The pathogenesis of atherosclerosis

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Abstract

The hypothesis that atherosclerosis is a 'response to injury' is now generally accepted. This paper briefly reviews factors that can damage the vascular endothelium plus the formation of fatty streak lesions, thrombogenic surfaces, fibrous plaques and complex advanced lesions of atherosclerosis. © 1997 Elsevier Science Ireland Ltd.

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1. Introduction

The pathologic appearance and clinical implications of atherosclerosis have been known for at least a century. However, understanding of the cellular and molecular mechanisms has been very largely a product of the last twenty years. Much of it has been derived from the work of Russell Ross and his colleagues at the University of Washington in Seattle and their contribution will form a central part of this brief review. In 1973, Ross and Glomset [1] proposed the hypothesis that atherosclerosis is a 'response to injury', specifically, of injury to the vascular endothelium. The hypothesis has been repeatedly revised and modified and is now accepted as a general concept by most investigators in this field [2]. One of the most significant changes in recent years has been the increasing number of recognized injurious agents, which are, of course, also 'risk factors' for atherogenesis.

2. The 'response to injury' hypothesis

In its most recent form, this hypothesis can be summarized as follows: (1) Many factors can damage and activate the endothelium (Table 1 lists those currently recognized, but the list will no doubt be extended); (2) endothelial dysfunction leads to increased permeability so that lipids (mostly as lipoprotein particles) and circulating cells (particularly monocytes that become macrophages in the vessel wall and T lymphocytes) enter the subendothelial space and form the initial characteristic lesion of atherosclerosis, the fatty streak; (3) as cell numbers increase, together with lipid accumulation, there may be increased endothelial disruption leading to thrombogenic surfaces to which platelets adhere; (4) platelets, macrophages, endothelial cells and probably smooth muscle cells (SMCs) themselves can all release growth modulatory factors, leading to proliferation of SMCs and fibroblasts and (5) this process leads to the formation of the fibrous plaque and ultimately to the complex advanced lesion of atherosclerosis. This includes all of the cell types mentioned above, together with large quantities of extracellular matrix proteins, such as collagens, and free
Table 1
Causes of endothelial injury or dysfunction

- Hyperlipidemia (especially low-density lipoproteins, [LDL] lipoprotein [a])
- Diabetes (hyperglycemia, dyslipidemia)
- Hypertension
- Smoking
- Hyperhomocysteinemia
- Ischemia/reperfusion
- Viruses (?)

Fig. 1. Schematic representation of the progression of atherosclerosis, based on Ross’ ‘response to injury’ hypothesis. M, monocyte/macrophage; E, endothelium; S, smooth muscle cell (later stages with lipid droplets); F, foam cell; P, platelet; L + C, core of extracellular lipid with calcification; X, collagen and other extracellular matrix proteins. Progression may not necessarily be linear in the sequence indicated (see Fig. 2).

and esterified extracellular cholesterol. It is thought that lesions with large amounts of such lipids are particularly unstable and liable to rupture, leading to thrombosis and vessel occlusion. The hypothesis is shown schematically in Fig. 1, and the possible interrelationship of the stages of the lesion are shown in Fig. 2.

It is likely that all of the stages of this process are potentially reversible, at least in part. Ross [2] has described atherosclerosis as an ‘inflammatory fibroproliferative process’, essentially a repair mechanism that becomes harmful, at least in part, because of the chronic and unremitting nature of the injury, for instance, hyperlipidemia or smoking.

3. Cellular interactions and mechanisms

3.1. Endothelium

The increased knowledge about atherosclerosis has paralleled the explosion of interest in the endothelium and the realization that it is far more than an inert cellular barrier. Nonetheless, it is clear that among the vital functions of the endothelium is maintenance of a non-thrombogenic surface for platelets, which is also non-adherent for neutrophils [3]. Of course, the endothelium is also a permeability barrier, but one that is highly dynamic and regulated. The most dramatic advances have come with the realization that endothelial cells are also sources of many growth-modulatory molecules [4,5], interacting particularly with SMCs, as well as agents that regulate vascular tone [6], notably nitric oxide, prostacyclin and the endothelins. There is substantial overlap between the two groups, with many, if not most, molecules possessing activity in both areas. Broadly speaking, vasoconstrictors are growth promoting while vasodilators are inhibitory. Another recently defined, and undesirable, property of the endothelium is its capacity to oxidize low-density lipoproteins (LDL) [7].

3.2. Monocytes/macrophages

The macrophage, that is to say, the monocyte that has become ‘resident’ in the vascular wall, is the principal inflammatory cell of the atherosclerotic lesion [8]. These cells act as scavengers, internalizing lipoproteins [9], especially oxidized LDL (oxLDL), forming foam cells. In fact, macrophages may actually be the main mediators of oxidation [10]. Macro-
phages replicate within atheromatous plaques and are also rich sources of growth modulators.

3.3. Smooth muscle

In the normal blood vessel, the SMC is the only cell type found in the media. Conversely, few SMCs are found in any other vessel layer. Despite this apparent uniformity, it seems highly likely that these cells are heterogenous, with distinct embryonic origins and varying responses to atherogenic stimuli [11]. These cells are the main proliferative cell within the plaque, as well as being largely responsible for the synthesis of extracellular matrix [12]. SMCs are often described as having two phenotypic states; 'contractile' or quiescent, their usual state, and 'synthetic' or proliferative, where the cells replicate as well as synthesize matrix proteins [13]. Although there is considerable evidence for such a distinction, it will undoubtedly prove to be an oversimplification [14]. It is also unclear how this concept relates to well-established observations that SMCs within a particular plaque are monoclonal [15]. In addition to the above activities, where autocrine growth factors may play a significant role, SMCs must also migrate from the media to the intima in response to chemotactic stimuli as the plaque is exclusively an intimal lesion [16].

Brief mention must be made of the T lymphocyte, which is found in abundance in plaques. The role of these cells remains obscure, though their numbers will undoubtedly be enhanced by proliferative cytokines secreted by nearby macrophages [8.17].

4. Oxidized LDL

All except a very few residual skeptics now accept that high circulating levels of LDL are very strongly associated with atherosclerosis. In the last decade, it has also become clear that these particles become modified to more actively atherogenic forms in the vessel wall, mostly by oxidation [18,19]. As suggested above, the macrophage is a key element in this process, as is the endothelial cell, and the extent of the oxidation has important pathogenetic implications. Highly oxidized LDL is cytotoxic to the endothelium, macrophages and smooth muscle [20], but less severely damaged lipoprotein also has the following important biological effects, though their relevance in vivo is uncertain: A mitogenic effect on SMCs [21]; chemotactic activity for these cells and for monocytes; activation of endothelial cells, with increased expression of adhesion molecules to which monocytes can attach and activation of monocytes/macrophages themselves [22]. OxLDL is therefore a very plausible participant and, indeed, initiator in the inflammatory fibroproliferative process described by Ross. It is also taken up by scavenger receptors on macrophages and probably also by a specific LDL receptor, leading to foam cell formation [9]. A similar process probably occurs in smooth muscle [23].

It must be remembered that LDL oxidation is constantly opposed by endogenous enzymatic and non-enzymatic antioxidants, even if some may not have access to the parts of the vessel wall where the lipoprotein particles are located. A particularly interesting, if largely indirect, antagonist of oxidation is high-density lipoprotein (HDL) [24] and it is tempting to suggest that this may be one mechanism by which HDL is protective in cardiovascular disease.

5. Growth modulators

Reference has been made previously to growth modulators produced by the various cell types involved in atherogenesis. Their main target is the SMC, though macrophage replication is also affected by some agents. An incomplete list is included in Table 2. The discovery by Ross et al. [25] of the most potent known smooth muscle mitogen and chemotactic agent, platelet-derived growth factor (PDGF) in fact dates from the same time as the original 'response to injury' hypothesis. Since then, there has been a vast proliferation of potential positive and negative growth regulators [2,5,23], supported by an increasing body of information on the expression of genes for the factors themselves and for their receptors [26], and of genes known to be involved in the proliferative process, such as the proto-oncogenes c-fos and c-myc [27]. At present, it is simply not possible to produce a coherent scheme for the multitude of possible interactions between all of these molecules and it may be some years before a clear picture emerges. The complexity is emphasized by
Table 2
Some factors that may modulate vascular smooth muscle growth

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGF* (E, S, M)</td>
<td>IL-1</td>
</tr>
<tr>
<td>bFGF* (E, S, M)</td>
<td>TGF</td>
</tr>
<tr>
<td>IGF-I (P, E, S, M)</td>
<td>IFN (M, T)</td>
</tr>
<tr>
<td>EGF/TGF (P, M)</td>
<td>Nitric oxide (E, M, S)</td>
</tr>
<tr>
<td>IL-1 (E, S, M, T)</td>
<td>Prostacyclin (E)</td>
</tr>
<tr>
<td>TGF* (P, E, S, M, T)</td>
<td>Adenosine (E, S)</td>
</tr>
<tr>
<td>VEGF* (M)</td>
<td>Heparan sulphates (E, S)</td>
</tr>
<tr>
<td>oxLDL* (E, M)</td>
<td></td>
</tr>
<tr>
<td>Angiotensin II (E)</td>
<td></td>
</tr>
<tr>
<td>Endothelin (E)</td>
<td></td>
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</tbody>
</table>

bFGF, basic fibroblast growth factor; EGF, epidermal growth factor; IGF-I, insulin-like growth factor; IL-1, interleukin 1; PDGF, platelet-derived growth factor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor; oxLDL, oxidized low-density lipoprotein; IFN, interferon.

Cells of origin: E, endothelium; M, macrophage; P, platelet; S, smooth muscle; T, T lymphocyte.

*Also has known chemotactic activity.

the appearance of two agents, interleukin-1 and transforming growth factor, as both growth stimulants and inhibitors, depending on the circumstances; it is very likely that many other modulators can also be bidirectional in their effects.

6. Problems and prospects

We now have a far clearer picture of the nature and mechanisms of atherosclerosis, but many details are still sketchy. For instance, has the importance of cell proliferation been overstated and should we be more interested in remodeling, where the vessel lumen is reduced but the mass of the vessel wall does not increase? This may in fact have greater relevance for the problem of restenosis following coronary angioplasty than for primary atherosclerosis [28]. As indicated above, we do not know which growth factors really matter. Even more importantly from a clinical standpoint, there are outstanding therapeutic questions. It is evident that reducing levels of circulating lipids, notably LDL, cholesterol and triglycerides, reduces cardiovascular morbidity and mortality [29,30]. But what else would be helpful? There has been much interest in antioxidants, especially in the hope that they may prevent LDL oxidation, but the issue is very far from being resolved [31]. There is also the proposition that existing cardiovascular drugs, such as calcium channel blockers [32], may have additional antiatherosclerotic effects. The clinical significance of these intriguing concepts still remains to be determined.

References


