2.1 Atherosclerosis Is a More Complex Process than Previously Thought

Atherosclerosis is a multifactorial and multipart progressive disease manifested by the focal development within the arterial wall of lesions – the atherosclerotic plaques – in response to various deleterious insults that affect the vessel wall’s cells. Among the risk factors, as identified by classical epidemiology, there are dyslipidemia, vasoconstrictor hormones incriminated in hypertension, products of glycoxidation associated with hyperglycemia, pro-inflammatory cytokines and smoking, out of which the first is a prerequisite for the initiation and progression of about half of arterial lesions. In other instances, an inflammatory reaction induced by putative antigens that stimulate T lymphocytes, certain heat shock proteins, components of plasma lipoproteins, and potentially, microbial structures induce atherosclerotic plaque in the absence of systemic hypercholesterolemia [1, 2]. Thus, the process is more complex than previously thought. The conventional view that stressed the role of dyslipidemia in the generation of atherosclerosis was rounded by extensive evidence that inflammation is a key contributor to all stages of this disease, from the initial lesion to the ruptured plaque [2]. In all cases, the atheroma formation entails a progressive process in which the gradual implication of various cells and their secretory products define a sequence of events that leads from the fatty streak to fibro-lipid plaque, and ultimately to plaque rupture and atherothrombosis.
2.2 Vascular Resident Cells and Circulating Blood Cells Emigrated Within the Arterial Wall Participate to Atherosclerotic Plaque Formation

Tunica intima, media and adventitia are the three layers that make up the vessel wall. The intima is made essentially of a monolayer of epithelial-like cells, the endothelial cells (EC), resting on a basal lamina they produce, and a few smooth muscle cells (in human arteries) that also synthesize their own basal lamina and contribute to the extracellular matrix (ECM) proteins. The internal elastic lamina separates the intima from the media that comprises numerous layers of smooth muscle cells (SMC), bordered by a basal lamina and intercalated between elastic laminae, all embedded within the ECM. An external elastic lamina separates the media from the adventitia, which is made up mainly of fibroblasts, mast cells, microvessels, lymphatic vessels and nerves, housed within an extended ECM.

The resident cells of the arterial wall (EC and SMC) in concert with cells emigrated from the blood (in particular T-lymphocytes, monocytes, dendritic cells, mast cells) and their secretory products (chemokines, cytokines, enzymes), through ample cross talk and signalling, contribute to the initiation, evolution and fate of the atherosclerotic plaque.

2.3 Atheroma Formation Is a Progressive Process Arbitrarily Delineated by Consecutive Stages

In the last 30 years, thorough exploration of the cellular and molecular modifications occurring in the arterial areas susceptible to plaque development uncovered the sequence of events and the consecutive stages that take place within the continuous process of atherosclerosis, either in hypercholesterolemic conditions or as an inflammatory reaction, in the absence of hypercholesterolemia (Fig. 2.1). Within this continuous process a pre-lesional, often reversible, phase (Fig. 2.1, stages I, II and III), occurring during the first three decades of life, and a phase of progressive atherosclerotic plaque formation (Fig. 2.1, stages IV, V and VI) can be distinguished.

2.3.1 Stage I. Commencement of Plaque Formation: Modulation of Endothelial Constitutive Functions

By position and large surface area exposed to the blood, EC are the first cells to experience the impact of any minute perturbation occurring in the blood or interstitial fluid homeostasis. In arterial lesion-prone areas, the initial event that takes place in response to changes in body homeostasis (i.e. hyperlipidemia, hyperglycemia, inflammation) is the modulation of EC constitutive functions.
Modification of EC controlled permeability and the ensuing increased transcytosis and deposition of plasma LDL within the intima. The close positive correlation between aortic LDL permeability in a given segment and the cholesterol accumulation in that particular segment suggests that the aortic permeability to LDL is a predictor for the development of cholesterol-induced experimental atheroma formation [3].

In experimental atherosclerosis models, plasma LDL concentration gradient generates a prominent increase in transcytosis [4–6]. The latter, in conjunction with the reduced efflux of LDL predominantly to the lumen of the artery [7] and the subsequent trapping of LDL within the subendothelial matrix concur to their accumulation in the subendothelium, within and outside the basal lamina, against the fragmented internal elastic lamina (Fig. 2.2).

(a) Modification of EC controlled permeability and the ensuing increased transcytosis and deposition of plasma LDL within the intima.
The intima-confined LDL interact with proteoglycans and matrix proteins that, among other factors, trigger their atherogenic conversion into oxidatively modified Lp (MLp), as demonstrated in animal models [8–11] and human aorta [12, 13]. The MLp are heterogeneous structures and appear in situ or after their isolation from experimental animals or human aorta as vesiculated, aggregated, or fused particles rich in unesterified cholesterol [12, 13]. Accumulation and retention of Lp in the subendothelium [14, 15] depend both on EC and Lp characteristics, such as their oxidation susceptibility [16]. The atherogenic modifications of LDL may take place either within the plasma, or when crossing the EC or within the subendothelial ECM. It is possible that the alteration of LDL occurs to different degrees in all three locations [17]. The small fraction of altered LDL (oxidised, glycated, enzymatically-modified, etc.) detected in circulation is possibly due to the powerful antioxidant systems existing in the plasma, as well as to the scavenger receptors (i.e. for asyaloglycoproteins) present in the liver and other organs of the mononuclear phagocytic system.

LDL has been consistently confirmed as a major risk factor for cardiovascular diseases (CVD) and is the basis of statins treatment. However, lipoproteins (Lp) alone do not explain all of the risks inherent in CVD; one-half of all heart attacks and strokes occur among individuals without hypercholesterolemia, and one-fifth of all cardiovascular events occur in the absence of any of the major risk factors. C-reactive protein is a circulating pentraxin that plays a major role in human innate immune response and provides a stable plasma biomarker for low-grade systemic inflammation. Among patients with stable angina and established CVD, plasma levels of CRP have consistently been associated with recurrent risk of cardiovascular events [18].

Fig. 2.2 Trapping of modified lipoproteins (MLp) in a hyperlipidemic hamster vessel’s intima. Note the subendothelial accumulation of MLp within the hyperplasic, multilayered basal lamina (bl). EC endothelial cells, L vascular lumen. Bar: 1 μm
Almost concurrently with increased transcytosis and retention of MLp within the intima, major changes in the biosynthetic capacity of EC occur. Structurally, EC switch to a secretory phenotype characterized by multiple copies of the rough endoplasmic reticulum, Golgi apparatus, centrioles and numerous caveolae (Fig. 2.3). Functionally, a progressive development of a hyperplasic multilayered basal lamina entrapping steadily MLp within its meshes takes place [19–21] (Fig. 2.2). The proliferation of the basal lamina and of the ECM disrupt the myo-endothelial junctions, as well as the gap junctions between neighbouring SMC, leading to an altered response of the vessel wall to external stimuli.

(c) Alteration of the endothelial net negative surface charge

Under normal conditions, the EC plasmalemma has a net negative charge that contributes to the characteristic non-thrombogenic surface of the endothelium (all circulating cells expose also a negatively charged surface) (Fig. 2.3, inset). In experimental atherosclerosis, the arterial EC plasmalemma exhibits gradually a reduced and non-homogenous distribution of anionic sites (revealed with in situ perfused cationic ferritin), as opposed to the uniform decoration of the EC membrane in control animals [22]. Long-term hyperlipidemia results in redistribution of anionic sites, which are significantly reduced on the EC plasmalemma, whereas they become clustered on the diaphragms of the caveolae (Fig. 2.3, inset). One can safely assume that the diminished arterial endothelial surface negative charge may account, in part, for the increased
permeability and the augmented adhesive characteristics of the vessel wall in specific arterial locations [23].

2.3.2 Stage II. EC Dysfunction

The dual assault on EC luminal and abluminal surface, namely the alteration of plasma lipid homeostasis and the subendothelial accrual of MLp generates, as a defence reaction, the initiation of a multipart inflammatory process manifested at first by the EC “activation”; this general term designates a set of stimuli-generated dysfunctions that elicit new structural and functional properties.

In early human and experimental atherosclerosis, the alterations of the EC non-adhesive and non-thrombogenic surface are an illustration of EC dysfunction. The latter is manifested by the expression on the EC plasmalemma of new or additional cell adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), E-selectin, and P-selectin (which function in the selective recruitment of monocytes), fractalkine, vascular cell adhesion molecule (VCAM)-1 that binds to monocyte cognate receptors (VLA-4 and CCR2) and trigger their adherence to EC. In addition, the cells synthesize monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8), which are chemoattractant for monocytes [24], a trio of CXC chemokines that function in T-lymphocytes recruitment [1] and eotaxin, which is chemoattractant for mast cells (via CCR3 receptors); all these molecules are overexpressed in human atherosclerotic plaque [25]. This set of molecular and cellular changes, denoting EC activation and dysfunction, is a defence reaction assisting the vascular endothelium to recruit specifically blood inflammatory cells.

2.3.3 Stage III. Robust Inflammatory Reaction: Adhesion and Extravasation of Monocytes and Lymphocytes, Fatty Streak Formation

(a) Adhesion, diapedesis and residence within the intima of a specific set of pro-inflammatory monocytes

Blood monocytes are heterogeneous; the two major human monocytes subsets are the CD14+CD16− and CD14−CD16+ [26]. The pro-inflammatory monocytes (characterised by specific surface molecules) undergo a coordinated process in which monocyte integrins and EC adhesion molecules and chemokines orchestrate the capture, rolling, adhesion and arrest of monocytes on the endothelium lining the MLp-rich arterial segments. The adhesion process is followed by transmigration (diapedesis) of monocytes through the EC junctions and their residence within the subendothelium (Fig. 2.4) [27, 28].

(b) Platelets assist the recruitment of blood monocytes, thus participating to the initiation of plaque formation

Initially considered the main contributor to arterial thrombosis, platelets were recently revealed as participants to all stages of atherosclerosis. In the early
phase, activated EC secrete and expose on their surface von Willebrand factor (vWF). The latter, by interacting with platelets glycoprotein Ib, triggers the recruitment and adherence of platelets to the intact EC surface. Upon adhesion, platelets are activated and secrete a variety of pro-inflammatory cytokines and chemoattractants (platelet factor 4, RANTES, P-selectin, soluble CD40 ligand, MMPs). The platelet membrane P-selectin mediates EC-platelet interaction also. The interaction between platelet P-selectin with monocyte P-selectin glycoprotein ligand-1 [29] leads to the formation of platelet–monocyte aggregates (Fig. 2.5); the activated platelets promote leukocyte binding to the vascular cell adhesion molecule-1 (VCAM-1) and increased their adhesiveness to inflamed or atherosclerotic endothelium. In atherosclerotic carotid arteries platelet–leukocyte aggregates are often detected; individual platelets directly adherent on atherosclerotic endothelium are rarely found [30].

(c) Recruitment of T-Lymphocytes

T-cells, mostly CD4+ T cells, are recruited and present in the prelesional stages of atherosclerotic plaque formation together with antigen-presenting dendritic cells and some CD8+ T cells [1, 31]. Circulating T-cells migrate into the atherosclerotic lesions in response to chemokines, monokines and chemoattractants, which bind to the cell specific receptors (Fig. 2.6). Within the plaque various antigens, such as MLp, induce T-cell proliferation (reviewed in [32]). Upon recognition of an antigen, the type 1 helper T cells (Th1) become activated, express and secrete a large array of cytokines and cell surface molecules, which contribute to macrophage activation and the potentiation of the inflammatory response.

(d) Dendritic cells are required for the activation of naïve T cells

Dendritic cells are specialized antigen presenting cells that are required for the activation of naïve T cells and the development of antigen-specific T cell
Fig. 2.5  The interaction between endothelial cells (EC), a circulating cell, most likely a monocyte (M) or a neutrophil, and activated platelets (P) in an early stage of aortic plaque formation in a hyperlipemic hamster. L vascular lumen. Bar: 0.8 μm

Fig. 2.6  Endothelial cells (EC), a group of lymphocytes (Ly) and macrophage-derived foam cells (MFC), are in close contact in a developing atheroma. Note, within the aortic lumen (L), the close contact between a monocyte (M) and an EC containing lipid droplets, and between a platelet (P) and a circulating monocyte. Bar: 1.7 μm
mediated immune responses. They are present from the early stages till the advanced atherosclerotic plaque, particularly in the rupture-prone shoulder region of the lesions [33]. MLp and other stimuli that accelerate atherogenesis (i.e. TNF-α) augment dendritic cells adhesion to the endothelium and their subsequent transmigration [34]. Vascular dendritic cells either in normal or in atherosclerotic arterial intima appear as a network of elongated cells with extended long, dendritic-like processes, often found in contact with T cells in areas of neovascularization and in the adventitia vasa vasorum (reviewed in [35]). It is possible that in these areas (as in other parts of the immune system) the vascular dendritic cells present antigens to naïve T cells, since these cells retain the antigen presenting function under conditions typical for atherosclerotic plaques [36].

(e) Polymorphonuclear neutrophils (PMN), whose role in inflammation is well established, were for a long time considered of insignificant relevance in atherosclerosis. Accumulated indirect evidence in humans and animal models indicate a close relationship between the number of circulating activated PMN, the coronary artery disease and their presence into culprit lesions [37]. Activated PMN release superoxide and pro-inflammatory mediators at the blood – vessel wall interface that may affect the EC properties, promote or amplify the recruitment of inflammatory cells and within the plaque, by the molecules they secrete, may contribute to its vulnerability [38]. Moreover, recent evidence indicates that in hypercholesterolemia-induced neutrophilia, PMN infiltrate arteries primarily during early stages of atherosclerosis, suggesting their role in the initiation of atherosclerosis. Moreover, lesion progression in Apoe−/− mice was blunted by depletion of circulating PMN, indicating a significant impact of PMN on atherosclerosis in this murine model [39]. The adhesion molecules that mediate rolling, adhesion and transmigration of PMN are present in atherosclerotic lesions. The paucity of PMN found in atherosclerotic lesion could be due to either their rapid apoptosis within the plaque [40], or to the cytotoxic effect of free fatty acids released from modified Lp [41]. In addition, there are indications that PMN may be important during destabilization of advanced plaques [42].

More research is necessary to acknowledge the mechanisms by which PMN contribute to atherogenesis and its progression. Thus far, the data imply a causative role of PMN in the inflammatory conditions associated with atherogenesis and athero-progression and suggest the potential importance of modulating neutrophilic inflammation as part of the strategy to prevent/treat atherosclerosis (reviewed in [43]).

(f) Mast Cells, known for their role in allergy, have recently being acknowledged as pro-inflammatory effector cells present in the human arterial intima and in evolving atherosclerotic lesions. When activated, mast cells secrete the rich content of their cytoplasmic granules, such as histamine, neutral proteases, growth factors, and pro-inflammatory cytokines within the plaque. These factors act on MLp, extracellular matrix, and intimal cells neighbouring the activated mast cells. Moreover, the immunoglobulin G immune complexes
containing MLp, present within the human atherosclerotic lesions, activate mast cells inducing the secretion of numerous pro-inflammatory cytokines (TNF-alpha, IL-8 and MCP-1) and the release of histamine and tryptase [44]. Thus, mast cells may contribute to fatty streak formation and to the generation of unstable plaques susceptible to rupture (reviewed in [45]).

(g) B cells were initially found within the vessels’ adventitia, and later immunoglobulin-positive cells were detected within the atherosclerotic plaques. Recently, indirect evidence on experimental animals revealed that B cells direct the immune response during the development of the atherosclerotic plaque and their immunoglobulin products may perform protective functions during the plaque progression (reviewed in [35]).

(h) Intimal differentiation of monocytes into activated macrophages and the subsequent formation of macrophage-derived foam cells

Within the intima, monocytes differentiate into macrophages by a regulated program that includes the upregulation of scavenger receptors (i.e. SR-B1 and CD-36). Scavenger receptors are operational in the uptake of MLp, advanced glycosylation endproducts, anionic phospholipids and even apoptotic cells. The non-regulated uptake of MLp mediates the switch of activated macrophages into cholesterol loaded macrophage-derived foam cells. Accumulation of macrophage-derived foam cells is the hallmark of fatty-streak type lesion (Fig. 2.7), which ultimately may evolve to advanced fibro-lipid plaque (reviewed in [46]).

Fig. 2.7 Fatty streak lesion in a hyperlipidemic hamster aorta. Numerous macrophage-derived foam cells (MFC) amass under a continuous, thin endothelium. A few smooth muscle cells (SMC) emigrated from or within the media contain lipid droplets (ld). EC endothelial cells, L vascular lumen. Bar: 2 μm
2.3.4 Stage IV. Fibrous Plaque Formation

While some human lesions may begin as intimal xanthomas, there is considerable evidence suggesting that the intimal thickening is most likely precursor leading to symptomatic coronary disease, since these lesions are found in children in similar locations as advanced plaques in adults, while fatty streaks are known to regress [47].

The inflammatory cells, through the factors they secrete within the plaque, send molecular messages: macrophage-derived-foam cells secrete cytokines, growth factors, tissue factor, IFN-gamma, matrix metalloproteases (MMPs), and produce reactive oxygen species (ROS); lymphocytes secrete among others CD-40 L. These messages govern the plaque development, including the clonal accumulation of SMC within the intima (reviewed in [21]).

A crucial event in the formation of the plaque is the migration of SMC from the vessels media into the intima, through the fragmented, partially degraded internal elastic lamina. The areas known as “intimal thickenings” can be either “eccentric” or “diffuse”, although these two types are often contiguous and can be difficult to distinguish from each other. Eccentric intimal thickenings tend to be focal and involve up to half of the circumference of the arterial wall. They are found in conserved locations, including branchpoints and areas of turbulent blood flow [47]. Other sources for intimal SMC, besides those migrated from the media, are the circulating bone marrow cells and the vascular progenitor cells present in the adventitia of all arteries. Just like the activated EC, the migrated SMC switch to a secretory phenotype, resulting in a hyperplasic, multilayered basal lamina and enlarged extracellular matrix enriched especially in collagen bundles and fibrils. The conversion of quiescent SMC and EC to a secretory phenotype may represent a functional adaptation/modulation of these cells to protect themselves from the vicious microenvironment [21]. In the coronary arteries of hyperlipemic hamsters, intimal SMC proliferate, accumulate lipid droplets, and further turn into foam cells [23] contributing to the formation of fibro-lipid lesions in the affected arteries (Fig. 2.8).

2.3.5 Stage V. Calcified Atherosclerotic Fibro-Lipid Plaque

The advanced atherosclerotic plaques are characterized by accumulation of extracellular lipid droplets, macrophage-, and SMC-derived foam cells, and calcification cores that develop further into big calcification centres, which occupy a large part of the coronary artery in experimental hyperlipemic hamsters (Fig. 2.9) and humans [20, 48].

Accumulation of free cholesterol within the plaque is a potent inducer of apoptosis of macrophage derived-foam cells; in addition, within the lesions, SMC and T-cells may also go through apoptotic cell death [46]. Apoptotic cells release their content initiating the formation of the necrotic core. The defining feature of this stage is a lipid rich necrotic core encapsulated by fibrous tissue [49]. Excess extracellular unesterified cholesterol nucleates into cytotoxic crystals and the
Atherosclerotic plaque evolves to complicated atheroma, eventually causing the total occlusion of coronary artery branches [20].

The fibro-lipid lesions endowed with a robust fibrous cap are considered stable plaques (Fig. 2.10a). Thinning of the fibrous cap concomitant with its infiltration with macrophages and T-lymphocytes, cellular apoptosis, and the accumulation of large cholesterol crystals generates the unstable (vulnerable) plaque (Fig. 2.10b),

Fig. 2.8 Fibrolipid plaque located in a hyperlipemic hamster aorta. (a) The endothelium (EC) overlays numerous macrophage-derived foam cells (MFC) and smooth muscle-derived foam cells (SFC). Note the expanded extracellular matrix (ECM) and the scattered fragments of elastic lamellae. Bar: 1 µm. (b) A large cholesterol monohydrate crystal (cc) originating from the extracellular lipid deposits, aggression an endothelial cell (EC) and almost penetrating through the cell. Bar: 1.3 µm
which is prone to rupture and the ensuing thrombus formation, that can occlude the lumen and cause myocardial infarction or stroke [50].

2.3.6 Stage VI. Complicated Plaque: Rupture, Thrombosis

The exact mechanism of plaque rupture is not known, but it includes cap thinning, excess inflammatory cytokines and proteases that mediate digestion of the matrix, decreased collagen synthesis and the presence of injured or apoptotic cells within the necrotic core. All the cells that contribute to the formation of the atherosclerotic plaque are also implicated in the plaque rupture and the consequent thrombosis.

_Endothelial cells_ covering the fibrous cap become either extremely thin (Fig. 2.10b) or loaded with lipid droplets turning into EC-derived foam cells (Fig. 2.9); in either case, they are fragile and susceptible to erosion. Ultimately, the EC are injured and their disruption exposes the ECM (rich in pro-inflammatory and pro-coagulant molecules) to the circulating blood cells, that initiate the thrombus formation.

_Macrophages_ infiltrate the thinned fibrous cap. They express and secrete a large number of inflammatory cytokines and proteases, especially MMPs, which digest the stabilizing matrix, thus having a key role in the weakening and ultimate rupture of the atherosclerotic plaque. Necrosis of the vulnerable plaque is due to a combination of macrophages death and defective phagocytic clearance of apoptotic cells. The dead or dying macrophages release an excess of inflammatory cytokines and...
matrix proteases that accelerate and/or induce plaque disruption. The mechanical stress caused by the necrotic core to the overlying cap may also produce the plaque rupture (reviewed in [49]).

SMC also participate to cap thinning. They exhibit a decrease in collagen synthesis that concurrently with the proteolytic digestion of the extracellular matrix by MMPs cause the thinning of the fibrous cap and the resulting rupture of the plaque.
Mast cells that are located especially in the rupture-prone shoulder regions of the plaque, secrete proteases (tryptase and chymase) that assist the destabilization of the atherosclerotic plaque [35].

Platelets have a major role in the thromboembolic complications of the vulnerable plaque. When the plaque ruptures, platelets adhere to the exposed extracellular matrix rich in pro-inflammatory factors, become activated, aggregate and form a thrombus on the surface of the disrupted lesion. The overlying thrombus is often in continuity with the underlying necrotic core rich in macrophages [51]. Thrombotic vascular occlusion is associated with ischemic episodes, such as acute coronary syndrome or cerebral infarction. Acute thrombosis is predominantly characterized by layered platelet aggregates with variable amounts of fibrin, red blood cells and acute inflammatory cells. At least 75–80% of sudden coronary deaths show occlusive acute or organized thrombi. In some cases, the matrix heals by a concerted biological process involving the infiltration of SMC, accumulation of extracellular matrix proteins (i.e., proteoglycans and collagen), neovascularization, inflammation, and luminal surface re-endothelialization [52].

2.4 Adventitia in Atherosclerosis

The role of the outermost layer of blood vessels, the adventitia (from the Latin “adventicius” meaning extraneous) in atherosclerosis was to a certain extent neglected; however, lately, the implications of this connective tissue-rich layer, which houses besides fibroblasts, microvessels that constitute the vasa vasorum, lymphatic vessels, mast cells, nerves and progenitor cells have been revealed.

The structural components of the adventitia undergo significant changes with the advancement of the atherosclerotic plaque formation. In humans, with the development of the lesions, the adventitial layer becomes infiltrated with inflammatory cells, initially with macrophages and T-lymphocytes and ultimately (in advanced stages) with B-lymphocytes [53].

Vasa vasorum is the source of neo-vessels that sprout into the atherosclerotic plaque. They are the provider of oxygen and nutrients for the cells present within the hypoxic microenvironment of the atheroma, thus contributing to its development. In humans, plaque neovascularization takes place in the early phases of atherosclerosis and is associated with the inflammatory reaction. The thin-walled new microvessels lined by a discontinuous endothelial layer and lacking SMC are also a conduit and a source of more inflammatory cells, monocytes/macrophages, T cells and mast cells, within the atherosclerotic plaque. Disruption of newly formed microvessels leads to intra-plaque hemorrhage and the ensuing accumulation of erythrocytes that may be a consequence or may induce plaque instability in the advanced atherosclerotic lesions (reviewed in [54]). Together, accumulated data highlight a key role for the adventitia in the development of atherosclerosis.
2.5 Conclusion

The atherosclerotic plaque is the end product of the activity and reactivity of the resident cells of the arterial wall, which under the assault of a large variety of aggressors and risk factors elicit an inflammatory process, manifested by the attraction and implication of the cells of the immune system.

EC are the first cells to react to minute changes occurring in the microenvironment and the last to surrender (i.e. cell death). They go progressively through modulation of their constitutive function (permeability, biosynthesis), followed by dysfunction (expression of new cell adhesion molecules and chemoattractants) and ultimately, in late stages of atherosclerosis, to injury and death. The EC dysfunction initiates a robust inflammatory reaction and the atherogenic MLp sustain and propagate the inflammatory response. The cross talk and the messages exchanged among the arterial wall cells depend on the mediators of inflammation and immunity.

SMC migrated in the intima from the tunica media, proliferate and elaborate a rich and complex extracellular matrix. They form the fibrous cap that stabilizes the plaque, and in concert with EC and macrophages, secrete MMPs that modulate numerous functions of vascular cells, including proliferation, migration, as well as neoaangiogenesis or degradation of the matrix.

As the lesion progresses, calcification and cell death commonly occurs; together with the accumulated extracellular lipids, they form the classic lipid-rich necrotic core that ultimately may rupture to generate atherothrombosis.

All the cells (resident or emigrated), every single chemokine, cytokine, MMP and vasa vasorum that contribute to the atherosclerotic plaque formation are the bona fide targets for therapeutic intervention to stop or retard its progression. There are already in use suitable drugs for lowering LDL blood concentration, the statins. Further pharmacological advances will allow reaching targets beyond LDL, such as increasing HDL level, blocking plaque neovascularization, or employing stem cells for regenerative strategies. Expectations in the field are dependent on the accumulated knowledge on the intricate cellular and molecular processes of atherosclerosis and on treating the cell as the “basic patient”. The future hope for patient-tailored treatment implies concurrently a “cell-tailored treatment”.

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