

'Cellular dysfunction in inflammatory-related vascular disorders'**Review Series****The inflammatory process:
a new dimension of a 19th century old story****Maya Simionescu ****Institute of Cellular Biology and Pathology, Nicolae Simionescu, Bucharest, Romania*

This issue of the *Journal* launches a new thematic series focused on the processes and mechanisms that underlie the cell dysfunction in inflammatory-related vascular diseases, a timely and appropriate topic. The primary role of inflammation in vascular diseases was predicted in the 19th century by the visionary pathologist R. Virchow [1], and lately substantiated by cell biologists and pathologists. Recent new facts and unexpected data uncovered the complexity and intricacy of the cellular mechanisms and factors involved and revealed that inflammation is a more complex process than previously thought.

Cell dysfunction, a generic, non-specific term, conceals in biological systems a large array of altered functions and mechanisms as a reaction to abnormal, offensive factors that distort the internal milieu and body homeostasis. Most cells respond to aggressors by a gradual, well-programmed process whose progression and course depends on the intensity, length and extent of the insults. As exemplified by the vascular endothelial cells (EC), to aggressive factors the cells initial response is *adaptation through modulation* of their constitutive functions; *i.e.* in hyperlipemia, the EC primary reactions are the increase in transcytosis of plasma lipoproteins and biosynthetic activity. Excessive hyperlipemia leads to the failure of EC to function adequately that characterises the state of *dysfunction*; ultimately, extreme aggression typifies the altered state of *injury* and apoptosis [2].

In the attempt to protect from harmful stimuli, the tissues and cells initiate an inflammatory process. Inflammation (in Latin, setting on fire) is a complex biological process generated as a response to aggressive factors that comprises an acute and a chronic phase with different roles and finality. In acute inflammation, circulating immune cells are attracted to the damaged sites where *via* a cascade of regulatory cytokines and chemokines (predominantly activated by NF- κ B, AP-1, NFAT and STAT families) may start the healing process. Chronic inflamma-

tion encompasses a shift in the cells involved in the process, an escalation of the inflammatory response and ultimately destruction of cells and tissues; it is characteristic for numerous diseases such as atherosclerosis, rheumatoid arthritis, diabetes and others.

The vascular disorders, and in particular atherosclerosis are complex multifactorial, multigenic diseases in which inflammation plays a key role [3]. It is now widely accepted that atherosclerosis is the result of a lipid disorder and an inflammatory process that ultimately result in atheroma formation [4].

As shown in Fig. 1, the initial change that takes place in atherogenesis is the increased transcytosis and retention of LDL within and outside the meshes of subendothelial hyperplastic basal lamina [5] where, by interaction with glycosaminoglycans and proteins of the extracellular matrix, LDL particles undergo modifications (*i.e.* oxidation) and turn into pro-atherogenic modified and reassembled lipoproteins (mLp). The mLp function as neoantigens, initiating a multipart inflammatory reaction inducing the EC activation manifested by the expression of novel cell surface adhesion molecules (ICAM-1, VCAM-1, E and P selectins) and secretion of MCP-1, and subsequent recruitment of inflammatory cells (neutrophils, T lymphocytes and monocytes). Neutrophils granules released on the EC surface [6] and the cell adhesion molecules induce monocytes diapedesis, and homing within the subendothelium where they turn into activated macrophages, expressing scavenger receptors that serve in the non-regulated uptake of mLp converting the cells into macrophage-derived foam cells [7]. These cells secrete factors involved in lipid metabolism (apoE, lipoprotein lipase), inflammation (cytokines) and proteolysis (MMPs, cathepsins), which together with the subendothelial accrual of mLp, growth factors, chemokines and accretion of smooth muscle cells lead to atheroma formation (reviewed in [2]).

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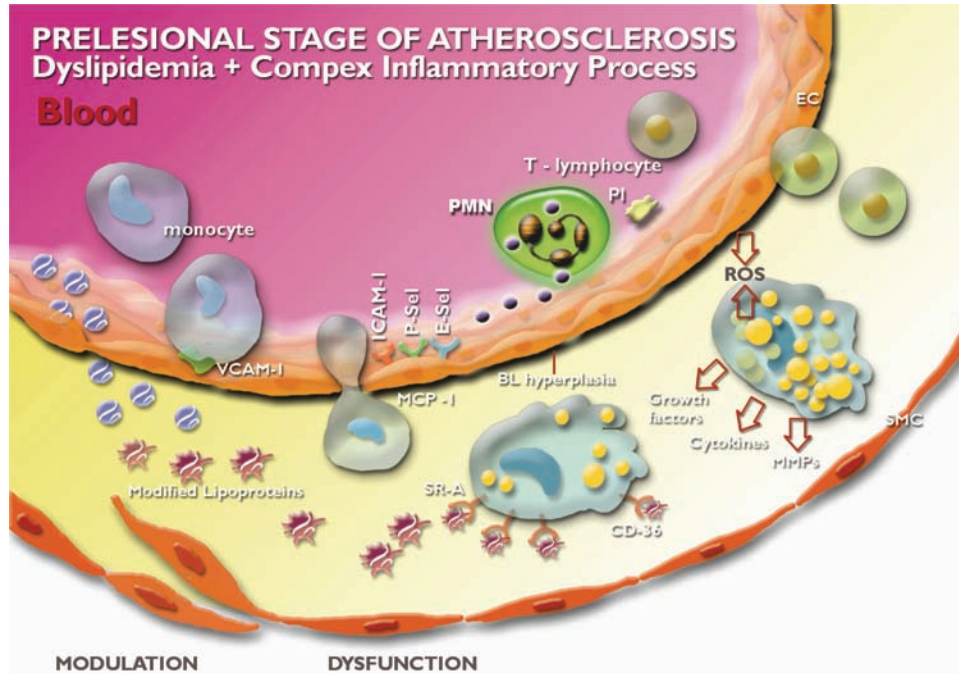


Fig. 1 Diagram depicting the initial steps and the main actors involved in the prelesional stage of atherosclerosis: endothelial cells (EC), polymorphonuclear leukocyte (PMN), monocytes, platelets (PI), smooth muscle cells (SMC).

If not reversed, chronic inflammation regulates the thrombotic complications of atherosclerosis. Pro-inflammatory cytokines produced by inflammatory cells impair the capacity of smooth muscle cells to synthesize collagen and concomitantly augment the macrophage synthesis of interstitial collagenases (MMPs 1, 13 and 8) and of CD40-ligand-stimulated tissue factor expression and secretion thus participating to the thinning and disruption of the plaque fibrous cap and subsequent thrombosis [reviewed in 8]. Thus, inflammation has a key role during the entire process of plaque development and in addition, favours the life-threatening thrombus formation.

Targeting specifically the inflammatory cells and pro-inflammatory molecules is a promising venue in the quest for novel anti-

inflammatory drugs, immunosuppressant agents, or vaccines for prevention, reversal or slow-down of vascular disorders.

This series, distinguished by comprehensive reviews written by some of the most authoritative scientists in the field, and highlighting the recent data to be translated in medical applications and diagnosis, will be a rich source of inspiration for all professionals interested in vascular diseases.

I reverently dedicate this review series to all scientists who contributed to our understanding of the elementary patient – the diseased cell – and in particular, to my mentors, outstanding scientists whose work had a major impact in cell biology and pathology of the vascular system, Professor George E. Palade and Professor Nicolae Simionescu.

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