

Keypoints in Cells and Atherogenesis

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ABSTRACT

Endothelial dysfunction is the initial event in the atherogenic process, resulting from several events, such as expression of leukocyte binding sites, production of growth factors, chemotactic and vasoreactive molecules, ability to oxidize low-density lipoprotein (LDL) and respond to oxidized lipoproteins, ability to express procoagulant activity, and modulation of vascular permeability. Thus, the endothelium, when subjected to different conditions and factors, plays an active role in the development of atherosclerotic plaque. The expression of several adhesion molecules, such as intracellular adhesion molecule-1 (ICAM-1), E-selectin, vascular cell adhesion molecule-1 (VCAM-1), P-selectin in atherosclerotic plaques, mediating the interaction between endothelial cells and leukocytes, has been described. The modification of LDLs, in conjunction with other chemotactic factors produced by injured endothelial cells, recruit circulating monocytes into the subendothelial space, where they become macrophages. The proliferation of smooth muscle cells is an important event in the progression of arterial injury, occurring in 3 stages: smooth muscle cell replication still within the media layer; migration from the middle layer to the intima and proliferation within the intima. Apoptotic cells were evidenced in the atherosclerotic lesion, suggesting that apoptosis is part of the normal vascular healing process. The final stage of atherosclerotic lesion development is conversion of the fibrotic lesion to an advanced lesion, a lesion in which a thrombus forms as a result of plaque ulceration or intraplaque hemorrhage.

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Received: November 28, 2023; **Accepted:** December 07, 2023; **Published:** December 11, 2023

Keywords: Atherogenesis, Adhesion Molecules, Macrophages, Smooth Muscle Cells, Lymphocytes, Apoptosis, Extracellular Matrix

Abbreviations
HDL: High Density Lipoprotein
LDL: Low Density Lipoprotein
SMC: Smooth Muscle Cell

Atherogenesis Mechanism

Atherosclerotic lesions begin after some type of injury to the endothelial layer, which is not only a simple mechanical barrier, but also synthesizes and releases vasoactive substances. Endothelial dysfunction is the initial event in the atherogenic process, resulting from several events, such as expression of leukocyte binding sites, production of growth factors, chemotactic and vasoreactive molecules, ability to oxidize low-density lipoprotein (LDL) and respond to oxidized lipoproteins, ability to express procoagulant activity, and modulation of vascular permeability [1-3].

Thus, the endothelium, when subjected to different conditions and factors, plays an active role in the development of atherosclerotic plaque. Animal studies show that diet-induced hypercholesterolemia and atherosclerosis produce more functional than anatomical abnormalities in the endothelium, altering endothelial function in the microcirculation as well [4,5].

In hyperlipidemic individuals, the transport of lipoproteins by endothelial cells from plasma to the arterial wall may result in modifications of some lipoproteins by the cells, and, in part, by their oxidation. These lipoproteins can, in turn, injure endothelial cells, resulting in adhesion of monocytes, T lymphocytes and production of chemotactic factors within the arterial wall, which conduct these leukocytes to the subendothelial intima layer [6].

Adhesion molecules: it is currently known that the expression of adhesion molecules in endothelial cells plays an important role in cell-cell interaction and in the adhesion of leukocytes to endothelial cells [7,8].

The expression of several adhesion molecules, such as intracellular adhesion molecule-1 (ICAM-1), E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and P-selectin in atherosclerotic plaques, mediating the interaction between endothelial cells and leukocytes, has been described [9-13]. The expression of adhesion molecules in smooth muscle cells (SMC) of vessels can be induced by mediators such as gamma interferon, interleukin 4 (IL-4), interleukin 1B (IL-1B), tumor necrosis factor alpha (TNF-α), suggesting that certain pro-inflammatory cytokines may regulate the expression of adhesion molecules and be related to the development of the lesion [14-16].

Macrophages: the modification of LDLs, in conjunction with other chemotactic factors produced by injured endothelial cells, recruit

circulating monocytes into the subendothelial space, where they become macrophages [17]. The modified lipoproteins inhibit the egress of macrophages from the lesion, in addition to making the cells capable of capturing large amounts of lipids. Unlike LDL uptake, which is mediated by LDL receptors and under negative feedback control, modified LDL uptake is mediated by scanning receptors, which are not subject to this type of control [18,19]. Because modified LDL uptake is not saturable, large amounts of modified LDL can be incorporated into macrophages and SMC, resulting in the formation of foam cells.

Within the lesions, macrophages also appear to be activated for an immune and/or inflammatory response, expressing major histocompatibility complexes, CD antigens, and a variety of cytokines and growth-regulating molecules [20-22].

Macrophages without lipid inclusions are often located closer to the lumen, while foam cells are found in deeper regions. When the lipid nucleus is present, the latter are usually more evident along the lumen and lateral margins of the nucleus. In places where the intima is relatively thin or in very complicated lesions, this distribution may not be as apparent.

Macrophages can express genes for proteins that participate in advanced lesion formation and modeling, such as monocyte chemotactic protein (MCP-1), tumor necrosis factor, genes for collagen and fibronectin, as well as collagenase and elastase. They can release lytic enzymes that degrade the fibrous cap, producing rupture of the atherosclerotic plaque. It has been found more frequently in patients with unstable angina and non-Q-wave myocardial infarction, suggesting that macrophages may be markers of unstable atherosclerotic plaques and play a significant role in the pathophysiology of acute coronary syndrome [23-27].

Smooth muscle cells: the proliferation of SMCs is an important event in the progression of arterial injury, occurring in 3 stages: replication of the SMC still within the media layer; migration from the middle layer to the intima and proliferation within the intima.

Two types of SMCs are observed in both initial and advanced lesions: those rich in myofilaments (contractile) and those poor in myofilaments, but relatively rich in rough endoplasmic reticulum (synthetic).

The function and activity of SMC in the artery are dependent on the medium created by the surrounding cells and the components of the extracellular matrix. In a normal, non-injured artery, the phenotype and function of SMCs are largely determined by the extracellular matrix and by factors released by endothelial cells. With endothelial injury, infiltration of monocytes and lymphocytes, thrombosis and platelets, as observed in advanced atherosclerosis lesions, the balance between vasoactive and growth-regulating factors present at the site is altered. These extracellular factors can alter the phenotype of SMC and its function, migration, proliferation and synthesis of extracellular matrix [6,28-31].

One of the platelet-derived factors, heparinase, is an enzyme that degrades heparan sulfate, a polysaccharide, in the extracellular matrix of the arterial wall, which inhibits the proliferative migration of SMCs [32]. The combination of heparan levels with decreased release of prostacyclin (PGI2) and endothelium-derived relaxing factor nitric oxide (EDRF-NO), due to endothelial cell injury, allows the conversion of SMC from the arterial medial layer in a contractile form to a non-contractile synthesizing cell. Modified SMCs can release enzymes that degrade the extracellular matrix, allowing these cells to migrate to the intima, where they proliferate under the action of mitogens such as platelet-derived growth factor (PDGF) and other growth factors.

Lymphocytes: T lymphocytes have been identified in advanced lesions by monoclonal antibodies to CD antigens, and both T cell phenotypes, CD4+ helper/inducing cells and CD8+ cytotoxic cells have been detected, in ratios ranging from 1:2 to 1:4. B cells are rare or even absent [33-35].

Evidence suggests the involvement of humoral and cellular immune reactions at all stages of atherosclerotic development [36-38]. Regarding the humoral response, granular deposits of immunoglobulins and complement components have been observed within the atherosclerotic lesion. Since rare B cells are found at any stage of injury, it is likely that these immunoglobulins will not be produced at the site. T cells are the first cells that infiltrate the intima arteriosis in the early stages of atherosclerosis, perhaps even preceding monocytes. However, the mere presence of T-cell infiltrate is not evidence of pathogenic significance, although most of the T lymphocytes in the plaques express activation markers (interleukin-2 receptor - IL2R and human leukocyte antigen - HLA-DR) indicating that they would have the ability to secrete lymphokines and that an active immune response could be occurring inside the plaque [39].

Apoptosis: apoptosis is a physiological process of cell death and is involved in many pathological conditions. Since in atherosclerosis there is an accumulation of cells in the intima, and within the sclerotic region of the advanced atheromatous plaque there is a low density of cells with little presence of cellular debris, this alteration may be due to apoptotic processes. Apoptotic cells have been evidenced in the atherosclerotic lesion, suggesting that apoptosis is part of the normal vascular healing process, while dysregulated apoptosis and/or inefficient removal of apoptotic bodies may contribute to the progression of atherosclerotic plaque and increase disease severity [40-42].

Low-density lipoprotein: arterial wall cells secrete oxidative products from multiple pathways that can initiate the oxidation of LDL retained in the subendothelial space, occurring in two stages: the first stage occurs before monocytes are recruited and results in the oxidation of lipids to LDL, with little change in apoprotein B. The second stage begins when monocytes are recruited into the lesion and transform into macrophages. At this stage, the protein portion is also modified, leading to the loss of recognition by the LDL receptor, and starting to be recognized by the sweep receptors and/or oxidized LDL receptor [43-45]. This deviation for recognition via the scan receptor leads to cellular uptake of LDL by receptors that are not regulated by the cholesterol content in the cell, which results in intense accumulation of cholesterol inside.

Modified LDL (deialized and glycosylated or oxidized) are atherogenic, unlike native LDL, and the interaction of anti-LDL antibodies with modified LDL increases their atherogenic potential. After forming an immune complex, the native LDLs, originally non-atherogenic, become atherogenic. By entering the subendothelial space of the arterial intima and interacting with subendothelial cells, lipoprotein-containing immune complexes can induce the full spectrum of atherosclerotic cellular disorders.

Circulating immune complexes with anti-LDL activity have been detected in the blood of patients with cardiovascular diseases as well as experimentally. Circulating immune complexes containing modified LDL and anti-LDL autoantibodies may be responsible

for the accumulation of cholesterol in vascular cells.

Macrophages derived from human monocytes are transformed into foam cells after incubation with LDL-containing immune complexes, which are internalized predominantly through Fc receptor-mediated phagocytosis [46]. In addition, activated macrophages release active oxygen radicals that may be involved in LDL oxidation.

High-density lipoprotein (HDL): has a protective role against the development of atherosclerosis by preventing the oxidation of LDL. This process can be mediated by two enzyme systems, demonstrated in vitro [47,48]. Thus, the inverse relationship between risk for atherosclerotic events and HDL levels may be due to the presence of HDL-associated enzymes that protect against LDL oxidation, in addition to acting in the reverse transport of cholesterol.

Extracellular matrix: the vessel wall is a component of the circulatory system that is continuously remodeling itself in response to hemodynamic and pathological conditions, its main structural components being: type I, III, IV and V collagens, elastin, proteoglycans and glycoproteins. These components interact, forming a complex structure in order to provide the physicoelastic characteristics of the blood vessel.

The composition of the matrix determines not only the physicoelastic properties of the vessel wall, but also its cellular composition, through the retention of cells and mediators in its structure [49]. Matrix metalloproteins (MMP) are enzymes dependent on Zn2+ and Ca2+, which are important in the resolution of the extracellular matrix, because, once activated, they can completely degrade the components of the extracellular matrix [50].

The integration of LDL apoprotein B with the sulfate group of glycosaminoglycans may be a mechanism for retaining LDL in the arterial intima. Sulfated glycosaminoglycans increase during the early stages of atherosclerosis and chondroitin sulfates positively correlate with accumulation of apoprotein B in the intima before lesions become macroscopically detectable [51,52]. Large extracellular proteoglycans, mainly molecules containing chondroitin sulfate, act on arterial permeability, ion exchange, transport and deposition of LDL-like plasma material. Small extracellular proteoglycans, such as molecules containing dermatan sulfate, can regulate collagen fibrinogenesis, and also ionically bind to LDL. The amount of heparan sulfate decreases or even remains unchanged, while the amount of dermatan sulfate increases as the lesion progresses. Increased sulfated glycosaminoglycans facilitates LDL retention in the intima. The association of LDL and proteoglycans may result in increased LDL retention, uptake of LDL by macrophages via the scan receptor, or make LDL more susceptible to oxidation [53].

After lipids, collagen is the main component of type V lesions, being produced by the SMC of the intima. The main type of advanced lesion collagen is type I fibrillar collagen, occurring mainly in the fibrous layer and in vascularized regions of advanced lesions. Alterations and accumulation of type I and III collagen occur primarily after extensive necrosis. Increases in collagen IV and V may result from hyperplasia of SMCs in atherosclerotic lesions [54,55].

Elastic fibers are fragmented and often appear to be associated with lipid and calcium deposits. Lipids bound to elastic fibers can modify the elasticity of the tissue, altering the conformation of elastin through hydrophobic interactions, in addition to facilitating the sensitivity of elastin to proteolytic degradation. Elastolysis is increased in aortas with advanced atherosclerotic lesions when compared to elastin isolated from uninjured aorta [56]. A significant decrease in elastin content is observed only in the most advanced lesions.

The transfer of lipoproteins and fibrinogen from plasma to the intima is a physiological process, but these proteins are found in much higher amounts in advanced lesions than in normal intima or early lesions.

The distribution of different molecular forms of fibrinogen in the vessel wall indicates that the accumulation of fibrinogen-derived proteins in the atherosclerotic vessel is not only related to thrombus formation or increased endothelial permeability, but is suggestive of an active interaction between macrophages, foam cells, and SMCs with fibrinogen.

Numerous in vitro studies have shown that fibrinogen, fibrin, and fibrinogen degradation products affect numerous biological functions of endothelial cells, SMCs, and macrophages, contributing to plaque growth and development [57]. The final stage of atherosclerotic lesion development is the conversion of the fibrotic lesion to an advanced lesion, a lesion in which a thrombus forms as a result of plaque ulceration or intraplaque hemorrhage [58,59].

Subsequent to plaque rupture, thrombosis occurs, which involves platelet aggregation and adhesion, as well as activation of the coagulation cascade. The coagulation cascade is initiated by the exposure of collagen from the interior of the plaque and by tissue factors produced by endothelial cells and macrophages. Tissue factors cause factor VIII to activate factor X, which then catalyzes the conversion of prothrombin to thrombin. The latter catalyzes the conversion of fibrinogen to monomeric fibrin, which subsequently undergoes polymerization to stabilize the thrombus. Thrombin also stimulates cell proliferation within the fractured lesion, promoting additional platelet deposition and release of platelet-derived growth factor by platelets and other cells present in the lesion.

Thrombosis can also be potentiated by lipoprotein (a), which inhibits thrombolysis, competitively preventing the conversion of plasminogen to plasmin [60,61].

All these events culminate in severe, often fatal clinical conditions and, therefore, the understanding of all stages of the atherogenic process will enable the therapeutic intervention of atherosclerosis, either through the modification of lipoprotein levels, the non-transformation into foam cells, the remodeling of the constituent matrix of the vascular wall, or even through the modification of immunological reactivity. Intervention in one of these stages can delay the progression to more advanced lesions, prolonging survival, since atherosclerosis is a disease with a slow and silent evolution.

Acknowledgments
None

Conflict of Interest
None

References

1. Consigny PM (1995) Pathogenesis of atherosclerosis. AJR Am J Roentgenol 164: 553-558.
2. Ross R (1995) Growth regulatory mechanisms and formation of the lesions of atherosclerosis. Ann N Y Acad Sci 748: 1-4.
3. Berliner JA, Navab M, Fogelman AM, Frank JS, Demer LL, et al. (1995) Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics. Circulation 91: 2488-2496.
4. Harrison DG (1994) Endothelial dysfunction in atherosclerosis. Basic Res Cardiol 89: 87-102.
5. Anderson TJ, Gerhard MD, Meredith IT, Charbonneau F, Delagrange D, et al. (1995) Systemic nature of endothelial dysfunction in atherosclerosis. Am J Cardiol 75: 71B-74B.
6. Shafi O (2020) Switching of vascular cells towards atherogenesis, and other factors contributing to atherosclerosis: a systematic review. Thromb J 18: 28.
7. Pertiwi KR, de Boer OJ, Mackaaij C, Pabittei DR, de Winter RJ, et al. (2019) Extracellular traps derived from macrophages, mast cells, eosinophils and neutrophils are generated in a time-dependent manner during atherothrombosis. J Pathol 247: 505-512.
8. Zhang J, Zu Y, Dhanasekara CS, Li J, Wu D, et al. (2017) Detection and treatment of atherosclerosis using nanoparticles. Wiley Interdiscip Rev Nanomed Nanobiotechnol Doi: 10.1002/wnan.1412.
9. Poston RN, Haskard DO, Coucher JR, Gall NP, Johnson-Tidey RR (1992) Expression of intercellular adhesion molecule-1 in atherosclerotic plaques. Am J Pathol 140: 665-673.
10. Van der Wal AC, Das PK, Tigges AJ, Becker AE (1992) Adhesion molecules on the endothelium and mononuclear cells in human atherosclerotic lesions. Am J Pathol 141: 1427-1433.
11. O'Brien KD, Allen MD, McDonald TO, Chait A, Harlan JM, et al. (1993) Vascular cell adhesion molecule-1 is expressed in human coronary atherosclerotic plaques. Implications for the mode of progression of advanced coronary atherosclerosis. J Clin Invest 92: 945-951.
12. Wood KM, Cadogan MD, Ramshaw AL, Parums DV (1993) The distribution of adhesion molecules in human atherosclerosis. Histopathology 22: 437-444.
13. Johnson-Tidey RR, McGregor JL, Taylor PR, Poston RN (1994) Increase in the adhesion molecule P-selectin in endothelium overlying atherosclerotic plaques. Coexpression with intercellular adhesion molecule-1. Am J Pathol 144: 952-961.
14. Li H, Cybulsky MI, Gimbrone MA Jr, Libby P (1993) Inducible expression of vascular cell adhesion molecule-1 by vascular smooth muscle cells in vitro and within rabbit atheroma. Am J Pathol 143: 1551-1559.
15. Couffinhal T, Duplàa C, Moreau C, Lamazière JM, Bonnet J (1994) Regulation of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 in human vascular smooth muscle cells. Circ Res 74: 225-234.
16. Wang X, Feuerstein GZ, Clark RK, Yue TL (1994) Enhanced leucocyte adhesion to interleukin-1 beta stimulated vascular smooth muscle cells is mainly through intercellular adhesion molecule-1. Cardiovasc Res 28: 1808-1814.
17. Ross R (1993) The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature;362(6423): 801-809. doi: 10.1038/362801a0
18. Witztum JL, Steinberg D (1991) Role of oxidized low density lipoprotein in atherogenesis. J Clin Invest 88: 1785-1792.
19. Wu H, Moulton KS, Glass CK (1992) Macrophage scavenger receptors and atherosclerosis. Trends Cardiovasc Med 2: 220-225.
20. Wculek SK, Dunphy G, Heras-Murillo I, Mastrangelo A, Sancho D (2022) Metabolism of tissue macrophages in homeostasis and pathology. Cell Mol Immunol 19: 384-408.
21. Kuznetsova T, Prange KHM, Glass CK, de Winther MPJ (2020) Transcriptional and epigenetic regulation of macrophages in atherosclerosis. Nat Rev Cardiol 17: 216-228.
22. Amengual J, Barrett TJ (2019) Monocytes and macrophages in atherogenesis. Curr Opin Lipidol 30: 401-408.
23. Nelken NA, Coughlin SR, Gordon D, Wilcox JN (1991) Monocyte chemoattractant protein-1 in human atheromatous plaques. J Clin Invest 88: 1121-1127.
24. Barath P, Fishbein MC, Cao J, Berenson J, Helfant RH, et al. (1990) Detection and localization of tumor necrosis factor in human atheroma. Am J Cardiol 65: 297-302.
25. Liptay MJ, Parks WC, Mecham RP, Roby J, Kaiser LR, et al. (1993) Neointimal macrophages colocalize with extracellular matrix gene expression in human atherosclerotic pulmonary arteries. J Clin Invest 91: 588-594.
26. Davies MJ, Richardson PD, Woolf N, Katz DR, Mann J (1993) Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content. Br Heart J 69: 377-381.
27. Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, et al. (1994) Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture. Circulation 90: 775-778.
28. Raines EW, Ross R (1993) Smooth muscle cells and the pathogenesis of the lesions of atherosclerosis. Br Heart J 69: S30-S37.
29. Allahverdian S, Chaabane C, Boukais K, Francis GA, Bochaton-Piallat ML (2018) Smooth muscle cell fate and plasticity in atherosclerosis. Cardiovasc Res 114: 540-550.
30. Durham AL, Speer MY, Scatena M, Giachelli CM, Shanahan CM (2018) Role of smooth muscle cells in vascular calcification: implications in atherosclerosis and arterial stiffness. Cardiovasc Res 114: 590-600.
31. Sorokin V, Vickneson K, Kofidis T, Woo CC, Lin XY, et al. (2020) Role of vascular smooth muscle cell plasticity and interactions in vessel wall inflammation. Front Immunol 11: 599415.
32. Castellot JJ Jr, Favreau LV, Karnovsky MJ, Rosenberg RD (1982) Inhibition of vascular smooth muscle cell growth by endothelial cell-derived heparin. Possible role of a platelet endoglycosidase. J Biol Chem 257: 11256-11260.
33. Jonasson L, Holm J, Skalli O, Bondjers G, Hansson GK (1986) Regional accumulations of T cells, macrophages, and smooth muscle cells in the human atherosclerotic plaque. Arteriosclerosis 6: 131-138.
34. Watanabe T, Shimokama T, Haraoka S, Kishikawa H (1995) T lymphocytes in atherosclerotic lesions. Ann N Y Acad Sci 748: 40-55.
35. Kyaw T, Peter K, Li Y, Tipping P, Toh BH, et al. (2017) Cytotoxic lymphocytes and atherosclerosis: significance, mechanisms and therapeutic challenges. Br J Pharmacol 174: 3956-3972.
36. Stemme S, Hansson GK (1994) Immune mechanisms in atherogenesis. Ann Med 26: 141-146.
37. Stemme S, Faber B, Holm J, Wiklund O, Witztum JL, et al. (1995) T lymphocytes from human atherosclerotic plaques recognize oxidized low density lipoprotein. Proc Natl Acad Sci USA 92: 3893-3897.
38. Wick G, Schett G, Amberger A, Kleindienst R, Xu Q (1995) Is atherosclerosis an immunologically mediated disease? Immunol Today 16: 27-33.
39. Hansson GK, Holm J, Jonasson L (1989) Detection of activated T lymphocytes in the human atherosclerotic plaque.

Am J Pathol 135: 169-175.
40. Geng YJ, Libby P (1995) Evidence for apoptosis in advanced human atheroma. Colocalization with interleukin-1 beta-converting enzyme. Am J Pathol 147: 251-266.
41. Han DK, Haudenschild CC, Hong MK, Tinkle BT, Leon MB, et al. (1995) Evidence for apoptosis in human atherogenesis and in a rat vascular injury model. Am J Pathol 147: 267-277.
42. Bu LL, Yuan HH, Xie LL, Guo MH, Liao DF, et al. (2023) New dawn for atherosclerosis: vascular endothelial cell senescence and death. Int J Mol Sci 24: 15160.
43. Sparrow CP, Parthasarathy S, Steinberg D (1989) A macrophage receptor that recognizes oxidized low density lipoprotein but not acetylated low density lipoprotein. J Biol Chem 264: 2599-2604.
44. Brown MS, Goldstein JL (1990) Atherosclerosis. Scavenging for receptors. Nature 343: 508-509.
45. Khatana C, Saini NK, Chakrabarti S, Saini V, Sharma A, et al. (2020) Mechanistic Insights into the oxidized low-density lipoprotein-induced atherosclerosis. Oxid Med Cell Longev 2020: 5245308.
46. Virella G, Muñoz JF, Galbraith GM, Gissinger C, Chassereau C, et al. (1995) Activation of human monocyte-derived macrophages by immune complexes containing low-density lipoprotein. Clin Immunol Immunopathol 75: 179-189.
47. Watson AD, Navab M, Hough GP, Hama SY, Ladu B, et al. (1994) Biologically-active phospholipids in MM-LDL are transferred to HDL and are hydrolyzed by HDL-associated esterases. Circulation 90: 353.
48. Watson AD, Navab M, Hama SY, Sevanian A, Prescott SM, et al. (1995) Effect of platelet activating factor-acetylhydrolase on the formation and action of minimally oxidized low density lipoprotein. J Clin Invest 95: 774-782.
49. Gialeli C, Shami A, Gonçalves I (2021) Extracellular matrix: paving the way to the newest trends in atherosclerosis. Curr Opin Lipidol 32: 277-285.
50. Dollery CM, McEwan JR, Henney AM (1995) Matrix metalloproteinases and cardiovascular disease. Circ Res 77: 863-868.
51. Wagner WD, Salisbury BG (1978) Aortic total glycosaminoglycan and dermatan sulfate changes in atherosclerotic rhesus monkeys. Lab Invest 39: 322-328.
52. Ylä-Herttuala S, Solakivi T, Hirvonen J, Laaksonen H, Möttönen M, et al. (1987) Glycosaminoglycans and apolipoproteins B and A-I in human aortas. Chemical and immunological analysis of lesion-free aortas from children and adults. Arteriosclerosis 7: 333-340.
53. Camejo G, Olofsson SO, Lopez F, Carlsson P, Bondjers G (1988) Identification of Apo B-100 segments mediating the interaction of low density lipoproteins with arterial proteoglycans. Arteriosclerosis 8: 368-377.
54. Rekhter MD, Zhang K, Narayanan AS, Phan S, Schork MA, et al. (1993) Type I collagen gene expression in human atherosclerosis. Localization to specific plaque regions. Am J Pathol 143: 1634-1648.
55. Murata K, Motayama T, Kotake C (1986) Collagen types in various layers of the human aorta and their changes with the atherosclerotic process. Atherosclerosis 60: 251-262.
56. Saulnier JM, Hauck M, Fülöp T Jr, Wallach JM (1991) Human aortic elastin from normal individuals and atherosclerotic patients: lipid and cation contents; susceptibility to elastolysis. Clin Chim Acta 200: 129-136.
57. Bini A, Kudryk BJ (1995) Fibrinogen in human atherosclerosis. Ann N Y Acad Sci 748: 461-471.
58. Fuster V, Stein B, Ambrose JA, Badimon L, Badimon JJ, et al. (1990) Atherosclerotic plaque rupture and thrombosis. Evolving concepts. Circulation 82: II47-II59.
59. Fuster V, Badimon L, Badimon JJ, Chesebro JH (1992) The pathogenesis of coronary artery disease and the acute coronary syndromes (1). N Engl J Med 326: 242-250.
60. Dahlén GH (1994) Lp(a) lipoprotein in cardiovascular disease. Atherosclerosis 108: 111-126.
61. Liu AC, Lawn RM (1994) Lipoprotein(a) and atherogenesis. Trends Cardiovasc Med 4: 40-44.