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From endothelial dysfunction to complicated atherosclerotic plaque -the long journey of the more lethal disease of our times-

De la disfunción endotelial a la placa aterosclerótica complicada -el largo viaje de la enfermedad más letal de nuestro tiempo-

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INTRODUCTION

Atherosclerosis is a pathological process extremely intricate and complex, in which factors of genetic, dietary, metabolic, hemodynamic, thrombogenic, rheological, inflammatory, oxidative, immune, psychosocial, and environmental nature, concur concomitantly. Nevertheless, dyslipidemia is, doubtlessly, the major risk factor for atherogenesis. In this brief review we will summarize the essential points of the long journey that goes from endothelial dysfunction to the building-up of atherosclerotic lesions, and its eventual complications, including plaque fracture and athero-thrombotic occlusion.

Definition of atherosclerosis. Atherosclerosis is a lesion composed by two processes termed atherosis and sclerosis. The former is defined as *the intracellular and extracellular accumulation of lipid in the subendothelial space, with foam cell formation and the triggering of a state of chronic inflammation,* while the latter, sclerosis, indicates *a fibrotic, tentatively scaring process, characterized by hyperplasia of vascular myocytes and dystrophy of extracellular matrix, with hardening of the vascular wall.* Atherosclerosis affects at the beginning the subendothelium, but then it spreads to the rest of the arterial wall, affecting only large and medium-caliber arteries.

First step: accumulation of lipids in the subendothelium. Normally there is an active trans-endothelial traffic of lipoproteins between the vessel lumen and the subendothelium, mainly through pinocytic vesicles hatching on the luminal surface of the endothelial cell and trapping lipoproteins containing apolipoprotein B100, internalizing them in the cytoplasm, and later, opening in the abluminal side, depositing their lipid load in the subendothelial space. Vesicles can coalesce forming real tunnels that cross the entire endothelial cell. Furthermore, sometimes the firm intercellular junctions, composed by union proteins, are broken, increasing endothelial permeability, and easily giving way to large protein molecules (paracellular traffic).

Second step: the entrapment of lipoproteins in the subendothelial space. Subendothelial extracellular vascular matrix (ECM) is composed by numerous substances, as elastin, collagen, and proteoglycans (chondroitin sulfate, dermatan, aggrecan, and heparan, among others). Low density lipoproteins (LDL), principally those small and dense particles, have a great affinity for some of the proteoglycans, and are trapped in fibrous network during a long period.

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Third step: oxidation modification of the trapped lipoproteins and inflammation. Reactive oxygen substances (ROS) are generated constantly during metabolism. Small and dense LDL particles are particularly prone to oxidative modifications. If just a few of the polyunsaturated fatty acids that are part of phospholipids, the most numerous components of the lipoprotein coating, undergo a process of oxidation, the entire particle is no longer recognized as a native substance, and in consequence unleashes a complex inflammatory and immune response. The minimally modified LDL particle (LDLmm) is then furthermore oxidized (LDLox), damaging all biomolecules within reach. The degradation of lipoprotein lipids forms a series of catabolic waste compounds, as phosphatidylcholine (LPC), which plays numerous and tangled roles in inflammation and atherogenesis. Its activities involve several cells like macrophages, vascular myocytes, white blood cells, and inclusive endothelial cells, regulating cell cycle, inflammation, immunity response, cell proliferation, and oncogenesis. Seems that LPC has a specific membrane receptor named G2a, member of the superfamily of G protein coupled receptors (GPCR). The interaction of LPC in its receptor initiates an intracellular signal cascade responsible of an inflammatory reaction and activation of target cells. In addition, LPC, other oxidized phospholipids, and LDLox, bind to Toll-like receptors, part de the pattern recognition receptors, which also awake an inflammatory response. In addition, since early atherogenesis, an autoimmune response, involving innate and adaptative components is unshackle. Moreover, cholesterol entrapped in the subendothelium crystallizes, and some of these sharpen microcrystals can cross the endothelial layer, causing small tears and holes through which LDLox can escape to bloodstream. LDLox acts as one the multiple ligands for the LOX-1 receptor, which is mainly placed in the caveola rafts of the endothelial cell membrane. The activated LOX-1 receptors start several signal pathways, eliciting endothelial dysfunction, oxidation, inflammation, apoptosis, autophagia, and expression of diverse cytokines, and molecules of monocyte attraction.

Fourth step. Activation of endothelial cells. Atherosis is completed when in additions to lipid accumulation, the activated endothelial cells, secrete several substances that attract monocytes to the vascular wall, immobilize them on the surface and impulse their translocation to the subendothelium. The monocytes, converted now in resident macrophages, gobble up the oxidized fat through pinocytic vesicles, phagocytosis, and scavenger receptors, until they are transformed in the so-called foam cells, pilled of lipids.

Fifth step. The response to the first injury. The body reacts to this primary injury, first sending macrophages to retire the extracellular fat. Macrophages are part of the mononuclear phagocyte system, in charge of eliminate foreign proteins and other type of debris from the blood and tissues. Angiotensin II (called the «honorary cytokine») plays a crucial role in this inflammatory reaction, as it is involved, among other actions, in the activation of oxidases and production of ROS, and in the awakening of the nuclear factor kappa B (NF-kappa B), a multiple transcription protein, capable of elicit a powerful inflammatory and immune response. At the beginning of atherogenesis, there is a dialectic confrontation between macrophage retention and its migration out of the vessel wall. As the process go on, the resident macrophages (mainly type 1, proinflammatory) loss mobility and remain confined in the atherosic lesion (the so-called «lobster trap»). Some of them initiate an apoptotic or necrotic dissolution, scattering their intracellular content in the nearby area: remains of the lysate proteins, oxidized lipids, and oxidized cholesterol, that together with the cellular debris form the necrotic core of what will be the atheroma. Myointimal cells (those migrant myocytes that changed their phenotype from contractile to secretory type) also have the capacity to scavenge lipids and convert themselves in foam cells. The latter produce all kind of tissue-harming substances: ROS, proinflammatory, proapoptotic and proautophagic cytokines, and ECM destroying enzymes like matrix metalloproteinases (MMP, as elastases, collagenases, gelatinases, fibronectinases, among others), which erode and debilitate the extracellular matrix. Teleologically, it seems that

this reaction tries to clear the way out to foam cells. But even if macrophages remain in the lesion, all these histotoxic substances damage the endothelium, first only functionally, but later also its anatomical structure. Endothelial denudation attracts and activates platelets, that not only initiate the first phase of coagulation paving the destroyed endothelium layer, but also through the secretion of growth factors (also coming from endothelial and myointimal cells). The substances launch a reparative, scaring process, stimulating the growth, proliferation, and mobilization of vascular myocytes and the fibrous dystrophy of the ECM. In this manner, the atherosclerotic plaque or atheroma is formed: an oxidized lipid and a necrotic debris core, with numerous inflammatory cells, cytokines, cholesterol crystals, tissue destroying enzymes, covered by a fibromuscular covering.

Sixth step. Evolution and destiny of the atheroma. Once the mature atherosclerotic plaque is formed (atheroma), its evolution can take several pathways. The young, soft, lipid-laden, inflamed plaque regularly has a very thin and fragile fibromuscular cap, likely to break up. It is called vulnerable plaque and its fracture induces a clot formation, which on many occasions shut down the lumen and unlashes an acute coronary syndrome. But there are many occasions in which the thrombus is limited or dissolved, and the fracture is spontaneously repaired. Other times, the plaque evolves slowly, decreasing its lipid content and inflammation, and thickening, hardening, and calcifying the fibrous cap. These phenomena make less possible the plaque rupture but compromise functional arterial lumen. The young plaques experiment an eccentric grow that do not reduce importantly the inner caliber of the vessel, while the hard, older atheroma grows concentrically, even up to the complete fibrotic closure of the artery.

Seventh step. Forces involved in atherogenesis and plaque fracture. There are two kinds of forces involved in plaque fracture. Some, internal, have already been mentioned: inflammation, and the lysis of ECM by tissue damaging enzymes. Others, are hemodynamic forces, playing in two different scenarios. Oscillatory perpendicular stress is a mechanical force applied to the thickness of the vessel wall, which depends on differential blood pressure and is governed by the Laplace's law ($S = [P \bullet r]/2h$, where S is the stressful force, P, systolic blood pressure, r, the cavity radium, and h the wall thickness). As the atherosclerotic plaque bulge into the lumen, the internal radius of the artery is smaller at the top of the atheroma and larger just at the site adjacent to the healthy vascular wall (the shoulder of the plaque). In this site, the sum of the accumulation of inflammatory cells and MMPs debilitating further the ECM and the perpendicular stress, conjugate to break up the cap. For these reasons, the plaque shoulder is the favorite place in which a perpendicular tear occurs. Other important mechanical factor is shear (misnamed «shear stress», because is not a force applied to the vessel thickness, but instead it is a tangential force on the surface of arterial inner layer). Normally, in most vessels flow is laminar, which means that hydric molecules are arranged in horizontal layers, rolling one over another. The flow stream has a parabolic front, since the liquid layers closest to the walls of the vascular container are slowed down by friction on the surface, and at the same time, the inner layers, free of shear, run faster. This frictional, «ironing» force is recognized by mechanoreceptors, arising signals that induce the normal development of the endothelium: its cells are arranged in an orderly direction in the same sense of flow current, have similar morphology and sizes, and very tight intercellular junctions. As well, the endothelium operates normally, secreting anti-inflammatory, antithrombotic, and antiproliferative substances. When laminar flow is lost and it is transformed in a disturbed, non-laminar one, shear is low and occurs the opposite; there is a derangement in the orientation of the endothelial cells, their size varies, and the intercellular junctions become looser and more distant. Furthermore, endothelium dysfunctions, and secretes «rogue» substances proinflammatory, prooxidants and proliferative. For that reason, in sites of low shear (for example, on external walls borders of bifurcations and branches) the development of atherosclerotic lesions is more commonly observed. But when shear is abnormally augmented there are also consequences:

platelets are activated, and the cutting effect of friction can cause longitudinal tears in the endothelial aspect of the atheroma.

Eighth step. Regression of some atherosclerotic lesions. Anichkov was the first who linked atherosclerotic lesions with cholesterol in rabbits fed with this lipid. He also documented that when experimental rabbits were returned to their normal vegetarian diet, lesions regressed dramatically. Recent studies utilizing intravascular ultrasound, a technique that allows to measure plaque volume, have shown that statins and PCSK9 antibodies can induce a small anatomical regression of the plaque, and a concomitant intraluminal gain. Notwithstanding, more important is a «biochemical regression», in which vigorous lipid treatment lessens the cholesterol content in the plaque, which in turn reduces inflammation, oxidation, and apoptosis, leading to less vulnerability to rupture and therefore a lower incidence of acute vascular syndromes.

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