The pathogenesis of atherosclerosis

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Abstract

Atherosclerosis is a chronic, inflammatory disease of the arterial wall that underlies many of the common causes of cardiovascular morbidity and mortality, including myocardial infarction (MI), and cerebrovascular and peripheral vascular disease. Early pathological descriptions viewed atherosclerosis as an end-stage degenerative process that inevitably resulted in a generalized narrowing of the arterial lumen. However, progress in our understanding of the pathophysiology and the underlying cellular and molecular mechanisms has revealed that atherosclerosis is a dynamic biological process. The identification of key roles for the endothelium, inflammation and vascular smooth muscle cells (VSMC) in plaque biology has indicated that the cellular composition and biology of the plaque are more relevant to disease progression and complications than luminal narrowing alone, which offers new opportunities to modify and treat different aspects of the disease process.

Keywords Atherosclerosis; cholesterol; endothelium; inflammation; nitric oxide

What's new?

- Endothelial-derived nitric oxide is critical for maintaining an anti-atherogenic environment in the vessel wall
- Inflammatory cell recruitment is a key determinant in the initiation and progression of atherosclerosis
- Statin treatment modifies and stabilizes plaques by reducing cholesterol concentrations, decreasing inflammation and improving vascular function
- Genome-wide association studies are revealing novel disease mechanisms and may identify new therapeutic targets for the treatment of atherosclerosis
- Modulation of miRNA may provide new therapeutic targets and circulating miRNA may be useful biomarkers for atherosclerosis

The normal vessel wall and endothelial function

A normal, healthy artery comprises three layers:

- endothelial cell layer (tunica intima) — a monolayer of endothelial cells and their basement membrane, which lines the lumen of all blood vessels
- media (tunica media) — concentric layers of vascular smooth muscle cells (VSMC), elastin fibres and extracellular matrix that control vascular tone
- adventitia (tunica adventitia) — surrounding layer of connective tissue, containing micro-vessels (*vasa vasorum*), and related to perivascular adipose tissue. May be an important site for inflammation and angiogenesis.

Endothelial cells act as an interface and functional link between circulating blood and the rest of the vessel wall; alterations in their phenotype can have dramatic effects on vessel wall function. Nitric oxide (NO) is one of the most important signalling molecules produced by the endothelium (Figure 1) and has multiple effects on:

- vascular smooth muscle cells — relaxation and inhibition of proliferation
- platelets — inhibition of activation and aggregation
- inflammation — inhibition of cell adhesion and migration.

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Pathogenesis of atherosclerosis

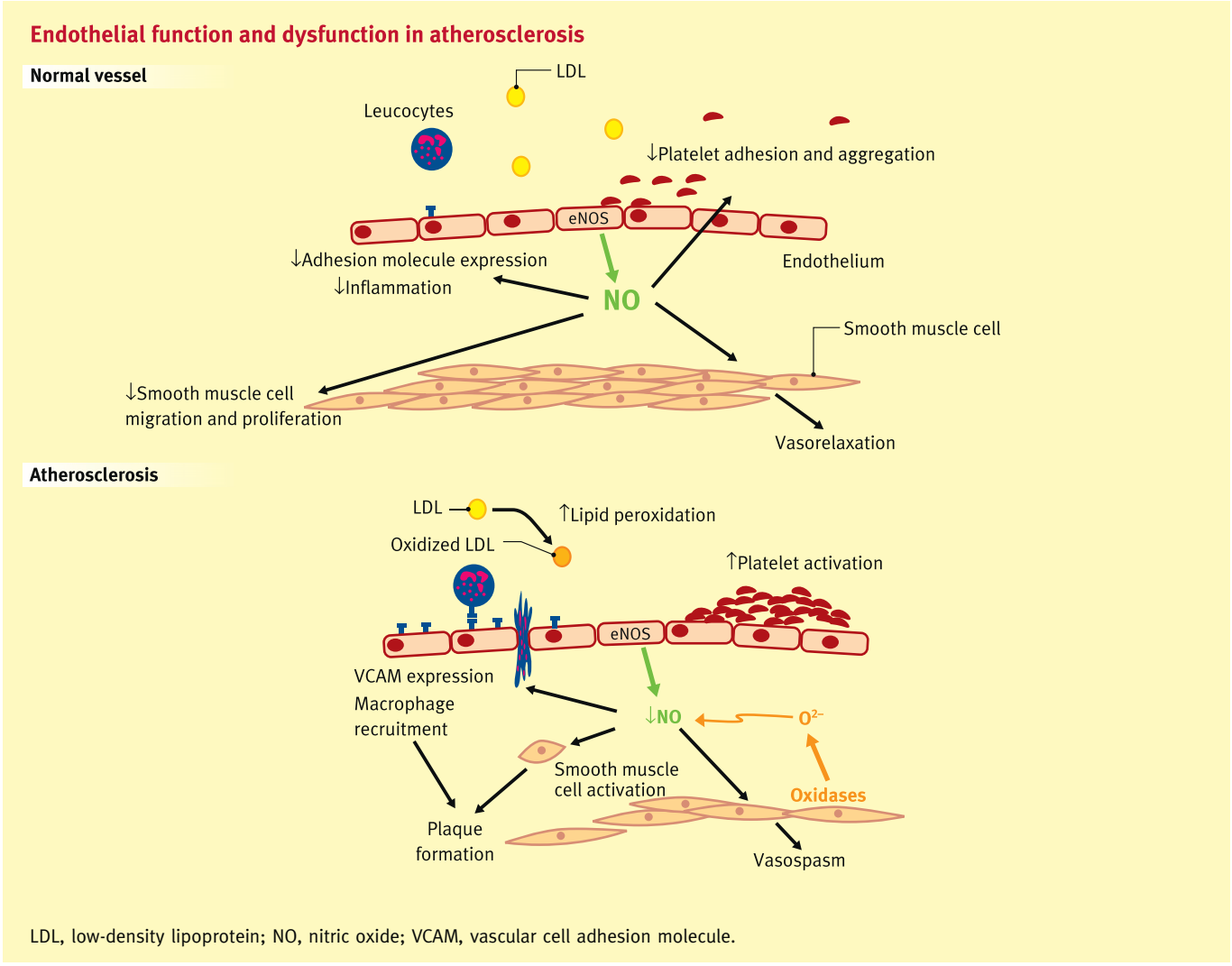
Atherosclerosis is a disease of large and medium-sized arteries, characterized by endothelial dysfunction, vascular inflammation and the accumulation of modified lipid, inflammatory cells and cell debris in 'plaques' within the vascular wall. Plaques are usually found only at specific sites in the vasculature, such as curvatures and bifurcations, characterized by non-laminar (turbulent) flow and reduced shear stress. In these regions endothelial cells undergo endoplasmic reticulum stress with decreased atheroprotective NO and increased superoxide production. This results in an increase in endothelial cell turnover, permeability and lipid accumulation in the sub-endothelial space.[1]

Low-density lipoprotein (LDL) is susceptible to modification, particularly by oxidation, resulting in oxidized LDL (oxLDL). Monocytes entering the plaque proliferate, differentiate into macrophages and take up oxLDL to form foam cells that potentiate the inflammatory response, leading to fatty streak formation — the first stage in plaque development. OxLDL is taken up by macrophage scavenger receptors that are not down-regulated as the cell increases cholesterol content. Death of foam cells leads to the formation of a necrotic lipid core within the intima. In response to cytokines and growth factors, some atherosclerotic plaques accumulate VSMC, which migrate from the media layer, proliferate and synthesize extracellular matrix proteins such as collagen and elastin. VSMC migration and proliferation may contribute to luminal narrowing but also to the formation of a strong fibrous cap, which maintains plaque stability by isolating the lipid core from circulating blood. These factors contribute to the growth and stability of the plaque (Figure 2).

Endothelial dysfunction in atherosclerosis

Endothelial dysfunction occurs at sites where the endothelial cell layer has been injured (low or non-laminar shear stress) and/or exposed to metabolic or chemical stress (diabetes mellitus, high serum cholesterol, effects of cigarette smoke), and is evident before the appearance of atherosclerotic plaques. Clinically, endothelial dysfunction is measured by abnormalities in endothelial-dependent vasodilatation.

Endothelial dysfunction is also associated with increased generation of reactive oxygen species, particularly superoxide.



LDL, low-density lipoprotein; NO, nitric oxide; VCAM, vascular cell adhesion molecule.

Figure 1

NO reacts rapidly with superoxide radicals to form peroxynitrite ($ONOO^-$), which has damaging effects on proteins and lipids and also removes NO from the blood vessel wall before it can bind to soluble guanylate cyclase. Although it is well recognized that superoxide has an important role as a signalling molecule in normal vascular function, excess production is highly pathological and linked to the progression of atherosclerosis.[1] Other contributors to reduced NO production include deficiency of essential co-factors for eNOS function (e.g. tetrahydrobiopterin) and reduced availability of the substrate L-arginine.

Inflammation and atherosclerosis

Monocytes and macrophages

Monocytes are produced in the bone marrow and circulate in the blood. Resident monocytes are also found in healthy arteries, where they patrol healthy tissue for sites of inflammation.[2] In response to oxLDL, local tissue produces chemokines that direct monocytes to areas of inflammation where they differentiate into macrophages and proliferate, further increasing monocyte recruitment. In genetically altered mice, inhibition of chemokine receptors results in almost complete prevention of macrophage accumulation and atherosclerosis. Once differentiated into macrophages, monocytes produce pro-inflammatory cytokines and take up oxLDL, leading to foam cell formation and plaque progression as previously described. It used to be thought that, once present, macrophages could not leave the plaque and that plaques could only progress and not regress, but it is now established that macrophages can leave the plaque in response to chemo-attractant signals such as CCR7. In addition, macrophages can offload cholesterol to circulating acceptors such as high-density lipoprotein (HDL) via reverse cholesterol transport, thereby decreasing lipid accumulation within the plaque.[3]

T cells

T cells are a subset of lymphocytes found in the adventitia of healthy non-diseased arteries, which play a central role in cell-mediated immunity. T cells have been found to also play a role in mature plaques. T-helper (T_h) 1 cells secrete a number of inflammatory pro-atherogenic cytokines (e.g. interferon-γ and tumour necrosis factor [TNF]), whereas regulatory T cells (T_{reg}), which secrete IL-10 and transforming growth factor (TGF)-β and are essential for controlling or dampening immune responses, are beneficial. Adoptive transfer of T_{reg} cells to $ApoE^{-/-}$ mice