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The Historical Link from Lipoproteins to Atherogenesis

Ihara SSM[1], Saldanha ALR[1], Margeotto APP[1], Gasparoto ALV[2] and Martinez TLR[1*]

[1]Nephrology Department, BP - A Beneficência Portuguesa de São Paulo, São Paulo, Brazil

[2]Intensive Care Unit, BP - A Beneficência Portuguesa de São Paulo, São Paulo, Brazil

[*]**Corresponding author:** Martinez TLR, BP - A Beneficência Portuguesa de São Paulo, Rua Comandante Ismael Guilherme, 358 - Jardim Lusitânia, CEP 04031-120 - São Paulo - SP, Brazil, Tel: 55 11 98323-9863; E-mail: tamar@uol.com.br

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Abstract

The growing interest in the mechanisms involved in atherogenesis is justifiable when it is verified that most of the deaths that occurred in the Western world are due to ischemic syndromes related to atherosclerotic disease, that is, coronary insufficiency, cerebral vascular and peripheral vascular. We can consider atherogenesis as a protective inflammatory response to injury of the endothelium and smooth muscle layer of the vessel, secondary to genetic, metabolic and hemodynamic influences, promoting the formation of a fibrofatty or fibrous plaque as a repair response of the arterial wall. Oxidized LDL has properties that alone can trigger and perpetuate atherogenesis, regardless of other agents that promote endothelial injury. Remaining lipoproteins rich in triglycerides and high-density lipoproteins: circulating lipoproteins rich in triglycerides at high levels may also be an endothelial injury factor, since intact vascular endothelium is a catabolism site of these lipoproteins. A great step was taken in this sense, with the use of lipid-lowering drugs in the control of dyslipidemias. Significant reductions in the overall mortality rate have been confirmed in prospective epidemiological studies, both in primary prevention and in the secondary prevention of coronary atherosclerotic disease. The intervention on complex mechanisms that promote atherogenesis, among others: preventing the modification of lipoproteins, blocking macrophages and hindering the formation of foamy cells, preventing cell proliferation and the deposition of immunocomplexes in the vascular wall opens a new horizon with drugs such as statins and Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors.

Keyword: ***Lipoproteins; Atheroma; Endothelium; Inflammation; Oxidation***

1. Abbreviations

IGF-1: Insulin-like Growth Factor-1; IL-1: Interleukin-1; LDL: Low Density Lipoprotein; PDGF: Platelet Derived Growth Factor; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; TNF-alpha: Tumor Necrosis Factor αlpha

2. Introduction

The growing interest in the mechanisms involved in atherogenesis is justifiable when it is verified that most of the deaths that occurred in the Western world are due to ischemic syndromes related to atherosclerotic disease, that is, coronary insufficiency, cerebral vascular and peripheral vascular [1-3].

Current hypotheses about atherogenesis recall those proposals from the middle of the 19th century.

Virchow proposed that a tenuous form of arterial wall injury promoted the formation of an inflammatory infiltrate and that there would be a greater passage of plasma constituents to the intimate layer of the vessel [4]. Rokitanski and, later, Duguid [5,6] believed that the fouling of a mural thrombus would occur in sites of arterial injury and that these thrombi were organized into structures that contained smooth muscle cells inside, which multiplied, causing the atherosclerotic process to progress. These later modified and supplemented concepts would serve as the basis for the composition of the injury response theory [7].

The basis for formulating the lipid infiltration hypothesis for atherogenesis dates back to studies from the beginning of the century, when spontaneous atherosclerotic lesions in rabbit aortas were described. Ignatowiski and Anitshkow [8,9] demonstrated that rabbits fed diets high in saturated fat and cholesterol developed atherosclerotic lesions in the aorta. Experimental studies "*in vitro*" and "*in vivo*", using animal model, carried out in recent decades, which elucidated the properties of low-density proteins (LDL - Low Density Lipoprotein) and their oxidative modifications, allowed a hypothesis to be proposed for the development of atheroma based on high LDL levels [10-12].

In fact, the hypotheses of the response to injury and lipid infiltration have many points in common, i.e.:

- lipoproteins in certain situations may callin the endothelium;
- the endothelium reviled by any agent allows a greater influx of lipoproteins;
- LDL and other lipoproteins may favor platelet aggregation and stimulate cell proliferation.

Thus, the interrelations between the mechanisms proposed in the two hypotheses allow them to be considered as two facets of a single hypothesis [13].

We can consider atherogenesis as a protective inflammatory response to injury of the endothelium and smooth muscle layer of the vessel, secondary to genetic, metabolic and hemodynamic influences, promoting the formation of a fibrofatty or fibrous plaque as a repair response of the arterial wall [13,14].

Constitution of atheroma: anatomical changes in atherosclerosis are characterized by fatty degeneration (atheroma) and thickening and hardening of the arterial wall (sclerosis). Atheroma is the basic lesion of atherosclerosis, consisting of a raised focal plate within the intimate layer, containing a lipid nucleus and a fibrous plaque of coating. Atherosclerotic lesions can be found and classified into six stages, according to their histological aspect, and which better characterize the different stages of their evolution [15,16] (FIG 1).

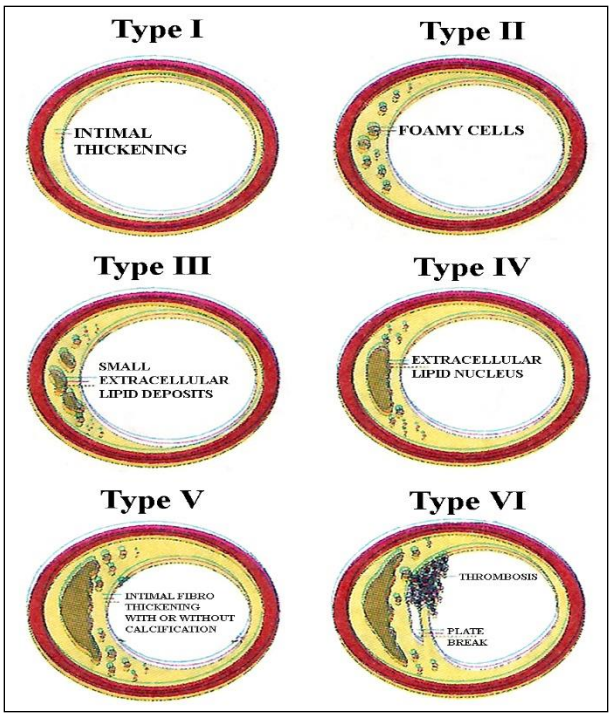

FIG 1. **Histological types of atheroma plaque (Modified by Stary et al.) [16].**

They are:

Type I lesion: consists of the first lipid deposits detected microscopically and chemically in the intima. It is described in children, although it can also be found in adults, particularly in those with little atherosclerosis [17].

Type II lesion: include fatty striations that can be macroscopically visualized as yellow striae on the intimal surface, and which are correlated with Sudam III or IV, and are therefore referred to as Sudanese lesions.

Type III injury: designation that applies only to those lesions that form a chemical and morphological bridge between type II lesions and atheromas, sometimes called intermediate, transition or pre-atheroma lesion.

Type IV lesion: this is a dense accumulation of extracellular lipids, occupying an extensive and well-defined region of the intima, known as lipid nucleus. It is also known as atheroma, being the first lesion considered advanced in its classification, due to severe intimal disorganization caused by the lipid nucleus.

Type V lesion: it is observed a new fibrous connective tissue that, associated with the lipid nucleus, constitutes fibroatheroma (Va type lesion). This can be multilaminated, where multiple lipid nuclei are overlapped, separated by a thin layer of fibrous connective tissue. Lesions containing a large amount of calcium are also distinguished, being called Vb-type lesions and lesions where the intima is replaced by fibrous tissue, becoming thicker, and being the lipid content minimal or absent, constituting the Vc type lesion.

Type VI injury: known as a complicated lesion due to plaque surface rupture, with the development of hematoma or hemorrhage and thrombosis.

Endothelial injury - initial event: different factors, among other systemic arterial hypertension, diabetes mellitus, dyslipidemias, smoking, lead to endothelial dysfunction. Not necessarily the injury promotes the denudation of the endothelium. Its function can be compromised even without denudation (type I injury), or when there is bare denudation and injury of the intimate layer of the vessel (type II injury) or, even when, in addition to the intima, the middle layer is also injured (type III injury) [18].

The injured endothelium has its main impaired functions facilitating the formation of atheroma [19]. They are:

- maintain nonthrombogenic arterial surface;
- maintain permeable arterial surface, allowing selective transport to the subendothelial space;
- maintain vascular tone by releasing molecules that modulate vasodilation (nitric oxide and prostacyclin) and vasoconstriction (endothelins);
- form and secrete cell growth regulatory molecules and cytokines;
- maintain the integrity of the basal membrane, formed by collagen and proteoglycans, on which rests the endothelium;
- maintain the arterial surface not adherent to leukocytes;
- have the ability to modify lipoproteins.

Experimental studies have shown that the physical and functional integrity of the endothelium is fundamental and any endothelial dysfunction leads to the triggering of several pathological processes, including atherosclerosis. Although erosion of the endothelial surface is not observed in the initial lesions, studies have shown a higher rate of cell renewal in regions with alterations than in normal ones. Hyperlipidemia and hypercholesterolemia are pathological factors sufficient to induce dysfunction of endothelial modulation of vasoactive reactions, verifying that endothelial modulation of arteriolar tone is abnormal during the development of atherosclerosis.

Manifestations of endothelial dysfunction, which contribute to atherogenesis, include increased penetration of lipoproteins into the subendothelial space, particularly LDL, generation of binding glycoproteins on the surface of endothelial cells, and secretion of growth factors and cytokines implicated in migration, cell proliferation, and coagulation [14,20].

Endothelial cells maintain the surface of non-thrombogenic and non-adherent vessels for platelets and leukocytes, acting in the maintenance of vascular tone, through the release of nitric oxide, prostacyclins (PGI2) and endothelins, produce growth factors and cytokines, in addition to maintaining the integrity of basal membrane rich in collagens and proteoglycans. Changes in any of these functions may trigger cellular interactions with monocytes, platelets, smooth muscle cells and lymphocytes, starting the formation of the atheroma plaque.

The expression of adhesion molecules in endothelial cells has an important participation in the migration of leukocytes from the blood to the site of development of atherosclerosis. Several molecules have been described in atherosclerotic plaques, such as ICAM-1 (Intercellular Adhesion Molecule-1), E-seletine, VCAM-1 (Vascular Cell Adhesion Molecule 1) and P-seletine, mediating the interaction between endothelial cells and leukocytes of peripheral blood [21,22].

The adhesion glycoproteins VCAM-1 and ELAM-1 (Endothelial Leukocyte Adhesion Molecule 1), generated by the endothelium, are related, respectively, to the adhesion of monocytes and polymorphonuclear leukocytes to the vessel wall [23]. The expression of the adhering molecules may also be induced by mediators such as gamma-interferon, IL-4 (Interleukin 4), IL-1 (Interleukin 1) beta and TNF-alpha (Tumor Necrosis Factor alpha), suggesting that certain pro-inflammatory cytokines may regulate the expression of the acceding molecules and be related to plaque development. After adhering to glycoproteins, monocytes migrate into the subendothelial space through intercellular junctions, under the influence of thygens, oxidized lipoproteins and mainly a specific protein called MCP-1 (Monocyte Chemotatic Protein -1), produced by endothelial cells and smooth muscles of the vessel wall [24].

In the subendothelial space, monocytes undergo a process of activation and differentiation, resulting in their phenotypic conversion to macrophages. Macrophages and, later, cells of the smooth muscle layer that migrate to the subendothelial space where they differ, accumulate lipids, giving rise to foamy cells. These, accompanied by T lymphocytes, will constitute the fatty stria, which is the earliest recognizable atherosclerotic lesion [25].

Free radicals and LDL oxidation: LDL reaches the subendothelial space by transcytosis, probably within plasmacles of endothelial cells [26].

The internalization of low-density lipoproteins by the macrophage depends on specific membrane receptors. B-E receptors recognize and capture native LDL and other lipoproteins that contain apoprotein B-100 or E in their composition. The number of receptors available for the internalization of lipoproteins is related to the concentration of cholesterol inside the negative feedback cell [27].

In vitro and "*in vivo*" studies have shown that LDL must undergo changes (acetylization, desialization, methylation, non-enzymatic glycoylate, conjugation with malondialdehyde, oxidation) prior to their internalization by the macrophage and formation of the foamy cell [28]. The uptake would occur through a different receptor, which would not recognize native LDL, but those modified, and which would not have lipoprotein influx controlled by negative feedback, called scanner receptor [29].

Oxidative changes in LDL, which are the most studied in atherogenesis, begin by peroxidation of its polyunsaturated fatty acids. LDL are exposed to free radicals, formed from molecular oxygen through chemical oxidation and reduction reactions, which occur in endothelial cells, smooth muscle cells and macrophages, undergoing changes in their molecular structure [24]. The chemical reactions involved depend on the concentrations of iron and copper of the medium, and can be inhibited by metal oilers and antioxidant substances. Lipid peroxidation propagates rapidly, causing changes in the structure of apoprotein B-100, and forming new epitopes in this apoprotein, which are recognized by the macrophage receptor [30].

Free radicals derived from molecular oxygen, implicated in lipid peroxidation and formation of oxidized LDL, are continuously produced in the cellular respiratory chain. These chemical elements are shown in CHART 1[31].

O_2^{o-}	Radical Superoxide
HO_2^{o}	Hydroperoxyl Radical
H_2O_2	Hydroperoxyl Peroxide
OH^{o-}	Hydroxyl Radical
ROO^{o-}	Radical Peroxide (R = Lipid)
$^1O_2$	Oxygen "Singlet"

CHART 1. **Potentially Toxic O_2-Derived Chemical Species.**

In lipid peroxidation, a free radical derived from oxygen removes a radical hydrogen from the carbon chain, producing a carbon-lipid radical. After molecular rearrangement, it reacts with molecular oxygen, forming a hydroperoxyl-lipid radical that, in turn, extracts a hydrogen atom from the carbon chain of an adjacent polyunsaturated fatty acid, promoting the formation of another lipid radical of lipid hydroperoxide [31,32].

Lipid hydroperoxide is a stable compound until it came into contact with transition metal ions, producing new free radicals that perpetuate chain reactions [33].

The oxidation of LDL "*in vitro*" can be induced by incubation in culture of endothelial cells, smooth muscle cells, macrophages, or interaction with heavy metal ions such as copper, generating lipoperoxides. "*In vivo*" can occur in the intra- or extracellular compartment, provided that the medium does not have natural antioxidants.

The fragmentation of LDL fatty acids allows the formation of highly reactive intermediate products, such as aldehydes and ketones, which can conjugate to the adjacent Apoprotein B.

Lysine residues from apoprotein B, components of its structure, are necessary for the interaction of LDL with the B-E receptor that interacts with native LDL. With the increase in the number of lysine residues of apoprotein B, derived from fatty acid fragmentation products, its molecular structure changes, preventing its recognition by the B-E receptor. Thus, new epitopes are generated in oxidized LDL that will be recognized by the macrophage-sweeping receptor, leading to the formation of the foamy cell [34].

Because free radicals are constantly being produced, all cells have mechanisms to modulate the oxireduction reactions they have determined. The antioxidant capacity of the medium can be maintained by the presence of certain enzymes (enzymatic system) or several substances with antioxidant activity (non-enzymatic system) [35].

Three enzymes are implicated in the free radical-sweeping mechanism. They are:

- Superoxide-dismutase - found in the mitochondria, accelerates the dismutation of the radical superoxide to hydrogen peroxide;
- Catalase - degrades the molecule of hydrogen peroxide to water and oxygen;
- Glutathione-peroxidase - inactive hydrogen peroxide and lipid peroxides.

Oxidized LDL has properties that alone can trigger and perpetuate atherogenesis, regardless of other agents that promote endothelial injury [29]. They are:

- increase the synthesis of binding glycoproteins;
- increase the release of growth factors and cytokines;
- inhibit the migration of monocytes from the subendothelial space to the blood;
- inhibit cholesterol esterification in endothelial cells;
- prevent the action of molecules with vasodilator capacity (nitric oxide).
- lead to the formation of immunocomplexes in the arterial wall - immunogenic capacity - which can be recognized by receptors for fragment c (Fc) of immunoglobulins present in macrophages.

Oxidative products secreted by arterial wall cells initiate the oxidation of LDL retained in the subendothelial space, occurring in 2 stages: in the first stage, occurring before monocytes are recruited, results in the oxidation of lipids in LDL, with little alteration in apo B. The second stage begins when monocytes are recruited for the lesion and turn into macrophages. At this stage, the protein part is also modified, leading to the loss of recognition of LDL receptors, being recognized by scanner receptors or oxidized LDL receptors, resulting in intense accumulation of cholesterol inside the cell [36].

Remaining lipoproteins rich in triglycerides and high-density lipoproteins: circulating lipoproteins rich in triglycerides at high levels may also be an endothelial injury factor, since intact vascular endothelium is a catabolism site of these lipoproteins [37]. Hydrolysis of triglyceride-rich lipoproteins in the vicinity of the endothelial surface may expose the endothelium to an excessive local concentration of free fatty acid anions that have been considered endothelial injury factors [38].

HDL levels present an inverse correlation with the development of atherosclerosis, facilitating the clearance of cholesterol from atheromatous plaques, transporting to the liver to be excreted. A protective effect has also been suggested, preventing LDL oxidation through enzymes associated with a small fraction of HDL particles [39].

Cell proliferation - evolution of plaque: parallel to the oxidation of lipoproteins, growth factors, cytokines and other chemical elements are released by endothelial cells, macrophages and platelets. Atherogenesis is implicated in cell recruitment, migration and proliferation and in the synthesis of lipids and proteins, including those components of the extracellular matrix. They are also involved in vascular events such as vasodilation, vasoconstriction and coagulation [14].

Among the molecules involved in the proliferation of smooth muscle layer cells are: PDGF (Platelet Derived Growth Factor), b-FGF (Basic Fibroblast Growth Factor), IGF-1 (Insulin-like Growth Factor-1), IL-1, TNF-alpha and TGF-beta (Transforming Growth Factor beta).

Others, in addition to mitogenic action, have chemotactic activity. Chemotactic action is both important in the recruitment of leukocytes and in the attraction of cells from the smooth muscle layer to the subendothelial space. Colony Stimulating Factors (CSFs) and TNF-beta (Tumor Necrosis Factor beta) have chemotactic action for leukocytes. The same capacity is observed by oxidized LDL, potentiating the migration of leukocytes through the endothelium. In the chemotaxis of smooth muscle cells are involved the PDGF and IGF-1.

The continuous influx of elements into the subendothelial space and cell proliferation lead to the progression of the atherosclerotic lesion. Smooth muscle cells and lipid-filled macrophages accumulate.

Inflammatory processes and immune mechanisms are also involved in atherogenesis, with immunoglobulins and T lymphocytes in atherosclerotic plaques. An inflammatory reaction could destabilize fibrous tissue, facilitating the risk of chronic thrombosis.

Lipoproteins are also deposited in the extracellular space between fibrils and proteoglycans of connective tissue and along the elastic lamina. Fatty striae expand, modifying the architecture of the arterial wall, causing the retraction of endothelium cells and the exposure of subendothelial connective tissue, facilitating interaction with blood elements, particularly with platelets.
In advanced stages, the fibrous plaque becomes vascularized, containing large amounts of capillary and venulas-like channels, which are formed secondarily to the release of angiogenic substances [40,41]. In acute ischemic syndromes, these channels play a crucial role. Changes in plaque structure (fissure, rupture or ulceration), promoted by the release of proteolytic enzymes (metalloproteins), lead to hemorrhage and triggering of the process that allows the formation of the platelet thrombus [24].

Present investigations focus mainly in the role of inflammation [42-44] and its correlations to thrombosis [45], calcium deposition and deal with the role that the hypolipidemic drugs may affect the process, mainly statins and PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) inhibitors. Statins are as well being studied as potential inhibitors of NF (Nuclear Factor)-kB in beta cells, fluvastatin attenuates CRP (C Reactive Protein)-ativation and also simvastatin and atorvastatin [46-49]. The PCSK9 inhibitors have mainly been studied as to atherogenesis by invasive diagnostic imaging and leading to promising results [50].

In conclusion, the search for the true mechanisms involved in plaque formation aims to find forms of intervention to prevent the emergence and development of atherosclerotic disease. A great step was taken in this sense, with the use of lipid-lowering drugs in the control of dyslipidemias. Significant reductions in the overall mortality rate have been confirmed in prospective epidemiological studies, both in primary prevention and in the secondary prevention of coronary atherosclerotic disease [51,52]. The intervention on complex mechanisms that promote atherogenesis, among others: preventing the modification of lipoproteins, blocking macrophages and hindering the formation of foamy cells, preventing cell proliferation and the deposition of immunocomplexes in the vascular wall opens a new horizon with drugs such as statins and PCSK9 inhibitors.

3. Acknowledgments

None

4. Conflicts of Interest

No conflict of interest.

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