

Atherosclerosis

Atherosclerosis is a chronic progressive disease of the vascular wall characterized by local accumulation of lipids and other components of blood and fibrous tissue in the intima of arteries, accompanied by changes in the media of the vascular wall. Atherosclerosis develops as a chronic inflammation with an excessive proliferative response of the intima and media of arteries to various stimuli, especially to modified LDL (low density lipoproteins).

Atherosclerosis mainly affects large and medium-sized arteries. The coronary arteries, thoracic aorta, popliteal artery, internal carotid artery and arteries of the circle of Willis are most often affected.

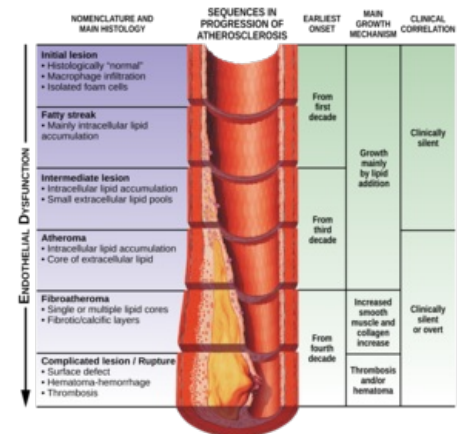
Stages of the development of atherosclerosis

Early phase - lipid accumulation

1. isolated macrophage-derived *foam cells* ;
2. *fatty streaks* – accumulation of foam cells containing intracellularly accumulated lipids; macroscopically, they are yellow and do not project into the lumen; they usually occur already in childhood;
3. *intermediate lesion* – small amounts of extracellularly stored lipids, originating from dead foam cells;
4. *atheroma* – the formation of a lipid core formed by extracellularly accumulated lipids.

Late phase – intimal proliferation and oncoming thrombosis

1. *fibroatheroma* – proliferation of smooth muscle cells in the intima and increased synthesis of extracellular matrix, containing collagen and elastic fibers, which creates a fibrous layer above the lipid core;
2. *complicated lesion* – calcification, rupture or exulceration, bleeding into atheroma, thrombus formation.



Various blood components and arterial walls contribute to the development of atherosclerotic changes:

- lipoproteins;
- endothelial cells;
- monocytes / macrophages ;
- T-lymphocytes ;
- platelets.

The most significant risk factor for atherosclerosis is represented by atherogenic lipoproteins, especially low-density lipoprotein LDL.

The role of LDL particles in atherosclerosis

LDL particles contain a high proportion of cholesterol, which is concentrated in a non-polar core. The characteristic protein structure in the LDL envelope is apolipoprotein B100 (apo B100). During normal metabolism, LDL particles are catabolized via LDL receptors (LDLR), located on the surface of hepatocytes and cells of extrahepatic tissues. These receptors recognize apo B100, which, in addition to LDL, is also part of VLDL (very low density lipoproteins) and IDL (intermediate density lipoproteins), and apo E on the surface of VLDL or IDL.

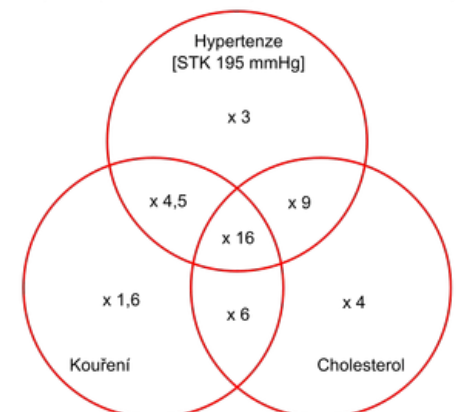
Through the LDL receptor, the regulation of cholesterol homeostasis and protection of the cell against the accumulation of cholesterol in the cell is enabled on several levels.

Excess intracellular cholesterol:

- suppresses the synthesis of other LDL receptors by reducing the transcription of LDL receptor genes; this limits the entry of other cholesterol molecules into the cell;
- prevents the synthesis of new cholesterol molecules by reducing gene transcription by inhibiting HMG-CoA (hydroxymethylglutaryl-CoA) reductase, which is the rate-determining enzyme of cholesterol biosynthesis;
- inhibits the release of transcription factors such as SREBP (sterol regulatory element binding protein);
- it is esterified by the enzyme acyl-CoA:cholesterol acyltransferase (ACAT).

LDL particles are represented by several subfractions, differing in size and density. We distinguish between LDL I and LDL IV. LDL-III and LDL-IV are referred to as small- **dense LDL** . They contain less cholesterol, and therefore, with their increased amount, the concentration of LDL cholesterol in the serum can be normal. However, compared to larger LDLs, they have more pronounced atherogenic properties. They are more easily modified, due to their smaller size they penetrate better into the subendothelial space and are not catabolized by LDL receptors.

Vzájemná potenciace rizikových faktorů aterosklerózy



An increased concentration of small dense LDL is usually accompanied by hypertriglycerolemia and a decrease in HDL. This metabolic triad is referred to as *the LDL size B phenotype*. An increase in small dense LDL is a risk factor for coronary heart disease and myocardial infarction.

In the initial stages of atherosclerosis, LDL which has migrated to the intima of the arteries, is used significantly. There may be several reasons for the increased penetration of LDL particles into the subendothelial space:

- increased concentration of LDL in some disorders of lipoprotein metabolism (eg familial hypercholesterolemia, polygenic hypercholesterolemia, familial combined hyperlipoproteinemia);
- increased permeability of the endothelium as a result of its damage, which involves, for example, turbulent flow, hypertension, vasoconstriction or hypoxia;
- insufficient removal of cholesterol from the subendothelial space due to low levels of HDL (high density lipoproteins).

Modified LDL particles

Chemical modifications of LDL particles such as their oxidation, glycation and acetylation occur in the intima of the arteries and, to a limited extent, in the plasma. The most studied change in LDL is **oxidative modification**, which is caused by free radicals arising from enzymatic and non-enzymatic reactions. The initial step of oxidative modification is the peroxidation of polyunsaturated fatty acids of surface phospholipids. Fatty acid fragments formed during lipid peroxidation covalently bind to the amino group of lysine and to other regions of the apolipoprotein B100 molecule and form adducts of lipid products and apo B100. The sterane core of cholesterol in LDL is also subject to oxidative modification with the formation of various oxidized forms.

Through oxidative modification, LDL particles acquire atherogenic properties.

Mildly oxidized LDL mainly contain lipid peroxides, but without significant changes in apoprotein B100. Their atherogenic properties are less pronounced.

Slightly oxidized LDL induces the synthesis of:

- MCP-1 (monocyte chemoattractant protein 1), which attracts monocytes to the arterial wall;
- specific adhesion molecules for monocytes, which mediate binding of monocytes to the endothelium;
- CSF (colony stimulating factor), which initiates the differentiation of monocytes into macrophages. The result is the entry of monocytes into the subendothelial space.

Heavily oxidized LDL particles have a more significantly altered structure, including the protein component. Their proatherogenic properties have more serious implications.

Highly oxidized LDL particles:

- they modulate the synthesis of proatherogenic cytokines and growth factors by macrophages and smooth muscle cells;
- damage endothelial cells by direct cytotoxicity;
- they can inhibit NO-synthase and thereby disrupt arterial vasorelaxation;
- they are immunogenic and induce both humoral and cell-mediated immunity.

Scavenger receptors

Heavily modified LDL particles are not removed by LDL receptors, which are unable to recognize the altered structure of apo B100. However, they can be picked up by other receptors, referred to as scavenger ("cleaning", "sweeping") receptors. Several structurally different receptors capable of binding modified forms of LDL have been described. We distinguish two basic classes **of scavenger receptors: class A (SR-AI/II/III)** and **class B (SR-BI, CD36)**. Apart from them, there are other classes of these receptors.

Scavenger receptors are found on the surface of macrophages, smooth muscle cells and endothelial cells. The activity of scavenger receptors is not regulated by the content of intracellular cholesterol. They are expressed even at a high concentration of cholesterol in the cell. Cholesterol can thus accumulate uncontrollably in the cell. As a result, macrophages are transformed into so-called foam cells, which remain trapped in the arterial wall. The appearance of which is characteristic of fatty streaks.

In addition to modified LDL, scavenger receptor ligands can also be native lipoproteins such as HDL and LDL, apoptotic cells and some pathogens. The occurrence of scavenger receptors is not limited to the cells of the arterial wall. SR-BI may be present on hepatocytes and other extrahepatic cells where, as a receptor for HDL, it may be involved in reverse cholesterol transport (see below).

The role of HDL particles in atherosclerosis

Similar to LDL and HDL particles, they represent a heterogeneous group of lipoproteins. The pre- β -HDL subfraction consists only of apoprotein AI, phospholipids and a small amount of free cholesterol. Pre- β -HDL is distinguished from other lipoprotein classes by its disk-shaped shape. With the gradual intake of cholesterol, it changes into alpha-HDL, which is further differentiated into HDL 2 and HDL 3.

HDL are carriers **of antiatherogenic effects**, which are expressed by several mechanisms:

- by reverse transport of cholesterol from the arterial wall to the liver;

- antioxidant effects;
- anti-inflammatory effects; by improving endothelial function;
- antiaggregation effect on platelets.

Reverse (reverse) transport of cholesterol is a process in which cholesterol is removed from extrahepatic tissues and transported to the liver. It is initiated by the transfer of non-esterified cholesterol from the cell (e.g. macrophage) and capture by pre- β -HDL particles. The release of free cholesterol from the cell is enabled **by ABCA1** (ATP binding cassette transporter) in cell membranes. Free cholesterol is then esterified with the help of the enzyme **LCAT (lecithin cholesterol acyltransferase)** and, as esterified cholesterol, moved to the center of HDL, which acquire a spherical shape. Cholesterol carried in HDL particles can be **directly transported** to the liver and delivered to hepatocytes with the help of **SR-B1 scavenger receptors**, which are on their surface. Another **indirect** way happens with the help of **CETP proteins (cholesterol ester transfer proteins)**, which ensure the exchange of cholesterol in HDL for triacylglycerols present in VLDL or LDL. These can then be taken up by LDL receptors on hepatocytes.

The enzymes paraoxonase (PON1) and **platelet-activating factor acetylhydrolase (PAF-AH)**, which are transported as part of HDL, are responsible **for the antioxidant effects of HDL**. The first of the enzymes, paraoxonase protects LDL from lipoperoxidation by reducing lipoperoxide content by hydrolyzing oxidized polyunsaturated fatty acids at the sn-2 position of phospholipids in oxidized LDL. Platelet-activating factor acetylhydrolase is also involved in the degradation of oxidized phospholipids, but unlike PON1, it acts on fatty acids with a lower number of carbons (≤ 9).

The anti-inflammatory effects are manifested by reducing the expression of adhesion molecules (e.g. VCAM-1, ICAM-1) on the endothelium and by inhibiting the adhesion of monocytes to the endothelial surface.

The role of monocytes/macrophages in atherosclerosis

Monocytes/macrophages represent the main inflammatory cell type in the intima of an atherosclerotic vessel. Monocytes penetrate the subendothelial space with the help of adhesion molecules and MCP-1, the expression of which is stimulated by oxidized LDL. Here they are differentiated into macrophages, which themselves synthesize a large number of biologically active substances (cytokines, growth factors, free radicals). After taking up more oxidized LDL via scavenger receptors, they turn into **foam cells**, which can disintegrate, and the cholesterol contained in them is released extracellularly, giving rise to a lipid core.

The role of smooth muscle cells in atherosclerosis

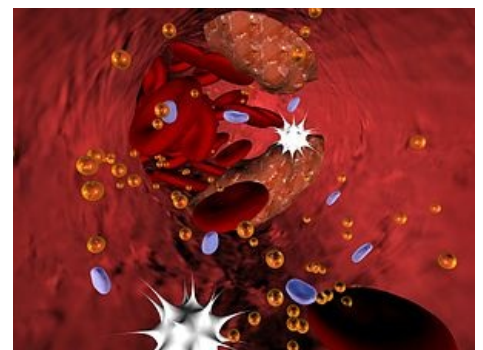
Smooth muscle cells are also involved in the formation of atherosclerotic lesions. Together with monocytes, they accumulate in the intima, especially in the stage of fibrous plates. They travel from the media into the intima in response to various cytokines and growth factors (e.g. IL-1, TNF-alpha, PDGF). For atherosclerotic lesions, the change **of the contractile phenotype** of the smooth muscle cell to **the synthetic phenotype is typical**. It is characterized by an increase in the rough endoplasmic reticulum and the Golgi apparatus, which is related to the increased synthesis of the extracellular matrix, especially collagen (type I, type II and others). The transformed smooth muscle cells, together with the components of the extracellular matrix, form a fibrous cover over the lipid core. The increasing amount of collagen is accompanied by changes in the mechanical properties of the vessel wall. Some smooth muscle cells, like macrophages, can transform into foam cells.

Stable and unstable atherosclerotic plaque

The atherosclerotic plaque consists of **a core** with abundant extracellular lipids and **a fibrous cover** (cap, cover), consisting of fibrous tissue with a predominance of collagen and proteoglycans, surrounding muscle cells. The composition of the atherosclerotic plaque significantly affects its stability, which is closely related to acute clinical events. We distinguish between stable and unstable (vulnerable) atherosclerotic plaque.

The stable plate is characterized by a thicker and intact fibrous cap, low lipid content.

Unstable plaques have a larger amount of lipids, foam cells, and T lymphocytes stored in the core, while the fibrous cap is thin with low collagen content. They are more prone to rupture, which is responsible for most acute coronary events. The inflammatory process that occurs in places where macrophages and T lymphocytes accumulate contributes to plaque instability. Macrophages are a source of **proteolytic enzymes** (metalloproteinases) collagenase, stromelysin, which can weaken the fibrous cover. On the contrary, T lymphocytes present in the plaque produce **interferon gamma** suppressing the synthesis of collagen by smooth muscle cells, and CD40 stimulating the synthesis of metalloproteinases. Plaque rupture is the reason for bleeding into the plaque and the formation of a thrombus.



Links

Reference

related articles

- Coronary artery atherosclerosis (preparation)
- Risk factors for cardiovascular diseases
- Lipoproteins
- Lipoproteins (clinic)

External links

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