

Current concepts of atherogenesis

C. C. Kartha

A progressive arterial lesion, atherosclerosis is the primary trigger for a wide range of common clinical syndromes that have potential lethal or crippling course. Hence, it is not surprising that considerable efforts are under way to decipher its genesis. Our understanding of atherogenesis has remarkably improved in recent years thanks to multidisciplinary approach and application of molecular biology techniques. The focus has now shifted from circulating lipids to cells in the arterial wall. Much light has been shed on the role of macrophages, growth factors, adhesion molecules and cytokines (Figure 1).

The archetypal lesion of atherosclerosis is a raised fibrolipid plaque in the inner wall (intima) of the arteries. The plaque

results from a building up of smooth muscle cells, macrophages, cell debris, extracellular matrix, cholesterol, and cholesteryl esters underneath the endothelial inner lining of arteries. The fundamental pathologic features are:

- 1) focal nature and characteristic distribution of lesions in blood vessels;
 - 2) predominant intimal manifestations;
 - 3) heterogeneous nature of the plaque constituents, and
 - 4) the presence of both proliferative and degenerative processes in the lesion.
- Two key events have been recognized in the genesis and progression of the atherosclerotic plaque. They are (i) entry into and retention in the vessel wall of intra and extracellular lipids which are

derived from the plasma, and (ii) monoclonal proliferation of smooth muscle cells within arterial intima with consequent synthesis of extracellular connective tissue elements.

Experimental studies suggest that the changes that occur in the arterial wall in the course of atherosclerosis are probably a reaction to injury to the endothelium. The endothelial injury may result in either loss of the lining cells or their dysfunction. The injury as such could be mediated by infections, immune mechanisms, mechanical disturbances in blood flow or chemical toxins.

Search for early events in atherogenesis received a new impetus with the discovery that the most important cell in atheroge-

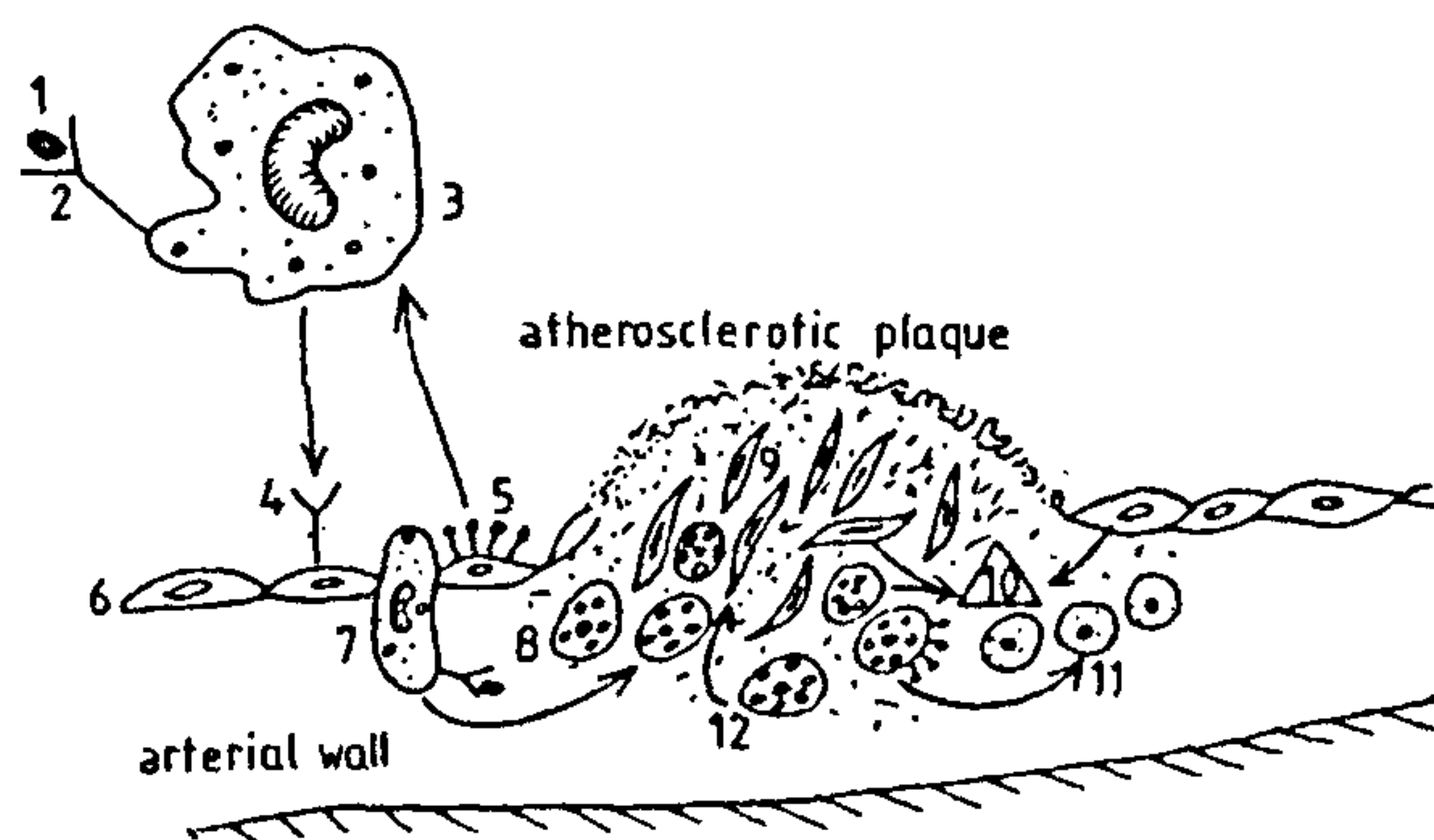


Figure 1. Schematic diagram of sequence of events in atherogenesis 1, Low density lipoprotein; 2, Scavenger receptor; 3, Monocyte; 4, Vascular cell adhesion molecule; 5, Monocyte chemoattractant factor; 6, Endothelium; 7, Monocyte migrating into arterial wall; 8, Foamy macrophage; 9, Smooth muscle cell; 10, Macrophage colony stimulating factor; 11, Newly recruited macrophages; 12, Macrophage-derived growth factors

nesis is the macrophage. Macrophages are not normally present in the arterial wall and are derived from the monocytes in circulating blood. They constitute a significant proportion of cells in atherosclerotic lesions. In addition to scavenging, which is their main function, the macrophages can also secrete cytokines with diverse functions. They can produce two potent stimulants for smooth muscle cell growth, viz. the platelet-derived growth factor (PDGF) and heparin binding epidermal growth factor (EGF).

The earliest lesions in atherogenesis are generally agreed to be the focal 'sticking' of monocytoïd cells to the luminal surface of the endothelial cells and the migration of the monocytes (diapedesis) into the subendothelial space in the arterial wall¹.

The mechanisms whereby macrophages infiltrate the vessel are beginning to be understood. The initial migration of monocytes into subendothelial space is probably mediated by the monocyte chemoattractant protein (MCP) synthesized by the endothelial cells in the presence of low density lipoprotein (LDL)^{2,3}. Interestingly, the production of MCP can be inhibited by high density lipoprotein (HDL), as well as antioxidants.

Another possibility of monocytes gaining entry into the arterial wall is through expression of cell adhesion molecules. The vascular endothelial cells can inducibly express a gene for a monocyte adhesion molecule⁴. The adhesion molecules which include both intercellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are induced by cytokines like interleukin-1 and tumour necrosis factor (TNF) derived from inflammatory cells. It has been demonstrated that ICAM-1 expression is increased also in both endothelial and other cells of atherosclerotic plaques⁵. The adhesion of blood monocytes to these molecules is receptor-mediated. *In vitro* studies have also shown that endothelial cells synthesize adhesion molecules in response to

scavenger receptor ligands on macrophages, thrombin and activated platelets.

The monocytes which enter the arterial wall transform into macrophages which express high levels of a receptor activity (macrophage scavenger receptor) which can mediate the endocytosis of chemically modified or oxidised LDL⁶. The macrophages thus get converted themselves into the foam cells, typically seen in large numbers in atherosclerotic lesions. When the scavenger receptor is occupied, the macrophages are stimulated to secrete various cytokines and growth factors. In addition to secretion of cytokines, macrophages in atherosclerosis are also activated to produce c-fos, apolipoprotein E as well as tumour necrosis factor. The cells also express major histocompatibility complex and leucocyte differentiation antigens and are thus capable of responding to activating signals associated with inflammatory and immune events.

Macrophages in atherosclerotic lesions can produce mediators that may contribute to lesion formation and its progression. They have been shown to express and secrete monocyte chemoattractant protein which is capable of attracting blood monocytes to the site of its production⁷. Another important factor expressed and secreted by the macrophages is a glycoprotein, the macrophage colony stimulating factor (MCSF).

MCSF is also produced by vascular endothelial cells and smooth muscle cells. It has been demonstrated that macrophages, smooth muscle cells and endothelial cells resident within atherosclerotic plaques express MCSF mRNA and immunoreactive protein⁸. A variety of stimuli can activate the arterial plaque cells to produce substantial amounts of MCSF. The local production of MCSF during atherogenesis may contribute to macrophage adherence, infiltration, survival and proliferation or activate specific macrophage functions such as expression of the genes encoding scavenger receptor and secretion of apolipoprotein E⁹.

The observations that the expression

of MCSF could be stimulated in endothelial cells, macrophages and smooth muscle cells by oxidised LDL¹⁰ and that the macrophages themselves are capable of oxidising extracellular LDL, suggest how the cycle of events is perpetuated and the lesions can further progress.

But it still remains mysterious why the monocytes stick to the endothelium. Is it to carry the lipid into the arterial wall?

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C. C. Kartha is in the Division of Pathology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram 695 011, India.