Role of Inflammation in Coronary Plaque Disruption

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Coronary plaque disruption, with consequent platelet aggregation and thrombosis, is the most important mechanism by which atherosclerosis leads to the syndromes of ischemic heart disease, including unstable anginal pectoris, acute myocardial infarction, and sudden cardiac death. This insight has been obtained from clinicopathological studies extending over many years.1-10 These studies have identified a spectrum of alterations involving the plaque surface, including fissuring, erosion, ulceration, and rupture of the plaque surface. All these changes involve disruption of the endothelium and the underlying connective tissue of the plaque capsule. From these studies, a picture has emerged as to factors that predispose to these complications. Particular attention has been given to the identification of certain types of plaques that are prone to plaque disruption. These are lipid-rich atheromatous plaques that have a thin, fibrous capsule.1-10 The prevailing concept has been that a certain stage or process in the evolution of atherosclerosis predisposes lipid-rich plaques to develop surface disruption, with hemodynamic forces precipitating the actual rupture.1-10 However, the mechanisms responsible for plaque rupture have not been clearly elucidated. As a result, there has been considerable recent interest in further defining factors contributing to plaque disruption.

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In this issue of Circulation, van der Wal and colleagues11 report interesting findings in support of the intriguing hypothesis that inflammation plays an important role in coronary plaque disruption. The study was designed to obtain further clarification of the properties of plaques at risk for disruption and to seek evidence for inflammation in the process of plaque disruption. The study was based on an analysis of thrombosed coronary arteries obtained from 20 patients who died from acute myocardial infarction within 3 days of onset of symptoms and usually between 0 and 2 days. Serial sections were used to identify the exact site of plaque rupture. In addition, immunocytochemical procedures were used to characterize the presence of macrophages, T lymphocytes, and smooth muscle cells. A deep intimal rupture extending into the lipid core was encountered in 12 plaques, whereas 8 had superficial erosions only. An important finding was that, although most plaques showed the typical features associated with rupture, this was not universally the case. Ten atherosclerotic plaques had a distinctly attenuated fibrous capsule covering a large atheroma, whereas seven had a thick fibrocellular cap overlying a lipid pool and three were fibrocellular lesions without a clear lipid core. However, despite this variation in plaque morphology, the cellular composition at the lesion site was found to be more consistent. Specifically, macrophages, and to a lesser extent, T lymphocytes, were the dominant cells at the immediate site of either rupture or superficial erosion in each case. Another important finding was that these sites always were characterized by abundant expression of HLA-DR (class II) antigens on both the leukocytes and adjacent smooth muscle cells, suggesting an active inflammatory reaction. This contrasted with the overall cellular composition of the ruptured plaques, which was more variable in terms of mixtures of macrophages and smooth muscle cells than at the rupture site. The authors concluded that, although the underlying atherosclerotic plaque morphology in complicated coronary artery lesions causing acute myocardial infarction is heterogeneous both with respect to plaque architecture and cellular composition, the immediate site of plaque rupture or erosion always is marked by an inflammatory process. This suggests that inflammation plays a role in destabilizing the fibrous cap tissue and thus in enhancing the risk of coronary thrombosis. Thus, this study provides provocative observations and insights, which, if confirmed, give new ways of thinking about mechanisms involved in plaque disruption.

The concept of the involvement of inflammation in atherosclerosis has its origins in the work of Virchow.12 Virchow postulated that atherosclerosis resulted from a local reaction of the vessel wall to insudation of blood products. This is embodied in the current conception of atherosclerosis as an exaggerated response of the vessel wall to injury in which inflammation and fibrocellular proliferation are of major importance.13-17 In the last several years, the important role of influx of blood monocytes and their involvement as macrophages in the evolving lesions has been recognized.18-20 Several roles for macrophages have been identified. They produce platelet-derived growth factor–like material and other growth factors that stimulate the proliferation of smooth muscle cells.14,17 They are involved in the local oxidation of low-density lipoprotein,21 and they cer-
tainedly accumulate large amounts of oxidized low-density lipoprotein to become foam cells. More recently, complex leukocyte–endothelial cell interactions have been found to be involved in monocyte uptake. This process involves the expression of multiple adhesion molecules on the monocytes and endothelial cells. With more severe endothelial injury, another blood element, the platelet, becomes involved by attachment to the surface of the lesions and release of growth factors. The role of macrophages and platelets in lesion development has been recognized for a number of years; however, it has been shown more recently that the lesions also contain T lymphocytes. Thus, it is now well established that the two key cellular elements of chronic inflammation, namely T lymphocytes and macrophages, are present in abundance in atherosclerotic lesions. It is likely that T cell–macrophage interactions are important in macrophage activation and proliferation in atherosclerotic lesions. Thus, in areas of advanced atherosclerosis, the intimal lesions contain numerous macrophages, many of which have been converted into foam cells as well as T lymphocytes in addition to smooth muscle cells.

The study of van der Wal et al. raises the intriguing possibility of an additional role of inflammation in the national history of atherosclerosis, namely, that inflammation is the key mediator of plaque rupture. Others have raised the possibility that inflammation cells, including lymphocytes and mast cells, mediate a potentially related pathophysiological event, namely, coronary vasospasm. Fuster and colleagues have emphasized that there are a number of factors associated with plaque rupture. These are plaque composition; stress forces operative in and around the plaque; coronary vasoconstriction; the predilection for involvement of angiographically small, modestly stenosing plaques; and the presence of macrophages. These fundamental factors are influenced by additional local and systemic factors that influence the severity and outcome of the plaque rupture. In his “Conner Lecture,” Fuster emphasized that specific vessel wall–related and systemic factors during plaque disruption influence the degree of thrombogenicity and therefore determine the consequence of plaque disruption and the ensuing spectrum of acute ischemic syndromes. These factors include rheological factors, degree of plaque damage and substrate exposure, vasoconstriction, and systemic factors, including serum epinephrine level, serum cholesterol level, impaired fibrinolysis, and hypercoagulability. These concepts are based on experimental evidence from a number of laboratories.

We have shown that coronary thrombosis and vasoconstriction are promoted by the local activation of thrombin and the accumulation of platelet-derived factors that cause platelet aggregation and accumulation such as thromboxane A2, serotonin, platelet activating factor, and adenosine diphosphate, together with the loss of the normally present and endothelium-derived inhibitors of platelet aggregation and vasoconstriction, including prostacyclin and endothelium-derived relaxing factor as well as by other humoral factors including epinephrine. We have also obtained evidence that urinary excretion of various leukotrienes is increased in patients with cardiac ischemia, suggesting that the leukotrienes as well as other inflammatory mediators participate in the pathogenesis of cardiac ischemic syndromes.

van der Wal et al. have suggested that the most important and universal factor in plaque rupture is inflammation characterized by the local accumulation of macrophages and T lymphocytes at the site of rupture. However, a number of issues must be resolved. Is the process really inflammation? The best evidence for this in the study of van der Wal is local expression of HLA-DR antigens on the surfaces of the cells adjacent to the plaque disruption and not elsewhere in the plaque. The mechanisms and signals responsible for discrete local accumulation of large numbers of macrophages at a focal point adjacent to the surface of a plaque must be determined. Specific data are needed regarding local accumulation of monocyte chemotactic protein-1 and other cytokines. Is there a role for the neutrophil in this and other aspects of inflammation in atherosclerosis? Neutrophils are generally not found to any great extent in the lesions. This suggests that mechanisms are operative for selective recruitment of lymphocytes and macrophages. However, van der Wal found that some of the lesions, particularly those with deep fissures, had neutrophils, but they considered the neutrophils to accumulate secondarily in the process. Another important question is the mechanism by which the accumulated macrophages lead to plaque rupture or erosion. It is tempting to speculate that, under certain conditions, macrophage activation leads to the release of hydrolytic enzymes such as collagenases, elastases, other proteases, cathepsins, and other lysosomal enzymes from the macrophages, and that these degradative enzymes then weaken and degrade the surface connective tissue of the plaque. Some evidence for such a process has been provided by the work of Henney et al., who demonstrated the presence of a gene for stromelysin in atherosclerotic plaques by in situ hybridization. The stromelysins are members of a family of extracellular matrix metalloproteinases that could contribute to disruption of the plaque capsule. Further work is needed to determine whether this gene product or other hydrolytic enzymes are released in significant concentrations to mediate the process of plaque rupture. Nevertheless, the study of van der Wal et al. has raised the significant possibility that inflammation plays an important role in the most important process involved in the evolution of acute ischemic heart disease, namely, alteration in coronary plaque morphology and function that subsequently leads to transient or permanent thrombosis and the continuum from unstable angina to acute myocardial infarction.

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