Atherosclerosis 234 (2014) 311–319

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Pathology of human plaque vulnerability: Mechanisms and consequences of intraplaque haemorrhages

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ARTICLE INFO

Article history:
Received 20 November 2013
Received in revised form
4 March 2014
Accepted 17 March 2014
Available online 27 March 2014

Keywords:
Red blood cells
Proteases
Neo-angiogenesis
Phagocytosis

ABSTRACT

Atherothrombotic diseases are still major causes of inability and mortality and fighting atherothrombosis remains a public health priority. The involvement of repeated intraplaque haemorrhages (IPH) in the evolution of atherothrombotic lesions towards complications was proposed as early as 1936. This important topic has been recently revisited and reviewed. Histological observations have been corroborated by magnetic resonance imaging (MRI) of human carotid atheroma, identifying IPH as the main determinant of plaque evolution towards rupture.

Beside the intimal integration of asymptomatic luminal coagulum, inward sprouting of neovessels from the adventitia towards the plaque, is one source of IPH in human atheroma. We recently described that directed neo-angiogenesis from the adventitia towards the plaque, across the media, is initiated by lipid mediators generated by the plaque on the luminal side, outwardly convected to the medial VSMCs. Subsequent stimulation of VSMC PPAR-γ receptors induces VEGF expression which causes centripetal sprouting of adventitial vessels. However, this neovascularization is considered to be immature and highly susceptible to leakage.

The main cellular components of IPH are Red Blood Cells (RBCs), which with their haemoglobin content and their cell membrane components, particularly enriched in unesterified cholesterol, participate in both the oxidative process and cholesterol accumulation. The presence of iron, glycophorin A and ceroids provides evidence of RBCs. IPH also convey blood leukocytes and platelets and are sites prone to weak pathogen contamination.

Therefore prevention and treatment of the biological consequences of IPH pave the way to innovative preventive strategies and improved therapeutic options in human atherothrombotic diseases.

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http://dx.doi.org/10.1016/j.atherosclerosis.2014.03.020
0021-9150/

1. Introduction: phylogeny of the arterial system and teleonomic consequences

Atherothrombotic diseases are still major causes of inability and mortality [1] and fighting atherothrombosis remains a public health priority. Conceptually, one can consider these diseases as the downside of a teleonomic success that has seen the circulatory system evolving from the simple diffusion of extracellular fluid in invertebrates, via a low-pressure circulating system animated by an archaic heart in fish, to a highly organized system with organ-regulated directional blood flow propelled through blood vessels with a defined wall structure by the pumping action of the mammalian heart. Indeed, the mechanistic and structural evolution that has enabled autonomous blood flow regulation in response to the metabolic demand of a given organ is also responsible for the initiating event of atherothrombotic diseases, the deposition and retention of atherogenic material in the arterial wall [2]. Arterial blood pressure, the necessary condition for regulation of tissue-specific perfusion, is also responsible for the outward hydraulic conductance and its corresponding unidirectional mass transport, in which circulating soluble molecules are outwardly, radially convected across the vessel wall [3]. Unfortunately, the molecules conveyed according to the pressure gradient existing between the lumen and the adventitia of blood vessels [4], include not only physiological nutrients but also circulating lipoproteins transporting phospholipids and cholesterol, such as LDL particles. The retention of such particles within the intimal layer is due, in part, to its enrichment in hydrophilic glycosaminoglycans [5] secreted by the stromal cells of the arterial wall, the vascular smooth muscle cells (VSMCs) [6] and their interactions with apolipoprotein B [7]. In this context, haem with its bound iron is probably the most significant oxidant of unsaturated fatty acids from phospholipids in LDL trapped in the intima after their association with intima proteoglycans [8,9]. Therefore, despite being essential structural and functional components of the vessel wall, VSMCs also support the initial lipid injury [10], notably by forming foam cells due to their ability to take up LDL by endocytosis [11–14]. Furthermore, in response to the outward convection of atheroma-generated mediators, VSMCs conversely mediate inwardly directed pathological remodeling of the arterial wall, such as the centripetal migration of VSMCs from the media to the intima and endothelial sprouting from the adventitia in the direction of the media (Fig. 1). As described in detail below, this latter process gives rise to the neovasculature, which is, at least in part, ultimately responsible for intraplaque haemorrhages (IPH).

However, one should bear in mind that besides the inherent drawbacks of the highly evolved human vascular system, atherothrombotic diseases are largely fuelled by another type of evolution, that of human behaviour that has led to the emergence of typically human risk factors, such as the so-called western diet or smoking. The fact that atherothrombotic diseases ensue from the unique combination of the aforementioned features of the mammalian circulatory system and human behaviour-related risk factors probably explains in part the difficulty of finding animal models that precisely recapitulate all the associated pathological processes. In particular, plaque neovascularization, IPH, and plaque rupture, three highly intertwined events that precipitate the evolution and clinical expression of atherothrombotic diseases, do not occur in hypercholesterolemic mice, the most commonly used model for atherosclerosis. For these reasons, most relevant data on IPH comes from clinical studies and analysis of human tissues. Nevertheless, a model resulting from a cross between apoE KO and fibrillin KI (Marfan) mice has been reported to develop important intraplaque neo-angiogenesis with the presence of IPH [15,16].

Besides neo-angiogenesis, another mechanism responsible for the presence of blood remnants within the atherosclerotic plaque is the incorporation of a luminal erythrocyte-rich thrombus (coagulum). Indeed, in large arteries the majority of plaque ruptures, inducing luminal thrombus formation, are clinically silent [17]. The agglutination of RBCs at the site of plaque injury probably depends on platelet aggregation. Indeed, Walker and colleagues recently showed that senescent erythrocytes could stick to immobilized platelets, via the platelet phosphatidyl receptors, CXCL16 and CD36 [18]. Thereafter, ulcerated plaques are healed by migration and proliferation of local VSMCs that accumulate at the rupture site. These VSMCs secrete an extracellular matrix rich in glycosaminoglycans and collagens, forming a fibrocellular cap, whereby the remnant coagulum is incorporated into the plaque [19]. In small

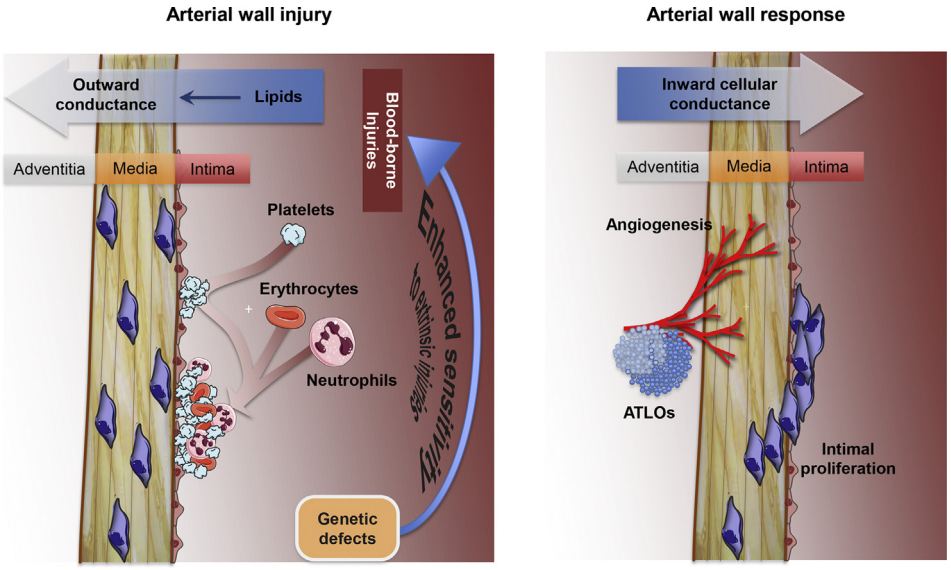

Fig. 1. Spatio-temporal paradigm of outward mass transport of blood-borne soluble mediators through the arterial wall (injury, left panel), and inward cellular migration, including migration of VSMCs from the media to the intima and sprouting of endothelial cells from the adventitia, in the direction of the plaque, through the avascular media (response, right panel).