Acute Coronary Syndromes: Molecular Basis for Cardiac Risk Factors

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Evolution of the Atherosclerotic Plaque

The path that leads from the initiation of an atherosclerotic plaque to an acute coronary event proceeds from a period of plaque formation to an episode of plaque rupture. Plaque disruption then initiates a number of physiologic responses, including activation of vasomotor, coagulation, and inflammatory control systems. Each of these processes is modified by both local and systemic factors. When plaque rupture is sufficiently severe to produce flow-limiting stenosis of the affected vessel, an acute coronary event ensues, the clinical sequelae of which are also modified by a number of factors. Based on the "response-to-injury" hypothesis described by Ross [32], Fuster et al. [9] and the American Heart Association have proposed and adopted a five-phase paradigm describing these events, which is now reviewed (Table 1).

Phase 1: The minimal plaque

The early atherosclerotic plaque is characterized by the accumulation of lipid material, mononuclear cells, and vascular smooth muscle cells (VSMC) within the vessel wall in a manner that does not encroach upon the vessel lumen. This process is thought to be initiated by a low level of chronic endothelial injury, resulting in impaired endothelial function [32]. Both local and systemic factors contribute to and modify this process. Local factors of importance include the vessel anatomy [14,32,34] (e.g., bifurcations) and vasomotor tone [35–37]. Systemic factors of importance include hypertension, hyperlipidemia, high levels of circulating glycosylated products (especially in diabetics), and chemical irritants, such as those contained in cigarette smoke [5,38]. Endothelial injury allows permeation by lipids (largely low-density lipoprotein (LDL) and lipoprotein a [Lp(a)]) and mononuclear cells into the vessel wall [9,32]. This initiates a positive feedback loop exacerbating the damage, because LDL (particularly oxidized LDL) induces tissue mononuclear cells to attract and activate more mononuclear cells from the vessel lumen [39–42]. Activated monocytes also release a large number of substances (e.g., free radicals) that can directly damage surrounding tissues as well as a number of mitogenic substances that may induce VSMC migration and proliferation [32,43]. Whether or not the net effect of VSMC activation is to enhance or inhibit the progression of the early atherosclerotic lesion remains controversial.

Phase 2: The vulnerable plaque

Several recent catheterization-based studies have shown that frequently the culprit lesion responsible for an acute cardiac event was previously mildly rather than severely stenosed [44–46]. These surprising data have altered the way we think about the biology of acute coronary syndromes. In many instances, the inciting thrombus in these syndromes likely arises from altered vascular wall biology, which tips the scales toward plaque rupture and thrombus formation, and not from the gradual encroachment of a plaque on the vessel lumen. Thus, the concept has emerged that acute events result from rupture of a vulnerable plaque in a biochemically disordered vessel segment, perhaps induced by a triggering event [47,48]. This hypothesis is supported by a number of pathological studies demonstrating a high prevalence of disrupted plaques with overlying thrombosis [9,14,15,18,49,50]. Based on these studies, a number of characteristics appear to predispose plaques to subsequent rupture, including minimal luminal compromise, high lipid content, a thin fibrous cap (especially vulnerable at the shoulder), high macrophage and low VSMC content, and exposure to high shear stress [1,2,5,51]. The actual rupture of a vulnerable plaque may in some cases be associated with an inciting event that increases catecholamine levels, such as early morning arousal or exercise [1,2,5,47,48]. Plaque rupture may be precipitated via a number of mechanisms, such as increased shear stress and increased thrombogenicity. However, Abela et al. have shown recently in a rabbit model that triggers require the presence

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Table 1. Summary of description and characterization of plaque morphology as it relates to the pathobiology of acute coronary syndromes

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>I</td>
<td>The minimal plaque</td>
<td>Accumulation of lipid, mononuclear cells, and VSMC within vessel wall without luminal compromise</td>
</tr>
<tr>
<td>II</td>
<td>The vulnerable plaque</td>
<td>Minimal luminal compromise, high lipid content, thin fibrous cap, high macrophage and low VSMC content</td>
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<tr>
<td>III</td>
<td>The nonocclusive disrupted plaque</td>
<td>Ruptured plaque that induces thrombotic, inflammatory, and vasospastic responses, resulting in critical the subendothelial lesions</td>
</tr>
<tr>
<td>IV</td>
<td>The occlusive disrupted plaque</td>
<td>Similar to phase III, but response to rupture results in occlusive lesion: Healed remnant of phase III or phase IV plaque</td>
</tr>
<tr>
<td>V</td>
<td>The organized plaque</td>
<td></td>
</tr>
</tbody>
</table>

VSMC = vascular smooth muscle cells.

This classification is based on that proposed by Foster et al. [9] and adopted by the American Heart Association.

of a vulnerable plaque in order to induce plaque rupture [52].

Phases 3 and 4: Disrupted, thrombosed plaques

Fissuring of a plaque leads to activation of the coagulation, vasoregulatory, and inflammatory systems. The end result of these processes is either (a) an increase in the plaque size without precipitation of acute clinical sequelae (an event that may occur repeatedly in a plaque over time), (b) a nonocclusive plaque that impedes flow sufficiently to cause unstable angina (phase 3), or (c) an occlusive plaque that may or may not result in myocardial infarction (phase 4) [1,9]. Which of these scenarios ensues depends on the net effects of a variety of both local and systemic factors. Local factors that influence the severity of the response following plaque rupture include the degree of plaque disruption, the degree of underlying stenosis, the composition of substances exposed to the lumen following disruption (e.g., exposure of lipid-rich contents is highly thrombogenic [11], the degree to which residual thrombus contributes to luminal narrowing, and vasospasm, which further increases shear stress on the fissured plaque [1]). Systemic factors that may influence the progression into either phase 3 or phase 4 include: (a) high levels of catecholamines, which contribute to worsened luminal narrowing by enhancing thrombosis as well as by inducing vasoconstriction [53–56]; (b) activation of the renin-angiotensin system, which may also facilitate thrombus formation, (perhaps by increasing the activity of plasminogen activator inhibitor) [57,58]; and (c) high circulating levels of a variety of other compounds, such as Lp(a) [59] and fibrinogen [60,61], which may also influence the thrombogenic state.

Phase 5: Organized severely stenotic or occlusive plaques

The phase 5 plaque likely represents the healed remnant of the phase 3 or 4 plaque. The phase 5 plaque may also progress to complete occlusion by processes similar to those described earlier, but this process is generally clinically silent. The infrequent precipitation of acute clinical events by the progression of phase 5 plaques may result from the induction of collateral vessels that provide sufficient blood flow to prevent infarction prior to complete occlusion of the vessel.

Factors that Modify Plaque Rupture and its Sequelae

Although in a general sense the progression from plaque initiation to plaque rupture follows the outline presented earlier, clearly a number of factors impact on this process to alter its course in clinically relevant ways. The contribution of modifiable cardiac risk factors to the biology of the atherosclerotic plaque and its evolution (Table 2) is now considered.

Cigarette smoking

Although there is abundant evidence demonstrating a link between cigarette smoking and clinical events such as stroke and MI, the mechanisms responsible for this relation remains controversial [62,63]. Cigarette smoking increases the risk for MI in both men and women, even after controlling for the extent of coronary artery disease [63,64]. Furthermore, the risk of MI decreases by approximately 50% in the first year following cessation of cigarette smoking for both men and women, despite a lack of significant change in the severity of coronary artery disease (CAD) [65,66]. Thus, it appears that the major effect of cigarette smoking is not to promote atherogenesis but rather to increase the propensity for plaque rupture and thrombosis. How then might cigarette smoking increase the risk for acute coronary syndromes? Smoking leads to a decrease in high-density lipoprotein (HDL) levels [67–69], which may alter the composition of the plaque, making it more vulnerable (see